HARRISON'S®

Guide to Inpatient Medicine

Common Internal Medicine Diseases and Workups

Edwards | Longo | Fauci | Kasper | Hauser
Jameson | Loscalzo | Holland | Langford



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Commonly Used Acronyms & Abbreviations

ABG	Arterial blood gas
ACE-I	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ACTH	Adrenocorticotropic hormone
AF	Atrial fibrillation
AIDS	Acquired immunodeficiency syndrome
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ARB	Angiotensin receptor blocker
ARDS	Acute respiratory distress syndrome
ARNI	Angiotensin receptor-neprilysin inhibitor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
BMP	Basic metabolic panel
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CABG	Coronary artery bypass graft
CBC	Complete blood count
CKD	Chronic kidney disease
CMP	Comprehensive metabolic panel
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography or computed tomographic
CXR	Chest x-ray
DAPT	Dual antiplatelet therapy
DLCO	Diffusing capacity for carbon monoxide
DOAC	Direct-acting oral anticoagulant
DVT	Deep venous thrombosis
ECG	Electrocardiogram; electrocardiography
ED	Emergency Department
EGD	Esophagogastroduodenoscopy
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
HDL	High-density lipoprotein
HF	Heart failure
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
ICU	Intensive care unit
INR	International normalized ratio
JVD	Jugular venous distention
JVP	Jugular venous pressure
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic antagonists
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LR	Lactated Ringer solution
LV	Left ventricle or left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NPO	Nil per os (nothing by mouth)
NS	Normal saline
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSTEMI or NSTE-ACS	Non–ST-segment elevation myocardial infarction or Non–ST-segment elevation acute coronary syndrome
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PET	Positron emission tomography
POCUS	Point of care ultrasound
PFTs	Pulmonary function tests
PRBCs	Packed red blood cells
prn	As needed
PT and PTT	Prothrombin time and partial prothrombin time
PTH	Parathyroid hormone
RBC	Red blood cell
RV	Right ventricle or right ventricular
SABA	Short-acting beta agonists
SAMA	Short-acting muscarinic antagonists
SCr	Serum creatinine
SGLT-2(I)	Sodium-glucose cotransporter-2 (inhibitor)
SIAD	Syndrome of inappropriate antidiuresis
SLE	Systemic lupus erythematosus
SSRI	Selective serotonin reuptake inhibitor
STEMI	ST-segment elevation myocardial infarction
SVT	Supraventricular tachycardia
TIA	Transient ischemic attack
TLC	Total lung capacity
TSH	Thyroid-stimulating hormone
UA	Urinalysis
UFH	Unfractionated heparin
UTI	Urinary tract infection
VBG	Venous blood gas
VTE	Venous thromboembolism
WBC	White blood cell



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GUIDE TO INPATIENT MEDICINE:

COMMON INTERNAL MEDICINE DISEASES AND WORKUPS

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Harrison's Guide to Inpatient Medicine: Common Internal Medicine Diseases and Workups

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Preface from the Harrison's Editors

Since 1950, the editors of *Harrison's Principles of Internal Medicine* have strived in each of the 22 editions to provide the reader engaged in a process of lifelong learning with the latest understanding of disease manifestations, pathogenesis, and management. The book represents the collective wisdom of hundreds of experienced physicians and researchers with deep expertise honed by years of experience. The amazing progress in medical science has led to remarkable improvements in patient management and treatment outcomes. However, the sheer volume of information in medicine has made the teaching of medicine a daunting task. Harrison's textbook in the latest edition is now 4000 pages long, with over 500 chapters in two large volumes, and despite its broad coverage, remains not entirely encyclopedic. Yet it is an unparalleled knowledge source if you are seeking a deep understanding of a disease process or a fruitful symptom-based approach to a sick patient.

The editors have recognized that a gap exists between using the textbook and having more focused information at hand ready to apply to a patient directly at the bedside. To address this practical need for information to directly guide the diagnosis, treatment, and care of the hospitalized patient, we have launched *Harrison's Guide to Inpatient Medicine*.

We have partnered with Mitchell Edwards, DO, who has written a useful and successful book, *Guide to the Most Common Internal Medicine Workups and Diseases*. His expertise at extracting the most salient and useful information from a larger format and organizing it in a useful way made him the ideal candidate to transform the content of *Harrison's Principles of Internal Medicine* into *Harrison's Guide to Inpatient Medicine*. This is a practical guide to bedside diagnosis, management, and hospital-based internal medicine clinical care for early-career clinicians, including medical students, nurse practitioners, physician assistants, interns, residents, and early career attendings. It is intended to bridge the gap between comprehensive Internal Medicine textbooks and pocket guides by offering clinically detailed, bedside-ready action plans for managing the most common conditions seen on hospital wards, while still maintaining the Harrison's principle of lifelong learning. We hope you find it useful.

The Editors

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"What are the most common conditions on Internal Medicine wards that I should know inside and out to prepare for intern year?"

A third-year medical student's simple question to their senior resident started a list of topics, sparking the creation of this work.

It was originally a plain notebook with a student's scribbled notes, an attempt to condense the vast amount of medical knowledge into a useful guide. *Harrison's Principles of Internal Medicine* was the primary reference, supplemented with data from other reputable sources and practical clinical insights. What resulted was something I could take to the bedside to guide through a history and exam, then sit down with to help interpret diagnostics and create a management plan.

In my fourth year of medical school, I transcribed these handwritten notes into a user-friendly, bullet-point Word document to reinforce what I had learned. The structure was reorganized, new sections were incorporated, and previous efforts were expanded. Its basic setup corresponded to the sequence of admitting a patient or examining a new symptom. Landmark clinical trials were added to support the evidence behind the information. As my clinical duties increased, I added admitting orders and discharge information. Prior to starting my internship, I took this new document to a local printer, creating a second version of my own personal guidebook.

My internship was rigorous, but this new guidebook built my confidence in managing common hospital conditions. With growing clinical experience, I added more information and solidified the content. Recognizing I had found a sweet spot between a textbook and a pocket guide for direct clinical flow, I wondered if it could assist others with comparable needs. I decided to self-publish the book "*Guide to the Most Common Internal Medicine Workups and Diseases*" at the conclusion of my intern year in 2017. To my surprise, over 22,000 copies have been sold since its publication.

Eight years later, McGraw Hill offered me a fantastic opportunity to rebrand my book. Revisions were made to every chapter, ten new chapters were created, and the *Harrison's* principle of lifelong learning was reinforced. Key points, clinical vignettes, and numerous high-yield diagrams, figures, and tables were added.

HOW SHOULD YOU USE THIS BOOK?

The perspective in the signs and symptoms chapters is that you are evaluating a patient with a new finding in the hospital, such as abdominal pain. What differential would you consider for that patient? What diagnoses should you 'not miss'? What questions would you ask at the bedside, and what would you look for on physical exam? What diagnostics would you consider ordering urgently? These short chapters focus on evaluation, with a brief management section that enables rapid patient stabilization pending diagnostic results.

The chapters on medical conditions are written from the perspective of the physician who has just received a call from the emergency department wishing to admit a patient with a common diagnosis, for example, heart failure exacerbation. What questions would you ask in the history? What would you look for on exam? Besides heart failure, what should be on your differential diagnosis? What caused the heart failure exacerbation? What diagnostic tests would you order, and how would you interpret them? How would you manage the patient? What medications would you prescribe on discharge to optimize their guideline-directed medical therapy? What landmark trials support those medications? What complications may arise that you could anticipate? What admitting orders would you place? Answers to these and other questions are presented in a highly templated, user-friendly, bulleted format that matches the steps you would take to admit a patient, streamlining your clinical workflow.

The concluding section outlines approaches for interpreting and managing common topics in Hospital Medicine. How do you interpret abnormal liver function tests, acid-base disorders, ECGs, and chest X-rays? How do you manage inpatient diabetes, alcohol withdrawal, replace electrolytes, and choose which antibiotic(s) to use?

What if you don't have the time to read the entire heart failure chapter, but need a refresher on diagnostics and management? Or need to place admitting orders quickly and want to make sure you order the basics? The beauty of these chapters is that you don't have to read the entire chapter if you don't have time. Pick and choose which section you need at the moment to care directly for your patient. Review the Key Points at the start of the chapter quickly. Then, when you have time, go back and read the rest of the chapter at your leisure to reinforce your learning.

This is the culmination of work from a Hospitalist who wants to make the transition and practice of inpatient medicine more practical. Its clear, concise, and detailed format highlights key points for direct clinical care and lifelong learning for common inpatient conditions. This resource is primarily intended for early-career clinicians and learners, but I'm confident it will also be a preferred choice for newly practicing Hospitalist clinicians. This was authored by a busy clinician with other busy clinicians in mind.

I am eager to continue learning inpatient clinical medicine alongside all of you,

Mitch Edwards, DO, FACP

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Most importantly, to Nicole, Julia, and my family: you are my people, world, and reason.

Mitch

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HARRISON'S ONLINE

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- Supplemental, online-only chapters of *Harrison's Guide to Inpatient Medicine*.
- All chapters from the print edition of *Harrison's Principles of Internal Medicine, 22nd edition,* plus more than two dozen supplementary chapters in print, atlas, and video formats. The content is regularly updated to reflect important new developments in medical research and practice.
- *Harrison's Review Questions,* consisting of more than 1500 self-assessment questions, with new questions added quarterly. Questions are presented in board-style clinical vignette format with multiple choice answers, making this a convenient resource for primary and recertification exam prep, rotational shelf exams, and general assessment of understanding of the principles of clinical medicine. The explanations for the questions are comprehensive and provide detailed guidance on correct and incorrect answers. Users can create personalized testing experiences and receive instant scores on practice tests.
- Harrison's Podclass, which delivers illuminating and engaging discussions led by Drs. Cathy Handy Marshall and Charlie Wiener of The John Hopkins School of Medicine on key topics in medicine, featuring board-style case vignettes from *Harrison's Review Questions* and chapters from *Harrison's Principles of Internal Medicine.* The hosts work through correct and incorrect answer choices and summarize cases with practical pearls that all students and clinicians will find helpful and interesting.

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1 Tachycardia

KEY POINTS

1. Tachycardia is an elevated heart rate exceeding 100 beats/min. Sinus tachycardia commonly occurs due to physiologic response to exercise or stress. Abnormal electrical signaling in the heart can lead to tachydysrhythmia, which can be either benign or life-threatening.
2. Patients with tachycardia can be asymptomatic, experience mild symptoms of palpitations and fatigue, dyspnea, or signs of end-organ damage (e.g., chest pain, dyspnea or hypoxemia, encephalopathy, hypotension or shock, acute HF, acute myocardial ischemia). The chronicity (acute or chronic) of the tachycardia should be assessed. A focused exam should include a thorough volume, cardiac, respiratory, and neurologic exam.
3. Sinus tachycardia is the most common etiology of tachycardia. An ECG can help determine other etiologies by determining if the rhythm is regular or irregular and if the QRS duration is narrow or wide. Common etiologies of *narrow* complex tachycardia include AF/flutter, other supraventricular tachycardias (SVTs), and focal atrial tachycardia. Common etiologies of *wide* complex tachycardia include ventricular tachycardia or SVT/AF with aberrant conduction.
4. Life-threatening causes of tachycardia include any tachycardia causing hypotension and/or end-organ damage. Any life-threatening medical condition (e.g., sepsis, PE, tamponade, tension pneumothorax, aortic dissection, alcohol withdrawal, GI bleeding, or hemorrhage) can cause tachycardia.
5. Vital signs and ABCs should be assessed immediately in case advanced cardiovascular life support protocols or emergent cardioversion needs to be performed. All patients with new tachycardia should have an ECG performed to delineate the specific rhythm and QRS duration. For patients with new tachycardia, consider blood work with a troponin, BNP, CBC, electrolytes, lactic acid, D-dimer, and TSH, as well as a CXR and transthoracic echocardiogram.

CLINICAL VIGNETTE

A 72-year-old woman with diabetes, COPD (on continuous 2 L of oxygen supplementation), and hypertension was admitted to the medicine floor 1 day ago for community-acquired pneumonia. IV ceftriaxone and azithromycin were initiated upon admission. You are paged by the bedside nurse because the last set of vitals included a heart rate of 142 beats/min (the highest prior heart rate was 76 beats/min). On arrival at the patient's bedside, the patient's BP is 120/82 mm Hg, the respiratory rate is 18 respirations/min, and SpO_2 is 92% on 3 L nasal cannula. She is breathing comfortably. She has no chest pain or dyspnea and is alert and oriented. On radial palpation, the rhythm is regular. An ECG reveals supraventricular tachycardia without evidence of myocardial ischemia.

GUIDING QUESTIONS

1. Does this patient have hemodynamically unstable or stable supraventricular tachycardia?
2. What diagnostic tests would you order?
3. What interventions would you consider to slow the patient's heart rate?

INTRODUCTION

Sinus tachycardia is a regular cardiac rhythm in which the heart beats faster than normal (> 100 beats/min). While sinus tachycardia is a common physiologic response to exercise or stress, it causes concern when it occurs at rest over long periods of time. It can also occur due to abnormal electrical signaling in the heart. Supraventricular tachycardia refers to a group of heart rhythm disorders originating at or above the atrioventricular node and is characterized by a narrow QRS complex (< 120 ms). Ventricular tachycardia is a wide complex dysrhythmia of ventricular origin, defined as ≥ 3 consecutive beats at a rate of > 100 beats/min with a prolonged QRS (> 120 ms). Some forms of tachycardia can be mild and benign, while others can be life-threatening.

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TABLE 1-1 QRS Morphology Can Narrow the Differential Diagnosis of Tachycardia

QRS MORPHOLOGY	DIFFERENTIAL DIAGNOSIS
Narrow and regular	Sinus tachycardia (physiologic sinus tachycardia, inappropriate sinus tachycardia)
	Atrioventricular nodal reentrant tachycardia (AVNRT)
	Atrioventricular reentrant tachycardia (AVRT)
	Focal atrial tachycardia (AT)
	Atrial flutter
	Junctional tachycardia
	Sinoatrial nodal reentrant tachycardia
	Ventricular tachycardia (VT) (rarely)
Narrow and irregular	Atrial fibrillation (AF)
	Multifocal AT (or sinus tachycardia with frequent atrial ectopy)
	Focal AT with variable atrioventricular (AV) block
	Atrial flutter with variable AV block
Wide and regular	Monomorphic VT
	Any supraventricular tachycardia with aberrant conduction, ventricular pacing, preexcitation, certain antiarrhythmic medications, or significant electrolyte abnormalities
	Antidromic AVRT with antegrade AV conduction via accessory pathway (i.e., Wolff-Parkinson-White syndrome)
Wide and irregular	AF, atrial flutter, or focal AT with aberrant conduction
	AF, atrial flutter, or focal AT with antegrade conduction via accessory pathway (Wolff-Parkinson-White syndrome)
	Polymorphic VT (including torsades de pointes)
	Ventricular fibrillation
	Antidromic AVRT due to nodoventricular/nodofascicular accessory pathway with variable ventriculoatrial conduction

DIFFERENTIAL DIAGNOSIS

- Determining the QRS morphology (narrow or wide) and rhythm (regular or irregular) simplifies the evaluation of tachycardia, despite its many causes (Table 1-1)
- Physiologic sinus tachycardia is the most common cause of tachycardia and has a broad differential (Table 1-2)

WHAT NOT TO MISS

- Hemodynamically unstable supraventricular and ventricular tachycardias
- Dysrhythmias associated with hypotension and/or end-organ damage
- Myocardial ischemia and infarction causing tachycardia and dysrhythmias (or vice versa)

TABLE 1-2 Common Causes of Sinus Tachycardia

Physiologic Causes
Emotion, physical exercise, sexual intercourse, pain, pregnancy
Pathologic Causes
Anxiety, panic attack, anemia, fever, dehydration, infection, malignancies, hyperthyroidism, hypoglycemia, pheochromocytoma, Cushing's syndrome, diabetes mellitus with evidence of autonomic dysfunction, PE, MI, pericarditis, valve disease, decompensated HF, shock, alcohol withdrawal
Drugs
Epinephrine, norepinephrine, dopamine, dobutamine, atropine, β_2-adrenergic receptor agonists (e.g., salbutamol), methylxanthines, doxorubicin, daunorubicin, β blocker withdrawal, caffeine, alcohol
Illicit Drugs
Amphetamines, cocaine, lysergic acid diethylamide, psilocybin, ecstasy

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- Pulseless ventricular fibrillation and tachycardia
- Any life-threatening medical condition that causes tachycardia (e.g., sepsis, PE, tamponade, tension pneumothorax, aortic dissection, alcohol withdrawal, GI bleeding, or hemorrhage)

FOCUSED HISTORY

- Always evaluate a patient with tachycardia *while* obtaining an ECG
- *Determine whether the patient has signs of end-organ damage or has hemodynamic instability*
  - Hemodynamically unstable patients with tachycardia have
    - Hypotension or shock
    - Chest pain
    - Dyspnea or hypoxemia
    - Encephalopathy or altered level of consciousness
    - Acute HF
    - Acute myocardial ischemia
  - If the patient is hemodynamically unstable and has a rhythm other than sinus tachycardia, *prepare for urgent cardioversion*
- *Patients with chest pain, dyspnea, altered mental status, and/or hypotension need to be seen urgently*

QUESTIONS AT THE BEDSIDE

- What are the vital signs?
- Any chest pain or dyspnea?
- Palpitations?
- Is the patient confused or somnolent?
- Why was the patient admitted?
- Recent alcohol cessation and/or binge?
- Recent illicit drug use (e.g., amphetamines, cocaine, lysergic acid diethylamide, psilocybin, ecstasy)?

FOCUSED EXAM

GENERAL

- Does the patient look distressed or ill?
- Examine for findings of hyperthyroidism, pheochromocytoma, Cushing's syndrome, and alcohol withdrawal
- Review telemetry, if available at bedside

VITALS

- Repeat now

CARDIOVASCULAR

- Heart rate and rhythm (palpate radial artery), JVP assessment
- Skin temperature and color
- Capillary refill
- Any new murmurs or a friction rub?

RESPIRATORY

- Is the trachea midline or deviated (tension pneumothorax evaluation)?
- Listen for crackles and breath sounds on both sides

NEUROLOGIC

- Evaluate for confusion, a change in level of consciousness, and anxiety

DIAGNOSTIC TESTS

- ECG and telemetry monitoring for all patients
- Consider the following for every patient
  - Troponin
  - BNP
  - CBC
  - Electrolytes
  - Lactic acid

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  - TSH
  - D-dimer
  - CXR
  - Transthoracic echocardiogram
- Other studies are ordered based on
  - Rhythm seen on ECG
  - Underlying etiology
    - For example, consider PE and further testing with CT pulmonary angiography to confirm the diagnosis if sinus tachycardia (with or without an S1Q3T3 present) and patient has pleuritic chest pain with an elevated D-dimer
- For aid in interpreting ECGs, see Chap. 53

MANAGEMENT

- Always complete ABCs first and ensure adequate oxygenation and IV access
- Place on telemetry; consider transfer to a higher level of care, if needed
- Cardioversion
  - May be required if the patient has
    - AF with rapid ventricular response
    - Supraventricular tachycardia
    - Ventricular tachycardia with either signs of end-organ damage or hypotension
  - Prepare for synchronized cardioversion when patient is unstable with the following serious signs and symptoms
    - Chest pain
    - Dyspnea or hypoxemia
    - Encephalopathy
    - Hypotension or shock
    - Acute HF
    - Acute myocardial ischemia
    - Ventricular rate of > 150 beats/min
  - Patients may require sedation prior to cardioversion
  - Do not perform cardioversion on patients with sinus rhythm
- For appropriate sinus tachycardia
  - Treat the underlying cause
  - IV β blockers may be appropriate in the presence of significant cardiac ischemia
- For inappropriate sinus tachycardia
  - Treat with a β blocker
- Supraventricular tachycardia (SVT) that is hemodynamically stable
  - Can sometimes be broken with Valsalva maneuvers and/or carotid sinus massage
    - Listen for bruits first
    - If no bruits are present, perform carotid massage on only one side at a time
  - If still in SVT after attempted Valsalva maneuvers and/or carotid sinus massage
    - Administer adenosine, 6 mg IV, followed by 12 mg IV, if necessary
    - Flush with at least 20 mL NS after administration
- AF with rapid ventricular response that is hemodynamically stable can be controlled with the following medications (see Chap. 21 for more details)
  - Diltiazem
    - Dosage: 0.25 mg/kg IV over 2 min
    - If no response, 0.35 mg/kg IV over 2 min and follow with an infusion at 5–15 mg/h
    - Use caution if the patient has HF (especially if they are admitted for a HF exacerbation)
  - Metoprolol
    - Dosage: 2.5–5 mg IV over 2 min every 5 min to a total of 15 mg followed by oral dosing
    - Best choice if myocardial ischemia is suspected
  - Esmolol
    - Dosage: 0.5 mg/kg over 1 min loading dose, followed by an infusion of 50 μg/kg/min max 300 μg/kg/min
  - Amiodarone
    - Dosage: 150 mg over 10 min, followed by an infusion of 1 mg/min for 6 h, then 0.5 mg/min for 18 h
    - Best choice if HF and/or an accessory pathway is present
    - Use caution if patient has not received appropriate anticoagulation

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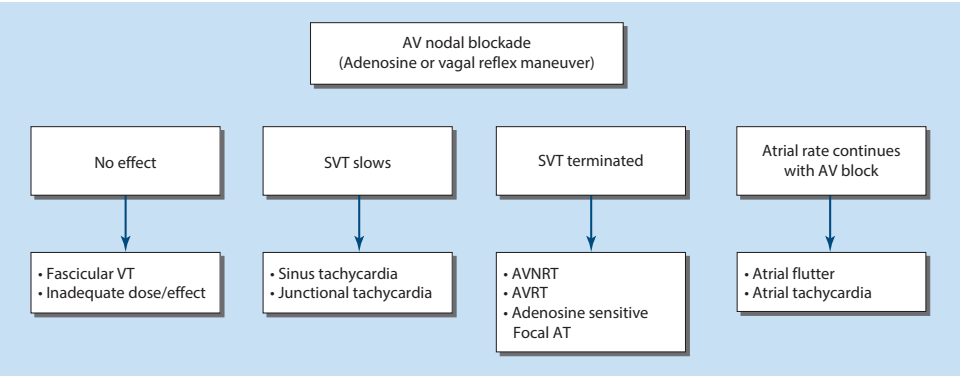

FIGURE 1-1 Diagnostic effect of increasing atrioventricular (AV) node blockade with vagal maneuvers, carotid sinus massage, adenosine, verapamil, or β blockers. AT, focal atrial tachycardia; AVNRT, atrioventricular nodal reentry tachycardia; AVRT, atrioventricular reciprocating tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia. (Reproduced with permission from Sauer WH, Zei PC. Approach to supraventricular arrhythmias, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Digoxin
        - Dosage: 0.25–0.5 mg IV, then 0.125–0.25 mg IV q6h to a total loading dose of 0.75–1.5 mg
        - Transition to 0.125–0.25 mg PO once daily
        - Slower effect, a good option if having HF exacerbation
- For ventricular tachycardia or fibrillation that is pulseless or without measurable BP, manage using the advanced cardiovascular life support protocol
- For any tachydysrhythmia that is associated with myocardial ischemia, IV β blockers are mostly considered first-line therapy
- Consult with cardiology for aid in diagnosis and management, if needed
- *Always search for the underlying etiology of the tachycardia and treat its cause*
    - For example, provide fluids and antibiotics if sepsis is present
- Sometimes, when the underlying dysrhythmia is unclear on ECG, clues from the effect of vagal maneuvers or adenosine can help aid the diagnosis (**Fig. 1-1**)

CASE ANSWERS

1. Hemodynamically unstable tachycardia presents as hypotension and/or signs of end-organ damage, including chest pain, dyspnea or hypoxemia, encephalopathy, hypotension or shock, acute HF, and/or acute myocardial ischemia. This patient currently has none of these findings; therefore, she has hemodynamically stable supraventricular tachycardia (SVT).
2. As this patient has had an ECG performed, blood work—including a troponin, BNP, CBC, electrolytes, lactic acid, and TSH—should be considered. A CXR is a quick test and should be performed in this patient admitted with pneumonia. If there are concerns about a structural or functional cardiac etiology, a transthoracic echocardiogram can be performed.
3. Hemodynamically stable SVT can initially be broken with Valsalva maneuver attempts and/or carotid sinus massage. If neither is successful, IV adenosine 6 mg can be attempted. If that is not successful, IV adenosine, 12 mg, can be administered.

FURTHER READING

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2 Bradycardia

KEY POINTS

1. Bradycardia is a reduced heart rate < 60 beats/min. Bradycardia can be categorized into sinus bradycardia or electrical abnormalities originating at the sinoatrial (SA) node or the atrioventricular (AV) node.
2. Patients with bradycardia can be asymptomatic; may experience mild symptoms of palpitations and fatigue; or may have chest pain, dyspnea, dizziness, or signs of end-organ damage. Acute bradycardia is more worrisome than chronic; therefore, a thorough history of the duration of the patient's symptoms is necessary. A focused exam should assess for clues to the bradycardia, including a thorough volume, cardiac, respiratory, and skin exam. While palpation of the radial artery and auscultation of the heart can establish whether the rhythm is regular or irregular, all patients should receive an ECG to determine the specific rhythm.
3. In older adults, sinus bradycardia occurring at rest or with sleep is common. Additionally, older adults commonly have dysfunction of either or both of the SA and AV nodes. In all patients, a thorough medication review should be performed, as iatrogenic bradycardia is common.
4. Bradycardia of any cause resulting in end-organ damage should be managed immediately. Irregular conduction deficits that need urgent evaluation (e.g., pacemaker insertion) include prolonged sinus arrest, second-degree type II AV block, and third-degree AV block.
5. Vital signs and ABCs should be assessed immediately in case life-threatening end-organ damage is present. All patients should receive an ECG and continuous telemetry monitoring. While diagnostic studies should be considered, IV atropine 1 mg is emergently necessary in patients with unstable bradycardia. Transcutaneous and/or transvenous pacing may be necessary in patients not responsive to atropine.

CLINICAL VIGNETTE

An 88-year-old woman with hypertension, HF with reduced ejection fraction, type 2 diabetes mellitus, and CAD was admitted to the general medical floor 2 days ago with an HF exacerbation due to running out of her furosemide for 2 weeks. Her goal-directed medical therapy was resumed upon admission, and IV furosemide twice a day has provided appropriate diuresis. You are paged in the middle of the night and informed by the bedside nurse that the patient's heart rate is 42 beats/min. Upon arrival in the room, the patient is asleep, resting comfortably, and breathing normally. The BP is 122/84 mm Hg and the Spo_2 is 96% on room air. There is 1+ edema of the bilateral lower extremities with some wrinkling noted, the radial pulse is regular, and she has no crackles in the lung fields. Neurologic exam reveals she is alert and oriented upon awakening. On chart review, you note the patient's heart rate during the day ranged from 60 to 70 beats/min. Electrolytes from this morning revealed a potassium of 3.6 mEq/L and magnesium of 1.6 mEq/L.

GUIDING QUESTIONS

1. Does this patient have hemodynamically unstable or stable bradycardia?
2. Besides an ECG, would you order any other diagnostic tests? If so, what would you order?
3. What else would you want to know about this patient?
4. How would you manage this patient?

INTRODUCTION

Sinus bradycardia is a cardiac rhythm with appropriate cardiac muscular depolarization initiating from the sinoatrial (SA) node with a rate of < 60 beats/min. Most patients are asymptomatic, while others present with fatigue, lightheadedness, dizziness, exercise intolerance, presyncope or syncope, worsening HF, or cognitive slowing. **SA node dysfunction** is the inability of the SA node to produce an adequate heart rate that meets the physiologic needs of an individual. **Atrioventricular (AV) node dysfunction** represents a delay or disturbance in the transmission of an impulse from the atria to the ventricles and can be due to an anatomic or functional impairment in the heart's conduction system.

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DIFFERENTIAL DIAGNOSIS

- Bradycardia can be separated into sinoatrial (SA) node dysfunction or atrioventricular (AV) node dysfunction
- SA node dysfunction, also known as sick sinus syndrome, is diagnosed when the ECG reveals sinus bradycardia, sinus pauses > 3 s or sinus arrest, or exit block (such as sinus arrest followed by a junctional beat or a premature atrial contraction)
    - Always evaluate for reversible causes of SA node dysfunction (Table 2-1)

TABLE 2-1 Reversible Causes of Sinus Node Dysfunction

Medical Conditions Associated with Sinus Bradycardia
• Hypothyroidism
• Sleep apnea
• Hypoxia
• Hypothermia
• Increased intracranial pressure
• Lyme disease
• Myocarditis
• COVID-19
• Vagal reflex (cough, pain, etc.)
Medications Associated with Sinus Node Dysfunction
Antihypertensive Medications
• β-Adrenergic receptor blockers
• Clonidine
• Methyldopa
• Nondihydropyridine calcium channel blockers
Antiarrhythmic Medications
• Amiodarone
• Dronedarone
• Flecainide
• Procainamide
• Propafenone
• Quinidine
• Sotalol
• Ivabradine
Psychiatric Medications
• Donepezil
• Lithium
• Opioid analgesics
• Phenothiazine antiemetics and antipsychotics
• Phenytoin
• Selective serotonin reuptake inhibitors
• Tricyclic antidepressants
Other
• Anesthetic drugs (propofol)
• Cannabis
• Digoxin
• Muscle relaxants

Reproduced with permission from Sauer WH, Koplan BA. The bradyarrhythmias: Disorders of the sinoatrial node, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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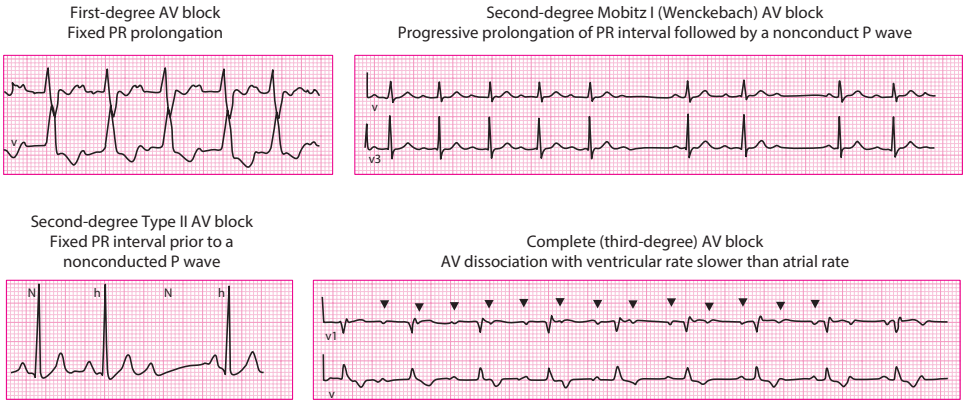

FIGURE 2-1 Types of atrioventricular (AV) block. The *upper left* figure displays fixed prolongation of the PR interval. The *upper right* figure demonstrates Mobitz I block (Wenckebach AV block) manifested as progressive prolongation of the PR interval followed by a nonconducted P wave ("dropped beat"). The *lower left* figure displays AV block with P wave with no QRS complex and no associated PR prolongation prior to the dropped beat (Mobitz type II AV block). The *lower right* figure demonstrates complete heart block manifested as dissociation between P waves and QRS complexes (AV dissociation). (Reproduced with permission from Sauer WH, Koplan BA. The bradyarrhythmias: Disorders of the atrioventricular node, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). McGraw Hill, 2025.)

- AV node dysfunction is diagnosed on ECG with bradycardia associated with first-, second-, or third-degree block (**Fig. 2-1**)
  - Always evaluate for and treat potential underlying etiologies of AV node dysfunction (**Table 2-2**)

WHAT NOT TO MISS

- Symptomatic and/or hemodynamically unstable bradycardia (especially from MI)
- Second-degree type II AV block
- Third-degree AV block
- Bradycardia of any kind leading to hemodynamic instability or worsening HF

FOCUSED HISTORY

- Always evaluate a patient with bradycardia while obtaining an ECG
- *Determine whether the patient is hemodynamically stable or unstable*
  - Hemodynamically unstable patients with bradycardia have
    - Hypotension
    - Dyspnea, including hypoxemia
    - Chest pain suggestive of myocardial ischemia
    - Encephalopathy
    - Acute HF
  - If the patient is hemodynamically unstable, *prepare to give IV atropine 1 mg*
- *Patients with chest pain, dyspnea, altered mental status, and/or hypotension need to be seen urgently*

QUESTIONS AT THE BEDSIDE

- What are the vital signs?
- Any chest pain or dyspnea?
- Is the patient confused more than their normal?
- Why was the patient admitted?
- Review all medications: any new medications? Any recent dose changes in medications?
- Is telemetry available (if so, review telemetry)?
- Quickly examine the patient and review the chart while waiting for the ECG

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TABLE 2-2 Etiologies of Atrioventricular Block

SYSTEM/CATEGORY	CAUSE OF AV BLOCK
Autonomic	Carotid sinus hypersensitivity Vasovagal
Metabolic/endocrine	Hyperkalemia Hypermagnesemia Hypothyroidism Adrenal insufficiency
Drug-related	β blockers Calcium channel blockers Digitalis Adenosine Antiarrhythmics (class I and III) Lithium
Infectious	Endocarditis Lyme disease Chagas' disease Syphilis Tuberculosis Diphtheria Toxoplasmosis
Heritable/congenital	Congenital heart disease Maternal SLE Kearns-Sayre syndrome Myotonic dystrophy and other muscular dystrophies
Inflammatory	SLE Rheumatoid arthritis Mixed connective tissue disease Systemic sclerosis
Infiltrative	Amyloidosis Sarcoidosis Hemochromatosis
Neoplastic/traumatic	Lymphoma Mesothelioma Melanoma Radiation Catheter ablation
Degenerative	Lev's disease Lenègre's disease
CAD	Acute MI

Modified from *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). McGraw-Hill Education, 2020.

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FOCUSED EXAM

- Assess for findings of hypothyroidism, sleep apnea, Lyme disease, SLE, rheumatoid arthritis, systemic sclerosis, amyloidosis, hemochromatosis, and sarcoidosis

GENERAL
- Does the patient look distressed or ill?

VITALS
- Repeat now

HEENT
- Examine for signs of elevated intracranial pressure (e.g., papilledema)

CARDIOVASCULAR
- Heart rate and rhythm (palpate radial artery), JVP assessment
- Skin temperature and color
- Capillary refill

RESPIRATORY
- Listen for crackles and breath sounds on both sides

NEUROLOGIC
- Evaluate for confusion or change in level of consciousness

SKIN
- Evaluate for skin rashes or lesions (e.g., erythema migrans of Lyme's disease)

DIAGNOSTIC TESTS

- ECG and telemetry monitoring for all patients
- Consider the following for every patient
  - Troponin
  - BNP
  - CBC
  - Electrolytes
  - Lactic acid
  - TSH
  - CXR
  - Transthoracic echocardiogram
- Other studies are ordered based on what is diagnosed on ECG, and what underlying etiology could cause the diagnosis
  - For example, order an enzyme immunoassay for a patient with third-degree atrioventricular block in whom Lyme disease is suspected
- For aid in interpreting ECGs, see Chap. 53

MANAGEMENT

- Observe asymptomatic patients with sinus bradycardia or sinoatrial (SA) node dysfunction
- If feasible, withdraw any medications that could contribute to the bradycardia
- Manage hypokalemia, hyperkalemia, hypomagnesemia, and hypercalcemia, if present
- *Hemodynamically unstable bradycardia*
  - Defined as bradycardia associated with hypotension, acute altered mental status, ischemic chest discomfort, or acute HF
  - Administer *atropine 1 mg*; can administer every 3–5 min up to 3 mg
  - If atropine is ineffective
    - Prepare for transcutaneous pacing and/or
    - Administer dopamine (5–20 μg/kg/min) or epinephrine (2–10 μg/min)
  - Consult cardiology for management recommendations, including potential need for transvenous pacing and a permanent pacemaker
- Always treat the underlying etiology
- Management of SA node dysfunction that is hemodynamically stable depends on the cause (Fig. 2-2)
- Management of AV node dysfunction that is hemodynamically stable depends on the rhythm and its cause (Fig. 2-3)

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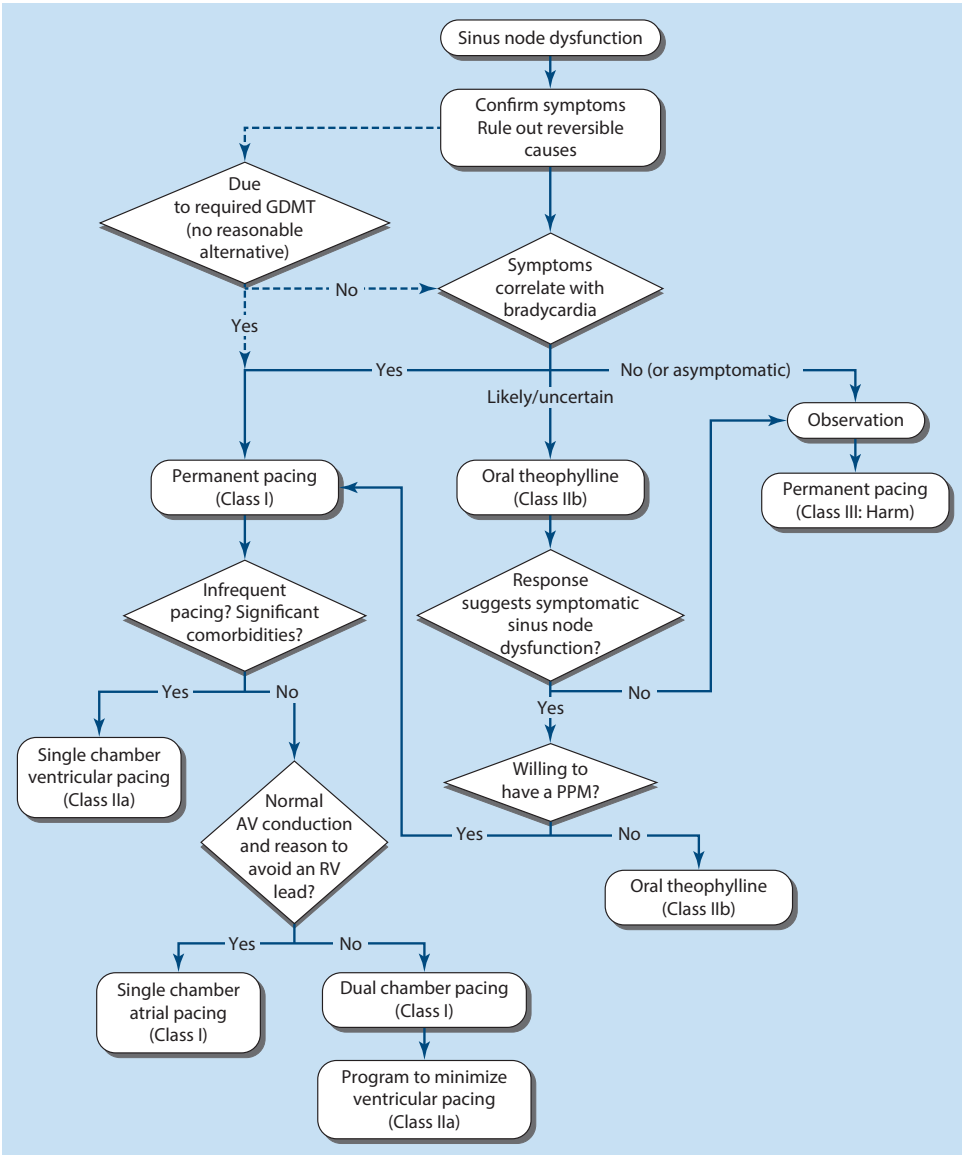

FIGURE 2-2 Management of sinus node dysfunction. Management of sinus node dysfunction begins with eliminating reversible causes and confirming whether symptoms correlate with bradycardia. If symptoms are clearly correlated, permanent pacing should be offered. If it is unclear, a trial of oral theophylline can be considered diagnostically. If there is no correlation between symptoms and bradycardia, then observation is appropriate. Class I recommendations should be performed or are indicated. Class IIa recommendations are considered reasonable to perform. Class IIb recommendations may be considered. Class III recommendations are associated with harm more than benefit. AV, atrioventricular; GDMT, guideline-directed management and therapy; PPM, permanent pacemaker; RV, right ventricular. (Reproduced with permission from FM Kusumoto et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. Heart Rhythm 16:e128, 2019.)

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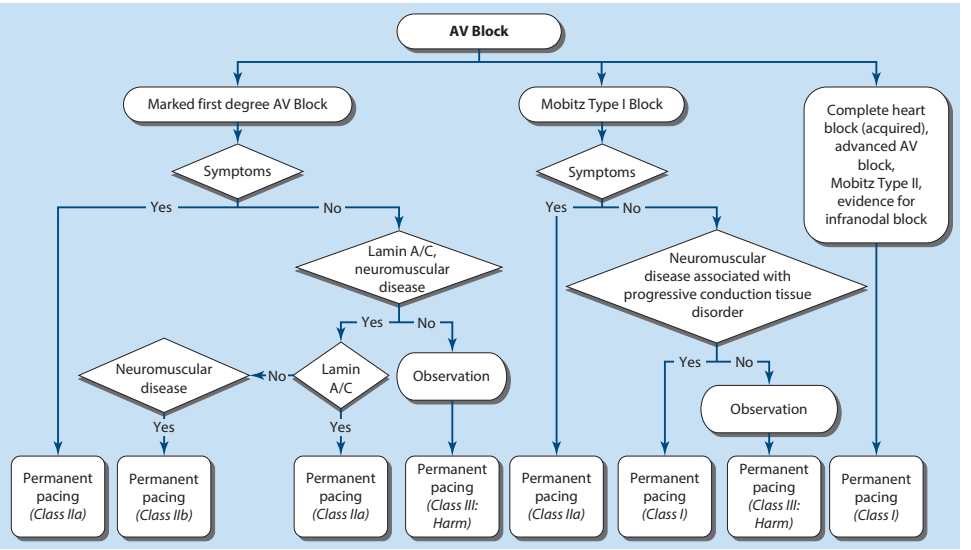

FIGURE 2-3 Indications for pacing in patients with atrioventricular (AV) block. In patients presenting with AV block, the category of AV block should be determined (first-degree, second-degree, or complete heart block). In first-degree AV block, permanent pacing may be indicated in the setting of symptoms or higher-risk systemic disease such as neuromuscular disease or Lamin A/C cardiomyopathy. In Mobitz I AV block, pacing may be considered in the setting of symptoms or the additional disease mentioned with first-degree AV block. In complete heart block or Mobitz II AV block, permanent pacing is generally indicated. Class I recommendations should be performed or are indicated. Class IIa recommendations are considered reasonable to perform. Class IIb recommendations may be considered. Class III recommendations are associated with harm more than benefit. (Reproduced with permission from FM Kusumoto et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. Heart Rhythm 16:e128, 2019.)

CASE ANSWERS

1. This patient has hemodynamically stable bradycardia. Besides the bradycardia, the other vital signs are normal, and there are no symptoms of end-organ damage to suggest hemodynamically unstable bradycardia.
2. While many diagnostic tests could be ordered, this patient is resting comfortably without signs of end-organ damage. The active management plan includes twice daily IV diuresis, and therefore, serum electrolytes (potassium and magnesium) can be investigated to ensure the levels are adequate in optimizing the cardiac function.
3. This patient with HF with reduced ejection fraction is likely taking a β blocker, which can cause bradycardia. A more thorough review should assess the patient's medications for causes of iatrogenic bradycardia.
4. Older patients taking medications that can cause bradycardia commonly have asymptomatic bradycardia during sleep. As the heart rate was normal during the day, it would be appropriate to observe closely while optimizing serum electrolytes.

FURTHER READING

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3 Hypotension

KEY POINTS

1. Hypotension, defined as systolic BP < 90 mm Hg or mean arterial pressure < 65 mm Hg, can be acute or chronic. When acute, life-threatening end-organ damage from tissue hypoperfusion can progress to shock. Chronic hypotension can occur as a result of chronic medical conditions and medications.
2. The chronicity of the patient's hypotension is important in determining the urgency of evaluation and management. Acute hypotension presents with dizziness, fatigue, lethargy, and end-organ damage. Chronic hypotension may be asymptomatic or have mild symptoms with certain movements (e.g., upon standing). Other symptoms may give clues about the underlying etiology of the hypotension.
3. In patients with acute hypotension, life-threatening conditions include shock, tension pneumothorax, cardiac tamponade, hemorrhage, aortic dissection, hemodynamically unstable PE, adrenal crisis, thyroid storm, myxedema coma, and hyper- or hypothermia. In chronic hypotension, chronic medical conditions (such as HF, cirrhosis, and orthostatic hypotension) and medications are common etiologies.
4. Vital signs and ABCs should be assessed immediately. A focused history and exam should be performed while waiting for ECG and other diagnostic test results. In patients with concern for hypovolemia, IV fluid boluses should be administered to restore intravascular volume. If the patient appears septic, broad-spectrum IV antibiotics should also be administered. Other management strategies depend on the suspected underlying etiologies (e.g., in patients with cardiac tamponade, a pericardiocentesis should be performed).

CLINICAL VIGNETTE

A 72-year-old man with COPD and hypertension was admitted to the medical ICU 2 days ago for acute hypoxemic and hypercapnic respiratory failure from a COPD exacerbation. On day 1, the patient was intubated for worsening encephalopathy while on bilevel positive airway pressure (BiPAP). The bedside nurse pages you due to worsening hypoxemia and acute hypotension. Upon entering the room, oxygen saturation is 74% on 100% Fio_2, BP is 68/48 mm Hg, heart rate is 132 beats/min, and telemetry monitoring shows sinus tachycardia. The patient appears uncomfortable on the ventilator, and the trachea is deviated to the right. There are no breath sounds on the left.

GUIDING QUESTIONS

1. What is the likely etiology of the patient's hypotension?
2. What immediate management is required for this patient?

INTRODUCTION

Hypotension (generally defined as systolic BP < 90 mm Hg or mean arterial pressure < 65 mm Hg) can be acute or chronic. When acute, life-threatening end-organ damage from tissue hypoperfusion can progress to shock. On the other hand, chronic medical conditions and medications can lead to chronic hypotension without end-organ damage. Orthostatic hypotension, a drop in BP upon standing, is more common in older adults, with prevalence rates increasing with age; it is also more prevalent in those with certain medical conditions and those taking specific medications.

DIFFERENTIAL DIAGNOSIS

The causes of hypotension are broad:

- Adrenal insufficiency and adrenal crisis
- Anaphylaxis
- Aortic dissection
- Cardiac tamponade
- Cirrhosis
- Dysrhythmias
- Hemorrhage
- HF (both chronic and in exacerbations)
- Hyper- or hypothermia

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- Hyper- or hypothyroidism
- Hypovolemia
- Medication side effects
- MI
- Orthostatic hypotension
- Pancreatitis
- PE
- Postprandial hypotension
- Sepsis
- Shock of any type
- Tension pneumothorax
- Valvular disease

WHAT NOT TO MISS

- Shock is a clinical diagnosis with a systolic BP < 90 mm Hg with evidence of inadequate tissue perfusion (elevated lactic acid) not responsive to fluids or requiring vasopressors or inotropes
- Shock is best addressed by looking at signs representing end-organ damage
  - Brain (encephalopathy)
  - Heart (angina)
  - Kidneys (low urine output)
  - Skin (cool and clammy)
- Tension pneumothorax
- Cardiac tamponade
- Hemorrhage
- Life-threatening dysrhythmias
- Dissection of the ascending aorta
- Hemodynamically unstable PE
- Adrenal crisis
- Thyroid storm and myxedema coma
- Hyper- or hypothermia

FOCUSED HISTORY

A high clinical suspicion of shock is critical for diagnosis. *Hypotension requires that you see the patient urgently, especially if it is acute.* A targeted history and exam, including ECG and POCUS, should be directed toward uncovering the type, severity, and cause of hypotension or shock. The chronicity of the hypotension is important, as acute hypotension is life-threatening compared with chronic hypotension. Following a comprehensive assessment that excludes life-threatening causes of hypotension, clinicians can conduct a more detailed investigation into the underlying etiology (Fig. 3-1).

QUESTIONS AT THE BEDSIDE

- What are the other vital signs?
- Is the patient unconscious, confused, or disoriented?
- Are they having chest pain or dyspnea?
- When was the last time the BP was normal?
- What was the reason for admission?
- Any potential for blood loss?
- Have they had recent initiation of new medications? Any recent changes in doses?
- What is their current IV access?

FOCUSED EXAM

GENERAL

- Does the patient appear distressed or ill?
- Assess for findings of adrenal insufficiency and hyper- or hypothyroidism

VITALS

- Repeat now and often
  - Measure BP in both arms (aortic dissection evaluation)
  - Evaluate for pulsus paradoxus (cardiac tamponade evaluation)

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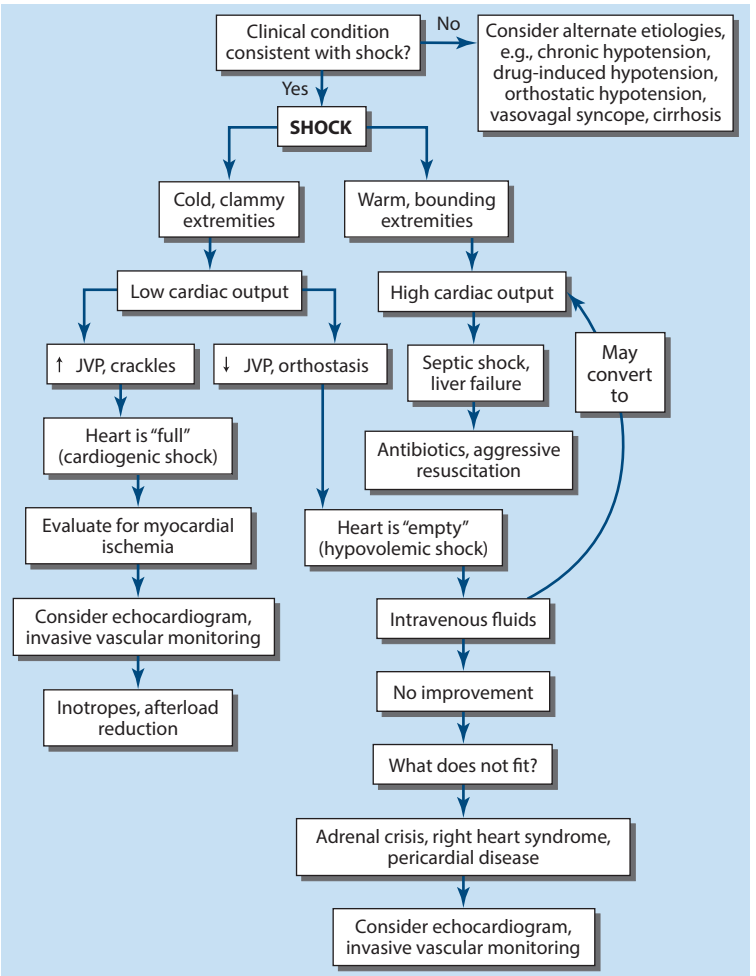

FIGURE 3-1 Approach to the patient with hypotension. (Reproduced with permission from Baron RM, Massaro AF. Approach to the patient with shock, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Fever and hypotension suggest sepsis
- A compensatory sinus tachycardia is expected in acute hypotension but may not be present in chronic hypotension
- Is their heart rate regular or irregular?
- If bradycardic, the patient may have autonomic dysfunction or heart block causing the hypotension
- Check orthostatic vital signs if feasible

HEENT

- Check mucous membranes, lips, and tongue for rashes, petechiae, and moist/dry appearance

CARDIOVASCULAR

- Heart rate, JVP, skin temperature, color, warmth, and capillary refill assessments
- Examine for murmurs, new or worsened

RESPIRATORY

- Listen for crackles and breath sounds on both sides
- Evaluate the position of the trachea (midline or deviated?)

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GI
- Any evidence of blood loss? May need to perform a digital rectal exam.

JOINTS
- Evidence of erythema and/or fluid accumulation?

SKIN
- Warm or cool and clammy
- Any new rashes?

EXTREMITIES
- Evaluate for edema or evidence of DVT (may have DVT and possibly PE)
- Acute limb ischemia with loss of pulse and pallor, especially to the upper extremities, can indicate aortic dissection

NEUROLOGIC
- Examine mentation and a focused neurologic function

POCUS
- Evaluate the inferior vena cava: is it small and collapsible with inspiration (hypovolemic)? Is it large and non-collapsible with respiration (hypervolemic)?

DIAGNOSTIC TESTS
- Consider the following in all patients
  - Troponins
  - ECG
  - ABG
  - Lactic acid
  - CBC
  - BMP, magnesium, phosphate, and glucose
  - Coagulation studies (PT, PTT, INR)
  - D-dimer
  - CXR
  - UA with reflux culture
  - Blood cultures
  - Transthoracic echocardiogram
- If considering adrenal insufficiency, order a cosyntropin stimulation test (unless it is acute adrenal crisis, then treat with IV hydrocortisone 100 mg)
- If considering thyroid disease, order a TSH

MANAGEMENT
- Examine the ECG and take the pulse yourself
  - Look for AF, supraventricular tachycardia, and ventricular tachycardia
  - These may cause hypotension because of decreased diastolic filling of the heart
- Administer IV fluid boluses to normalize intravascular volume, especially in shock
  - Use LR or NS
    - Evidence suggests LR causes less AKI and metabolic acidosis compared with NS
  - Cardiogenic shock is an exception
    - Instead of fluids, may require preload and afterload reduction and/or inotropic/vasopressor support
  - Hypovolemic, anaphylactic, and septic shock require fluids
    - Administer boluses of 500 mL to 1 L, and repeat if no response
- Anaphylactic shock
  - Epinephrine 0.01 mg/kg IM immediately and repeated every 5 min PRN
  - Methylprednisolone 80–125 mg IV if the patient has residual bronchospasm and needed more than two doses of IM epinephrine
  - Diphenhydramine 25–50 mg IV is administered for residual itching or urticaria

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- Septic shock
  - IV fluid boluses and broad-spectrum IV antibiotics
  - Continuing hypotension requires ICU admission for vasopressors
- Cardiogenic shock
  - Can be the result of an acute MI or worsening HF; treat the underlying cause
  - Other causes of hypotension and elevated JVD should be ruled out and managed (e.g., acute cardiac tamponade, PE, and tension pneumothorax)
- Adrenal crisis
  - Rapid volume resuscitation
  - IV hydrocortisone (100-mg bolus, followed by 50 mg q6h)
- Cardiac tamponade
  - Fluid resuscitation and pericardiocentesis
- MI
  - Anticoagulation (heparin infusion)
  - Antiplatelet therapy (aspirin 325 mg)
  - Anti-ischemic control (sublingual nitroglycerin, β-blocker, and possibly IV morphine)
  - Cardiology consultation for percutaneous coronary intervention or thrombolytic therapy (see **Chap. 19**)
- Tension pneumothorax
  - Perform needle decompression in the second intercostal space at the midclavicular line followed by chest tube placement
- Hemorrhage
  - Fluid resuscitation
  - Blood transfusion(s)
  - Control of bleeding site (see **Chap. 23**)
- Life-threatening dysrhythmias
  - For life-threatening tachydysrhythmias, urgent cardioversion and/or IV adenosine; ACLS management if indicated (see **Chap. 1**)
  - For life-threatening bradydysrhythmias, IV atropine and possibly transcutaneous/transvenous pacing (see **Chap. 2**)
- Hemodynamically unstable PE
  - Either embolectomy or thrombolytic therapy with anticoagulation (see **Chap. 18**)
- Orthostatic hypotension
  - Can be difficult to manage
  - Discontinue culprit medications
  - Administer compression stockings
  - Consider midodrine, fludrocortisone, or pyridostigmine (see **Chap. 22**)
- Always treat the underlying etiology and discontinue any offending medications if feasible

CASE ANSWERS

1. This patient was mechanically ventilated for a COPD exacerbation and now has worsened hypoxemia and hypotension. Exam findings of absence of breath sounds on the left and tracheal deviation to the right are consistent with a left-sided tension pneumothorax.
2. To acutely relieve the tension pneumothorax, emergent needle decompression via the left second intercostal space at the midclavicular line is indicated. This should be followed by placement of a chest tube on the left side.

FURTHER READING

- Baron RM, Massaro AF. Approach to the patient with shock, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- Gaieski DF, Mikkelsen ME. Evaluation of an initial approach to the adult patient with undifferentiated hypotension and shock. UpToDate. https://www.uptodate.com/contents/evaluation-of-and-initial-approach-to-the-adult-patient-with-undifferentiated-hypotension-and-shock. Accessed November 16, 2025.

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4 Hypertension

KEY POINTS

1. **Hypertension** is generally defined as BP > 120/80 mm Hg and is categorized by the degree of elevation (Table 4-1). **Hypertensive urgency** (severe asymptomatic hypertension) is a severe elevation of systolic BP > 180 mm Hg or diastolic BP > 100 mm Hg *without* the presence of acute end-organ damage. **Hypertensive emergency** is a severe elevation of BP (> 180/> 100 mm Hg) in the *presence* of acute end-organ damage.
2. Most patients with long-standing hypertension are asymptomatic, but end-organ damage may develop gradually. In patients with hypertensive emergency, headache, blurry vision, encephalopathy, chest pain, and dyspnea may develop, indicating the presence of acute end-organ damage.
3. Essential hypertension is the most common etiology of long-standing hypertension. Secondary hypertension (hypertension caused by an underlying medical condition) is most commonly due to obstructive sleep apnea, medications, hypercalcemia, and hyperaldosteronism.
4. Hypertensive emergency can be present in life-threatening conditions, including aortic dissection, intracranial hemorrhage, MI, acute LV HF with pulmonary edema, scleroderma renal crisis, and ischemic or hemorrhagic strokes.
5. In patients with hypertension in the hospital, understanding whether the hypertension is acute or chronic (the rate in the rise of the hypertension is more important than the absolute value) is vital. If acute, a focused history and exam should evaluate for the presence of end-organ damage. If end-organ damage is present, diagnostic tests, including ECG, troponin, CBC, BMP, UA, and CXR, should be considered.

CLINICAL VIGNETTE

A 72-year-old woman with no known medical history was admitted to the general medical floor 2 days ago for community-acquired pneumonia with mild acute hypoxemic respiratory failure requiring 2 L nasal cannula. Because of allergies to cephalosporins, IV levofloxacin and azithromycin were initiated. When you see the patient in the morning, she is less responsive but is able to articulate progressively worsening, severe, tearing chest pain that radiates to the back starting 2 h ago. The BP in the right arm is 210/94 mm Hg. Yesterday, the BP was in the normal range. On physical exam, the right radial pulse is normal, while the left is diminished. The BP in the left arm is 146/76 mm Hg. The patient is oriented only to herself. An ECG shows sinus tachycardia with a rate of 116 beats/min without ischemic findings. Lab studies are collected. A bedside CXR reveals a similar-appearing left lower lobar consolidation compared with admission, with a newly widened mediastinum.

GUIDING QUESTIONS

1. What type of hypertension does this patient have?
2. What is the most likely underlying diagnosis?
3. What imaging study would you order?
4. How would you manage this patient once the diagnosis is confirmed?

INTRODUCTION

Hypertension affects a significant portion of the adult population worldwide. In the United States, nearly half of adults have hypertension. The prevalence increases with age, with > 70% of adults ≥ 60 years of age having hypertension. Factors like sex, race, and ethnicity also influence prevalence, with men, non-Hispanic Black adults, and older individuals being more likely to have hypertension. Table 4-1 describes categories of hypertension. In the hospital setting, hypertensive emergency (severe elevations of BP in the presence of acute end-organ damage) requires urgent management. Identifying the cause of the hypertensive emergency is important to control the underlying etiology.

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TABLE 4-1 Definition of Hypertension

CATEGORY	SYSTOLIC PRESSURE (mm Hg)		DIASTOLIC PRESSURE (mm Hg)
Normal	< 120	and	< 80
Elevated	120–129	and	< 80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥ 140	or	≥ 90

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DIFFERENTIAL DIAGNOSIS

- Hypertensive emergency and urgency are what you need to worry about in the hospital
- *Hypertensive emergency*
  - Severe elevations of BP in the *presence* of acute end-organ damage (> 180/> 100 mm Hg)
  - Signs of end-organ damage
    - Encephalopathy, headaches, vision deficits, nausea, vomiting, seizures
      - The patient may also have posterior reversible encephalopathy syndrome (PRES)
    - Intracranial hemorrhage
    - Unstable angina or myocardial ischemia
    - Acute left ventricular failure with pulmonary edema
    - Aortic dissection
    - Eclampsia
    - AKI attributed to the hypertension
- *Hypertensive urgency*
  - Severe elevations of BP *without* the presence of acute end-organ damage
  - Hypertension in the setting of optic disc edema and severe perioperative hypertension also define hypertensive urgency
- For both conditions, the underlying etiology of the hypertension should be investigated and managed, especially if a secondary cause of hypertension is present
- A small subset of patients have "secondary" hypertension, with an overt underlying anatomic or biochemical cause for their hypertension
  - Patients with secondary hypertension have
    - Treatment-resistant hypertension
    - Abrupt worsening of hypertension
    - Disproportionate target organ damage for level of hypertension
    - Lab or diagnostic findings such as unprovoked hypokalemia, proteinuria, or LV hypertrophy
  - Causes include
    - Obstructive sleep apnea
    - Medication and other substances
    - Renal artery stenosis
    - Coarctation of the aorta
    - Renal parenchymal disease
    - Pheochromocytoma
    - Hyperaldosteronism
    - Hypertensive disorders of pregnancy (pre-eclampsia and eclampsia)
    - Cushing's disease
    - Thyroid disease
    - Hypercalcemia (e.g., hyperparathyroidism)
    - Acromegaly

WHAT NOT TO MISS

- Hypertensive emergencies with acute end-organ damage
  - Remember to always seek the underlying etiology of the hypertensive emergency and treat it
    - Aortic dissection
    - Scleroderma renal crisis
    - Acute pulmonary edema

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- Acute MI
- Eclampsia
- Stroke (ischemic and hemorrhagic)

FOCUSED HISTORY

Patients with chest pain, confusion, dyspnea, or focal neurologic deficits need to be seen urgently.

QUESTIONS AT THE BEDSIDE

- What are the vitals?
- What has the patient's BP been historically (i.e., has it always been high, or is it acutely high)?
  - *The rate of rise of the BP itself is more important than a high BP reading*
- What was the reason for admission?
- What BP medications has the patient been taking?
- Is the patient confused, or does the patient have decreased urine output, chest pain, or dyspnea?
- Does the patient have a headache, blurred vision, nausea, or vomiting?

FOCUSED EXAM

GENERAL

- Does the patient appear distressed or ill?
- Examine patients for signs of scleroderma, HF, Cushing's disease, thyroid disease, and acromegaly

VITALS

- Repeat BP in both arms (for aortic dissection evaluation)

HEENT

- Check fundi (if possible) for papilledema, retinal hemorrhages, or other hypertensive changes

CARDIOVASCULAR

- Examine the JVP, capillary refill, murmurs, and pulses in all extremities

RESPIRATORY

- Listen for crackles and breath sounds on both sides

NEUROLOGIC

- Evaluate the patient for confusion, delirium, and focal neurologic deficits

DIAGNOSTIC TESTS

- Consider the following tests in every patient
  - Troponin (and possibly serial troponins)
  - ECG
  - ABG (if respiratory distress or hypoxemia are present)
  - CBC
  - BMP
  - UA
  - CXR
- Other tests are determined by suspicion of underlying etiology (e.g., CT angiography of the chest for aortic dissection, CT of the head for stroke)

MANAGEMENT

- *Treat the patient, not the BP*
  - Acute lowering of BP in asymptomatic patients with long-standing hypertension can be dangerous (can decrease perfusion to the brain, causing a stroke, or lead to higher rates of AKI and acute MI)
- Permissive hypertension is usually advised by neurologists for patients with an acute ischemic stroke
  - Indications to lower the BP in ischemic stroke (treat as hypertensive emergency)
    - BP is severely elevated (> 220/120 mm Hg)
    - Conditions such as acute coronary syndrome, decompensated HF, aortic dissection, encephalopathy, AKI, or eclampsia coexist

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TABLE 4-2 Specific Hypertensive Conditions and Their Preferred Pharmacologic Agents

CONDITIONS	PREFERRED ANTIHYPERTENSIVE AGENTS
Acute pulmonary edema/systolic dysfunction	Nicardipine or nitroprusside in combination with nitroglycerin and a loop diuretic
Acute pulmonary edema/diastolic dysfunction	Esmolol, labetalol, or verapamil in combination with low-dose nitroglycerin and a loop diuretic
Acute myocardial ischemia	Labetalol or esmolol in combination with nitroglycerin
Hypertensive encephalopathy	Nicardipine or labetalol
Acute aortic dissection	Labetalol or esmolol for impulse control, then either nitroprusside or nicardipine if BP goal not achieved
Pre-eclampsia, eclampsia	Labetalol or nicardipine
AKI/microangiopathic anemia	Nicardipine
Sympathetic crisis/cocaine overdose	Diltiazem or nicardipine in combination with a benzodiazepine
Acute ischemic stroke/intracerebral bleed	Nicardipine or labetalol
Scleroderma renal crisis	Captopril or enalaprilat

- Hypertensive emergencies require an ICU setting
  - The goal is to reduce the mean arterial pressure by no more than 25% in the first 2 h
  - Titratable drips (*not* IV pushes) of BP-lowering agents are used
    - See Tables 4-2 and 4-3 for options of medications and dosages based on the condition
  - If mitral regurgitation or pulmonary edema is present, consider nitroglycerin
  - If aortic dissection, use IV labetalol or an esmolol infusion for impulse control (goal heart rate < 60 beats/min)
    - If the goal BP has not been achieved (< 120/80 mm Hg), add IV nitroprusside or nicardipine infusion
- Hypertensive urgency can usually be managed with oral medications
  - The goal is to reduce the BP over 24–48 h
  - Examples include captopril 25–50 mg, clonidine 0.1–0.2 mg, or labetalol 200–400 mg; these can be repeated or titrated every 2–4 h
  - Also consider starting long-acting hypertension medications (Table 4-4) if indicated
  - Close follow-up after discharge is essential
- Notice how IV pushes are *not* medications used for hypertensive emergency or urgency
  - IV pushes have been associated with acute episodes of hypotension leading to worsening of clinical status in the hospital, as well as higher readmission rates and a trend toward increased 90-day mortality in patients who received IV pushes of BP-lowering agents
- All patients should be counseled on the six proven nonpharmacologic interventions that lower BP
  - Dietary Approaches to Stop Hypertension (DASH) diet
  - Weight loss to an ideal BMI
  - Low sodium intake
  - Adequate potassium diet
  - Exercise
  - An alcohol intake goal of ≤ 2 and ≤ 1 standard drinks per day for men and women, respectively

TABLE 4-3 Usual IV Doses of Antihypertensive Agents Used in Hypertensive Emergencies

ANTIHYPERTENSIVE AGENT	IV DOSE
Nitroprusside	Initial 0.3 (mcg/kg)/min; usual 2–4 (mcg/kg)/min; maximum 10 (mcg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg *or* 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 mcg/kg over 1 min, then 50–300 (mcg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 mcg/min, then titrate by 5 mcg/min at 3–5 min intervals; if no response is seen at 20 mcg/min, incremental increases of 10–20 mcg/min may be used

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TABLE 4-4 Summary Information for the Major Antihypertensive Drug Classes Used to Manage High Blood Pressure

EXAMPLES	DOSE (mg) AND FREQUENCY[a]	MOST COMMON ADVERSE EFFECTS	COMMENTS
Diuretics (thiazide and thiazide-like)			
Chlorthalidone Hydrochlorothiazide Indapamide	12.5–25 once 12.5–50 once 1.25–2.5 once	Hyponatremia Hypokalemia Hypercalcemia Hyperuricemia Hyperglycemia Dyslipidemia	Chlorthalidone preferred due to long half-life and use in most U.S. trials.
ACE inhibitors			
Enalapril Lisinopril Benazepril Ramipril Trandolapril	5–40 once or twice 10–40 once 10–40 once or twice 2.5–20 once 1–4 once	Cough Hyperkalemia in CKD AKI in severe bilateral RAS Hypotension Angioedema	Do not use in combination with ARBs Contraindicated in pregnancy
ARBs			
Losartan Valsartan Azilsartan Candesartan Olmesartan	50–100 once or twice 80–320 once 40–80 once 8–32 once 20–40 once	Hyperkalemia in CKD Reduced GFR AKI in severe bilateral RAS Hypotension	Do not use in combination with ACE inhibitors Contraindicated in pregnancy
CCBs (DHP)			
Amlodipine Felodipine Nifedipine LA	2.5–10 once 2.5–10 once 30–90 once	Peripheral edema (dose dependent) Gingival hyperplasia	Amlodipine may be preferred CCB if tolerated Not recommended in HFrEF
CCBs (non-DHP)			
Diltiazem ER Verapamil ER	120–360 once 100–300 once (Evening administration recommended)	Bradycardia Nausea Constipation	Do not use in combination with β blockers Do not use in HFrEF or in high-grade AV or SA block
β Blockers			
Metoprolol Carvedilol Nebivolol	50–200 once 20–80 once 5–40 once	Asthma Bradycardia Fatigue Exercise intolerance Impaired concentration	First-step drugs when clinically indicated, e.g., in IHD and HF Contraindicated in high-grade heart block
MRAs			
Spironolactone Eplerenone Finerenone	25–100 once 50–100 twice 10–20 once	Hyperkalemia, especially in CKD and with K^+-sparing agents Spironolactone may cause tender breasts, gynecomastia, and erectile dysfunction in men	Especially useful in resistant hypertension and low-renin states

(*Continued*)

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TABLE 4-4 Summary Information for the Major Antihypertensive Drug Classes Used to Manage High Blood Pressure (*Continued*)

EXAMPLES	DOSE (mg) AND FREQUENCY[a]	MOST COMMON ADVERSE EFFECTS	COMMENTS
K^+-Sparing Diuretics			
Amiloride Triamterene	5–10 once or twice 50–100 once or twice	Hyperkalemia, especially in CKD or with other agents that favor potassium retention	Minimal effect on BP Used to counteract hypokalemic effect of diuretics
Loop Diuretics			
Furosemide Torsemide	20–80 twice 5–10 once	Hypokalemia Volume depletion Hyperuricemia	Preferred in CKD with GFR < 30, in symptomatic HF, and when using potent direct vasodilator minoxidil
α_1 Receptor Blockers			
Doxazosin	1–16 once	Orthostatic hypotension, especially in older adults	Less cardioprotective than diuretics Used mostly in men with prostate hypertrophy
Direct Vasodilators			
Hydralazine Minoxidil	100–200, 2–3 times 5–100, 1–3 times	Reflex tachycardia Fluid retention Hydralazine-induced lupus syndrome (rare) Minoxidil-induced hirsutism in women	Potent antihypertensive agents Usually reserved for fourth- or fifth-step treatment in resistant hypertension Usually combined with diuretic (loop agents for minoxidil) and β blocker to minimize side effects
Central α_2 Agonists and Other Centrally Acting Drugs			
Clonidine (oral) Clonidine patch Guanfacine Methyldopa	0.1–0.8 twice 0.1–0.3 once/week 0.5–2.0 once 250–1000, 2–3 times	Sedation Dry mouth Bradycardia Fatigue Constipation Orthostatic hypotension	Infrequently used due to side effects and potential for hypertensive crisis following abrupt withdrawal Methyldopa has a good safety record in pregnancy

[a]Doses are daily unless otherwise noted.
Adverse event estimates based on U.S. Food and Drug Administration labeling at http://dailymed.nlm.nih.gov/dailymed/. Estimates of BP lowering versus placebo are "artificially" higher with older agents than with newer agents because the former were compared to placebo alone, whereas the latter were evaluated in patients who were already being treated with other antihypertensive medications.
Ang II, angiotensin II; AV, atrioventricular; CCB, calcium channel blocker; DHP, dihydropyridine; ER, extended release; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; LA, long-acting; MRA, mineralocorticoid receptor antagonist; RAS, renal artery stenosis; SA, sinoatrial.
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CASE ANSWERS

1. This patient has an acutely elevated BP and signs of end-organ damage (chest pain and encephalopathy). Therefore, this patient has hypertensive emergency.
2. Acute, severe, and tearing chest pain that radiates to the back; a BP discrepancy of > 20 mm Hg between arms; discrepant radial pulses; and a CXR showing a widened mediastinum are highly suggestive of acute aortic dissection.
3. A CT angiography of the chest is the best imaging method to confirm the diagnosis of acute aortic dissection.
4. The first goal of management of acute aortic dissection is impulse control with a goal heart rate of < 60 beats/min. To accomplish this, IV labetalol or esmolol infusion is administered. The second goal is to achieve a BP of < 120/80 mm Hg. If IV esmolol or labetalol infusions does not reach the BP goal, nitroprusside or nicardipine infusions can be added.

FURTHER READING

- Whelton PK. Hypertension, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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5 Fever

KEY POINTS

1. Fever is an elevation of body temperature (> 38°C [100.4°F]) that exceeds the normal daily variation and occurs with an increase in the hypothalamic set point. Hyperpyrexia, hyperthermia, and fever of unknown origin are separate entities and are more commonly due to noninfectious etiologies.
2. A thorough history and physical exam help identify clues to the underlying cause of a patient's fever. Associated symptoms of fever are incredibly broad and depend on the underlying source.
3. Etiologies causing fever can be grouped broadly into six categories: infections, autoimmune and inflammatory disorders, cancer, medications, endocrine disorders, and intrinsic hypothalamic malfunction. Of these categories, infections and autoimmune disorders are the most common.
4. Most conditions that cause fever can be life-threatening if not recognized and treated appropriately. Urgent life-threatening conditions causing a fever include sepsis and septic shock, acute meningitis, infective endocarditis, neutropenic fever, viral hemorrhagic fevers, necrotizing fasciitis, erythroderma, toxic shock syndrome, clostridial myonecrosis, thyroid storm, acute pericarditis with tamponade, serotonin syndrome, neuroleptic malignant syndrome, and cerebral hemorrhage.
5. After a thorough history and exam, a CBC, CMP, UA with culture, lactic acid, sputum culture and Gram stain, respiratory viral panel, ESR and CRP, two sets of blood cultures, and CXR should be considered in all patients. Further studies, depending on the clinical context, may be necessary (e.g., if the patient has concerning findings for acute meningitis, a lumbar puncture with CSF studies is required). Empirical IV antibiotics are indicated in immunocompromised patients and patients with sepsis but should be carefully considered in hemodynamically stable immunocompetent patients without an obvious source of infection.

CLINICAL VIGNETTE

A 70-year-old man with acute myeloid leukemia is admitted to the hospital for induction chemotherapy with venetoclax and azacitidine. On hospital day 8, the bedside nurse pages you that the patient's temperature is 38.6°C (101.4°F). Upon entering the room, the other vital signs are normal. With a full review of systems, the patient denies new symptoms. On physical exam, the lungs are clear to auscultation bilaterally, there are no murmurs, he is fully alert and oriented, and there are no skin abnormalities. There are no abnormalities of the mucous membranes, and he does not have a history of staphylococcal or streptococcal infections. The patient's peripherally inserted central catheter (PICC) does not have erythema, fluctuance, or tenderness on palpation. On review of the patient's morning lab data, the WBC count is 8400 cells/μL, hemoglobin 8.9 mg/dL, platelets 80,000 cells/μL, absolute neutrophil count (ANC) 120 cells/μL, and CMP is normal. CXR and UA are normal.

GUIDING QUESTIONS

1. Based on the information given, what is the current diagnosis?
2. How would you initially manage this patient's fever?

INTRODUCTION

Fever is an elevation of body temperature (> 38°C [100.4°F]) that exceeds the normal daily variation and occurs with an increase in the hypothalamic set point. Fever is a common symptom in response to a variety of clinical etiologies. Hyperpyrexia (a fever > 41.5°C [106.7°F]) can develop in patients with severe infections, but most commonly occurs in patients with CNS hemorrhages. Hyperthermia (heat stroke), on the other hand, is an elevated temperature but does not represent a fever. Fever of unknown origin is defined as meeting the following criteria: (1) fever ≥ 38.3°C (101°F) on at least two occasions, (2) an illness duration of at least 3 weeks, (3) no known immunocompromised state, and (4) an uncertain diagnosis after undergoing a thorough history, exam, and lab analysis.

DIFFERENTIAL DIAGNOSIS

Since many specific conditions cause fever, focus on disease categories with fever as a key symptom (Table 5-1). Then, after identifying a category, pinpoint the specific cause (e.g., if infectious disease is the leading differential category, does the patient have pneumonia, cellulitis, a central line infection?).

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TABLE 5-1 Disease Categories That Present with Fever as a Cardinal Sign
Infectious diseases
Autoimmune and noninfectious inflammatory disorders
Cancer
Medication related (e.g., vaccines, drug fever)
Endocrine disorders (e.g., hyperthyroidism)
Intrinsic hypothalamic malfunction

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WHAT NOT TO MISS

- The following is not an exhaustive list, as most conditions causing a fever can be life-threatening if not recognized and treated appropriately
  - Sepsis and septic shock
  - Acute meningitis
  - Infective endocarditis
  - Neutropenic fever
  - Viral hemorrhagic fevers
  - Necrotizing fasciitis, erythroderma and toxic shock syndrome, and clostridial myonecrosis
  - Thyroid storm
  - Acute pericarditis with tamponade
  - Serotonin syndrome
  - Neuroleptic malignant syndrome
  - Malignant hyperthermia
  - Cerebral hemorrhage (causing hyperpyrexia)

FOCUSED HISTORY

- Patients with any of the following need to be seen urgently
  - Other vital sign abnormalities (e.g., hypotension, tachycardia, hypoxemia)
  - Symptoms concerning for meningitis
  - Immunosuppression

QUESTIONS AT THE BEDSIDE

- What are the patient's other vitals?
- What was the reason for admission?
- Is this fever a new finding?
- Any associated symptoms?
  - Cough
  - Headache
  - Change in mental status
  - Nausea and vomiting
  - Diarrhea
  - Dysuria
  - New skin lesions or rashes
- Is the patient receiving any antipyretics or antibiotics?
- Has the patient been hospitalized recently?
- Is the patient immunocompromised?
- Does the patient take any antidepressants or antipsychotic medications (serotonin syndrome)?
- Any recent surgeries or procedures?
- Any recent travel or sick contacts?

FOCUSED EXAM

GENERAL

- Does the patient appear distressed or ill?
- Check all catheter sites (e.g., IVs, central line, Foley, G-tube)

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VITALS
- Repeat now
  - Check for pulsus paradoxus (pericarditis with tamponade evaluation)
  - Tachycardia is an expected finding with fever
  - However, fever with relative bradycardia could indicate conditions such as
    - Typhoid fever
    - Brucellosis
    - Leptospirosis
    - Factitious fever

CARDIOVASCULAR
- Examine the JVP
- Assess skin temperature and color
- Auscultate for murmurs, and make note if there are new or worsened murmurs
- Evaluate capillary refill

RESPIRATORY
- Listen for crackles and breath sounds on both sides

ABDOMEN
- Assess for localized tenderness and bowel sounds

EXTREMITIES
- Check calves for signs of DVT and joints for effusions
- Assess for any new or worsening rashes or skin lesions

NEUROLOGIC
- Assess mentation
- Photophobia?
- Neck stiffness?
- Assess the Brudzinski and Kernig signs if indicated
- Assess for abnormal deep tendon reflexes (serotonin syndrome, neuroleptic malignant syndrome, and intracranial hemorrhage)

DIAGNOSTIC TESTS
- Consider the following tests in every patient
  - Blood cultures (at least two sets at different sites; if a central line is present, obtain one blood culture set from the line and one at a peripheral site)
  - CBC
  - CMP
  - UA and culture
  - Lactic acid
  - Sputum culture and Gram stain
  - Respiratory viral panel
  - ESR and CRP
  - CXR
- Add rheumatologic serologies if indicated per differential diagnosis after history and exam
- Lumbar puncture with CSF studies if meningitis is suspected
- Fluid collections (e.g., pleural effusions, ascites, abscesses) may need to be drained and sent for chemistry and cultures
- Consider *Clostridioides difficile* stool toxin, ova and parasite stool studies, and/or stool PCR testing if indicated (fever associated with diarrhea)
- Imaging of the suspected infectious site if indicated (e.g., ultrasound for acute cholecystitis, CT for appendicitis)
- Culture any skin lesions or rashes if obtainable

MANAGEMENT
- Always treat the underlying etiology of the fever
- Make sure the patient is hemodynamically stable and has IV access

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- Review medications and obtain cultures
- Administer antipyretics (acetaminophen 650 mg PO)
- Bolus IV fluids if septic, and consider maintenance fluids for insensible losses
- Consider changing or removing Foley catheters and any indwelling IV sites
- Consider antibiotics carefully
    - Withholding antibiotics and awaiting culture results may be prudent when the patient
        - Is hemodynamically stable
        - Is immunocompetent
        - Does not appear toxic
        - Has no clear source of infection
    - Broad-spectrum antibiotics and IV fluids or vasopressors are required for unstable patients (those with fever, tachycardia, and hypotension)
- Patients with fever and meningitis symptoms require antibiotics (after dexamethasone) as soon as possible
    - Ideally, a lumbar puncture is performed *before* antibiotics are given
    - If the lumbar puncture cannot be performed for several hours, administer dexamethasone and antibiotics before lumbar puncture
- Neutropenic fever (febrile neutropenia)
    - Fever of > 38.3°C (101°F) with an absolute neutrophil count (ANC) ≤ 500 cells/μL
    - Cefepime
        - Dosage: 2 g IV q8h
        - If the patient has a penicillin allergy, administer ciprofloxacin 400 mg IV q12h or aztreonam 2 g IV q8h
    - Other alternatives to consider based on individual institutions local frequency of resistant bacteria include
        - Meropenem 1 g IV q8h
        - Imipenem 500 mg IV q6h
        - Piperacillin-tazobactam 4.5 g IV q6–8h
        - Ceftazidime 2 g IV q8h
    - Add vancomycin 1 g IV q12h if any of the following are present
        - Severe mucositis
        - Evidence of catheter-related infection
        - Known colonization with resistant *Staphylococcus* or *Streptococcus*
        - Sudden temperature spike > 40°C (104°F)
    - Consider metronidazole 500 mg IV q8h if oropharyngeal or intra-abdominal infection is suspected
    - Consider gentamicin 5 mg/kg IV daily × 72 h and possibly micafungin if clinically unstable after fluids and initial antibiotics
    - Consider antifungal therapy in high-risk patients (e.g., patients with hematologic malignancies and hematopoietic cell transplant recipients) who are expected to have a total duration of neutropenia > 7 days and have persistent or recurrent fever and in whom reassessment does not yield a cause

CASE ANSWERS

1. This immunocompromised patient with severe neutropenia has neutropenic fever. While no identifiable source of fever is evident, it should be assumed that patients with neutropenic fever have an infection until proven otherwise.
2. Two sets of blood cultures—one from the peripherally inserted central catheter (PICC) line and one from a peripheral site—should be obtained. Afterwards, IV cefepime is the initial antibiotic of choice. This patient does not have severe mucositis, evidence of catheter-related infection, or known colonization with resistant *Staphylococcus* or *Streptococcus*; if he did, IV vancomycin would be added to the initial management. A continued search for an identifiable source of infection with close monitoring is indicated.

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6 Chest Pain

KEY POINTS

1. Due to a broad differential diagnosis, chest pain (or discomfort) can be described in a number of ways: squeezing, pressure, tightness, tearing, ripping, or burning.
2. Two leading causes of chest pain: GI conditions (e.g., esophageal reflux, peptic ulcer, gallbladder disease) and ischemic heart disease (ranging from stable angina to ACS). Neuromuscular causes are another common etiology (e.g., costochondritis, trauma, strain).
3. Patients must be seen urgently to rule out life-threatening causes of chest pain: MI, aortic dissection, acute pericarditis (with or without cardiac tamponade), PE, pneumothorax, and esophageal rupture.
4. Obtain a thorough history, including a description of the pain, associated symptoms, and risk factors for CAD. Presence of asymmetric BP measurements in the arms, elevated JVP, pulsus paradoxus, absence of breath sounds on one side, friction rub, Hamman's crunch, and signs of DVT may give clues to life-threatening etiologies.
5. After hemodynamic stability is assessed, urgent ECG should be performed followed by CXR, troponin, CBC, CMP, D-dimer, and ABG (if respiratory distress or hypoxemia is present). Depending on a narrowed differential, CT pulmonary angiography or CT angiography of the chest can evaluate for a PE or aortic dissection, respectively.

CLINICAL VIGNETTE

A 65-year-old man with stable CAD, hypertension, and type 2 diabetes mellitus was admitted to the medicine floor 2 days ago for a gout flare causing inability to ambulate safely. During morning rounds, you are paged by the bedside nurse who reports that the patient is reporting left-sided chest pain that began 15 min ago. On arrival at the patient's bedside, he appears sweaty and pale, and the pain is radiating to both arms.

GUIDING QUESTIONS

1. What additional questions would you ask in your focused history? What other vital signs should you assess, and what would you look for on physical exam?
2. What diagnostic tests would you order immediately while you are evaluating the patient?
3. How would you manage this patient acutely while awaiting results of diagnostic tests?

INTRODUCTION

The sensation of chest pain is one of the three most common reasons for visits to the ED, accounting for 6–7 million visits each year in the United States. More than 60% of patients are admitted to the hospital for further workup. However, ACS is diagnosed in only 10–20% of patients. The most common diagnoses made in patients presenting with chest pain are of GI causes. Therefore, a thorough history and exam to develop a prioritized differential diagnosis is essential to prevent unnecessary testing. Historically, however, 2–6% of patients with chest discomfort of presumed nonischemic etiology who are discharged from the ED were later deemed to have had a missed MI (Fig. 6-1).

DIFFERENTIAL DIAGNOSIS

- Causes of chest pain can be divided by organ systems and by life-threatening conditions
  - Table 6-1 lists the cardiopulmonary conditions
  - Table 6-2 lists the noncardiopulmonary conditions
  - Table 6-3 lists clinical findings and confirmatory tests of life-threatening conditions

WHAT NOT TO MISS

- MI
- Aortic dissection
- Acute pericarditis (with or without tamponade)

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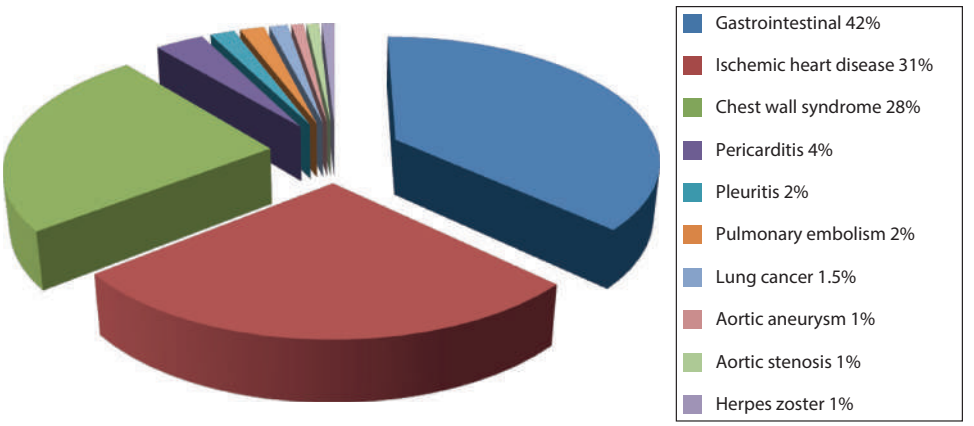

FIGURE 6-1 Distribution of final discharge diagnoses in patients with nontraumatic acute chest pain. (Reproduced with permission from D Longo et al (eds). *Harrison's Principles of Internal Medicine*, 22nd Edition. McGraw Hill; 2025.)

- PE
- Pneumothorax
- Esophageal rupture

FOCUSED HISTORY

- To guide workup and management, consider asking these key questions
  - Could the chest discomfort be due to an acute, potentially life-threatening condition that warrants urgent evaluation and management?
    - Unstable ischemic disease
    - Aortic dissection
    - Pericarditis with cardiac tamponade
    - Pneumothorax
    - PE
    - Esophageal rupture
  - If not, could the discomfort be due to a chronic condition likely to lead to serious complications?
    - Stable angina
    - Aortic stenosis
    - Pulmonary hypertension
  - If not, could the discomfort be due to an acute condition that warrants specific treatment?
    - Pericarditis
    - Pneumonia/pleuritis
    - Herpes zoster
  - If not, could the discomfort be due to another treatable condition?
    - Many conditions are included here; examples include esophageal reflux, peptic ulcer disease, gallbladder disease, and costochondritis

QUESTIONS AT THE BEDSIDE

- What are the patient's vitals?
- What was the patient admitted for?
- Where is the pain? Does it radiate anywhere?
- Is it worsened with exertion and relieved by rest?
- Has nitroglycerin been given? If so, did it improve the pain?
- Associated symptoms:
  - Presyncope or syncope?
  - Dyspnea?
  - Diaphoresis?
  - Pain with inspiration?
  - Associated with meals?

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TABLE 6-1 Typical Cardiopulmonary Features of Major Causes of Acute Chest Discomfort

CONDITION	ONSET/DURATION	QUALITY	LOCATION	ASSOCIATED FEATURES
Cardiac				
Myocardial ischemia	*Stable angina:* Precipitated by exertion, cold, or stress; 2–10 min *Unstable angina:* Increasing pattern or at rest *MI:* Usually > 30 min	Pressure, tightness, squeezing, heaviness, burning	Retrosternal; often radiation to neck, jaw, shoulders, or arms; sometimes epigastric	S_4 gallop or mitral regurgitation murmur (rare) during pain; S_3 or crackles if severe ischemia or complication of MI
Pericarditis	Variable; hours to days; may be episodic	Pleuritic, sharp	Retrosternal or toward cardiac apex; may radiate to left shoulder	May be relieved by sitting up and leaning forward; pericardial friction rub
Vascular				
Acute aortic dissection	Sudden onset of unrelenting pain	Tearing or ripping; knifelike	Anterior chest, often radiating to back, between shoulder blades	Associated with hypertension and/or underlying connective tissue disorder; murmur of aortic regurgitation; loss of peripheral pulses; unequal upper extremity BP
PE	Sudden onset	Pleuritic; may manifest as heaviness with massive PE	Often lateral, on the side of the embolism	Dyspnea, tachypnea, tachycardia, and hypotension
Pulmonary hypertension	Variable; often exertional	Pressure	Substernal	Dyspnea, signs of increased venous pressure
Pulmonary				
Pneumonia or pleuritis	Variable	Pleuritic	Unilateral, often localized	Dyspnea, cough, fever, crackles, occasional rub
Spontaneous pneumothorax	Sudden onset	Pleuritic	Lateral to side of pneumothorax	Dyspnea, decreased breath sounds on side of pneumothorax

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- Ask about or chart review for risk factors of ACS/CAD
  - Smoking
  - Diabetes mellitus
  - Hypertension
  - Dyslipidemia
  - Obesity
  - Family history of CAD
- How far can you walk without stopping? What stops you?
- Is the pain associated with deep inspiration (pleuritic)?
- Is the location of pain tender to the touch?
- Does the pain occur when you move?
- Is the pain worse when lying flat and relieved with sitting upright?
- Does eating make the pain worse?
- Was there any trauma in the area?
- Chest pain characteristics and their likelihood of an acute MI are shown in **Fig. 6-2**.

FOCUSED EXAM

A normal physical exam is *not* always reassuring.

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TABLE 6-2 Typical Noncardiopulmonary Features of Major Causes of Acute Chest Discomfort

CONDITION	ONSET/DURATION	QUALITY	LOCATION	ASSOCIATED FEATURES
GI				
Esophageal reflux	10–60 min	Burning	Substernal, epigastric	Worsened by postprandial recumbency; relieved by antacids
Esophageal spasm	2–30 min	Pressure, tightness, burning, intense squeezing	Retrosternal	Can closely mimic angina; may be relieved by nitroglycerin or dihydropyridine calcium channel antagonists
Esophageal injury	Prolonged	Intense squeezing	Retrosternal	Includes Mallory-Weiss tear or esophageal rupture (Boerhaave's syndrome) from vomiting
Peptic ulcer	Prolonged; 60–90 min after meals	Burning	Epigastric (most common), substernal	Relieved with food or antacids
Gallbladder disease, including cholecystitis and biliary colic	Prolonged; steady, usually hours	Aching or colicky	Epigastric, right upper quadrant; sometimes to the back, scapula, and lower chest	May follow meal and may subside spontaneously
Pancreatitis	Prolonged	Typically aching	Epigastric, radiates to the back	Worse after eating
Neuromuscular				
Costochondritis	Variable	Aching	Sternal	Sometimes swollen, tender, warm over joint; may be reproduced by localized pressure on exam
Cervical disk disease	Variable; may be sudden	Aching; may include numbness	Arms and shoulders	May be exacerbated by movement of neck
Trauma or strain	Usually constant	Aching	Localized to area of strain	Reproduced by movement or palpation
Herpes zoster	Usually prolonged	Sharp or burning	Dermatomal distribution	Vesicular rash in area of discomfort
Psychological				
Emotional and psychiatric conditions	Variable; may be fleeting or prolonged	Variable; often manifests as tightness and dyspnea with feeling of panic or doom	Variable; may be retrosternal	Situational factors may precipitate symptoms; history of panic attacks, depression

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GENERAL

- Quickly assess ABCs
- Does the patient appear distressed or ill?
- Are they pale, cyanotic, or diaphoretic?

VITALS

- Hypotension is an ominous sign of severe cardiopulmonary disease
- Sudden hypertension may suggest a cardiopulmonary cause, such as aortic dissection or acute MI
- Tachycardia may stem from a PE or from any cause of pain
- Bradycardia may be from an atrioventricular block with inferior MI

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TABLE 6-3 Life-Threatening Causes of Chest Pain and Their Clinical Findings

DIAGNOSIS	HISTORY	DESCRIPTION OF PAIN	KEY PHYSICAL FINDINGS	CONFIRMATORY TESTS
Acute coronary syndromes	Pain worsened with exertion; + coronary risk factors	Oppressive, constrictive, or squeezing; may radiate to arm(s), neck, back	Diaphoresis, pallor; S_4 common; S_3 less common	Serial ECGs Serial cardiac markers (esp. cardiac troponin)
Aortic dissection	Hypertension or Marfan's syndrome	"Tearing" or "ripping"; may travel from anterior chest to mid back	Weak, asymmetric peripheral pulses and BP; possible diastolic murmur of aortic regurgitation	CXR: Widened mediastinal silhouette CT or transesophageal echocardiogram: Intimal flap visualized
Acute pericarditis	Recent upper respiratory tract infection or other conditions that predispose to pericarditis	Crushing, sharp, pleuritic; relieved by sitting forward	Pericardial friction rub (usually three components, best heard by sitting patient forward)	ECG: Diffuse ST elevation and PR segment depression Echocardiogram: Pericardial effusion often visualized
PE	Recent surgery or other immobilization	Pleuritic, sharp; possibly accompanied by cough/hemoptysis	Tachypnea; possible pleural friction rub	Normal D-dimer makes diagnosis unlikely CT angiography or lung scan: V/Q mismatch Pulmonary angiogram: Arterial luminal filling defects
Tension pneumothorax	Recent chest trauma or history of COPD	Very sharp, pleuritic	Tachypnea; decreased breath sounds and hyperresonance over affected lung field	CXR: Radiolucency within pleural space; possible collapse of adjacent lung segment If tension pneumothorax, mediastinum (including trachea) is shifted to opposite side
Rupture of esophagus	Recent recurrent vomiting/retching	Intense substernal and epigastric; accompanied by vomiting with or without hematemesis	Subcutaneous emphysema; audible crepitus adjacent to sternum (Hamman's crunch)	CXR: Pneumomediastinum Esophageal endoscopy: Diagnostic

Modified *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). McGraw-Hill Education, 2020.

- Tachypnea
  - One of the most common signs of PE
  - May point toward a pulmonary cause
- Measure BP in both arms to evaluate for aortic dissection
- Fever
  - May raise suspicion for PE, pneumonia, or pericarditis
  - Can also be present in MI
- Hypoxemia stems from serious pulmonary pathology, MI with new-onset HF, PE, or pneumonia, amongst other etiologies

CARDIOVASCULAR

- Are they clutching their chest (Levine's sign)?
- Palpate the location of pain for reproducibility of symptoms
- Palpate costochondral and chondrosternal articulations for signs of costochondritis (swelling, redness, localized tenderness)

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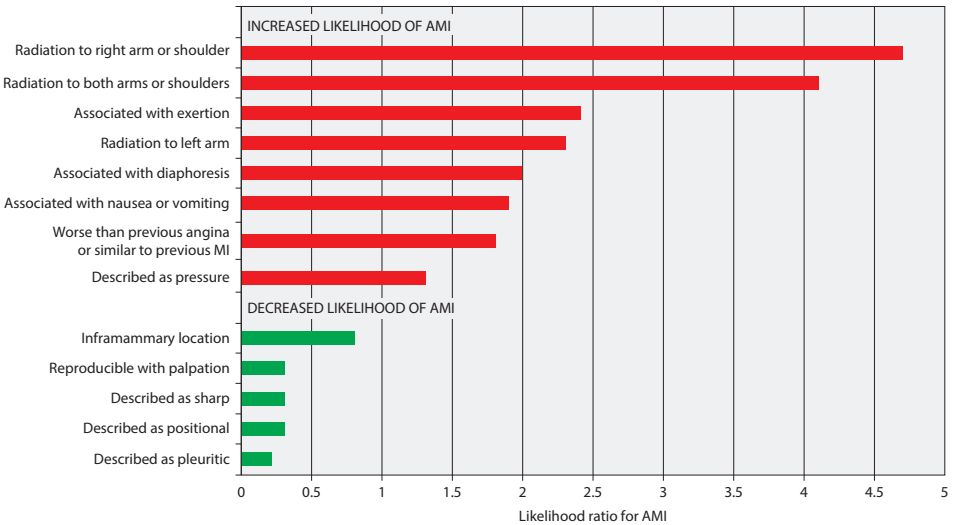

FIGURE 6-2 Association of chest pain characteristics with the probability of acute myocardial infarction (AMI). Note that a subsequent larger study showed a nonsignificant association with radiation to the right arm. (Reproduced with permission from Longo D (eds). *Harrison's Principles of Internal Medicine*, 22nd Edition. McGraw Hill; 2025.)

- Evaluate for
  - Skin lesions (such as herpes)
  - Mediastinal crunching (Hamman's sign)
  - Murmurs (especially new regurgitant murmurs)
  - Rubs (friction rub in pericarditis)
  - Gallops
- Measure the JVP for distention and signs of tamponade (pulsus paradoxus)

RESPIRATORY

- Listen for
  - Crackles (pulmonary edema)
  - Absent breath sounds on one side (pneumothorax)
  - Hyperresonance or dullness on percussion (pneumothorax)

ABDOMEN

- Examine for distention, tenderness, and bowel sounds
- Abdominal pathology can cause lower chest pain

EXTREMITIES

- Evaluate for edema or evidence of DVT (may have DVT and possibly PE)
- Acute limb ischemia with loss of pulse and pallor, especially to the upper extremities, can indicate aortic dissection

DIAGNOSTIC TESTS

- Every patient should have an ECG
  - Review any prior ECGs
  - Review telemetry, if applicable
- Consider the following for all patients
  - Troponin, and measure serially if indicated
  - ABG if respiratory distress or hypoxemia is present
  - CBC
  - CMP
  - D-dimer

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- CXR
  - Widened mediastinum is suggestive but nondiagnostic of aortic dissection
  - Hampton's hump or Westermark's sign in PE
  - Absence of lung markings and tracheal deviation in pneumothorax
  - Lobar consolidation in pneumonia
- Transthoracic echocardiogram (and POCUS of the heart if available)

- Consider CT pulmonary angiography or ventilation perfusion scan if PE suspected (use Wells' score and D-dimer to stratify risk)
- Consider contrast CT angiography of the chest if aortic dissection suspected

MANAGEMENT

- Initial orders
  - Confirm IV access
  - ECG with continuous telemetry monitoring
  - Initial troponin, and possibly serial repeats
  - Administer oxygen via nasal cannula to keep Spo_2 > 92%
  - Sublingual nitroglycerin 0.4 mg and aspirin 324 mg if felt to be anginal chest pain
  - If very high suspicion of angina, ACS, or PE, start a heparin infusion or subcutaneous enoxaparin
- If evidence of acute MI on ECG (ST elevation of ≥ 1 mm in at least two contiguous leads or new left bundle branch block)
  - Consult cardiology for consideration of reperfusion therapy (angioplasty or thrombolytics)
  - Aspirin 324 mg and consider β blockers, nitrates, morphine, and heparin (see **Chap. 19**)
- Aortic dissection
  - Immediate transfer to ICU
  - Impulse control with labetalol or esmolol infusion for goal heart rate < 60 beats/min
  - Once the heart rate is controlled, if BP is still not < 120/80 mm Hg, add an infusion of either nicardipine or nitroprusside
  - Vascular or thoracic surgery consult
- PE
  - Supplemental oxygen to keep Spo_2 > 92%
  - Enoxaparin, heparin infusion, or DOAC (if hemodynamically stable)
  - Consider thrombolytics if indicated (see **Chap. 18**)
- Pneumothorax
  - Supplemental oxygen to keep Spo_2 > 94%
  - Tension pneumothorax
    - Perform needle decompression in the second intercostal space at the midclavicular line followed by chest tube placement
  - Other pneumothoraxes (not tension)
    - Perform chest tube placement if > 20% of lung space is involved
- Pericarditis
  - Either high-dose aspirin (750–1000 mg) or NSAIDs (ibuprofen 600 mg tid)
  - Colchicine 0.5 mg bid reduces symptom severity and recurrence compared with NSAIDs or aspirin alone
  - If the patient has cardiac tamponade, administer IV fluids and consult cardiology for pericardiocentesis
- Esophageal rupture
  - Make the patient NPO
  - Provide broad-spectrum antibiotics (e.g., ampicillin-sulbactam), IV fluids, and IV proton pump inhibitor therapy
  - Surgery consult
- Esophageal reflux
  - Antacids: famotidine or omeprazole
  - Elevate the head of the bed, especially after meals
- Refractory chest pain
  - Re-evaluate what you thought was causing the chest pain
  - Repeat the history, ECG, vital signs, and physical exam
  - For ongoing cardiac ischemia with elevated troponins and/or ST-segment depression
    - Continue heparin infusion, daily aspirin, and β blockers
    - Start a nitroglycerin infusion
    - Consider clopidogrel or ticagrelor
    - Consider urgent cardiology consultation

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- Consider stress testing modalities when differential includes CAD but patient not having active ischemia
  - Myocardial perfusion scan
  - Exercise stress test
  - Coronary CT
  - Stress echocardiogram

CASE ANSWERS

1. Additional questions in the history should query the character, intensity, and precipitating and exacerbating factors (e.g., positional pain differences) of the chest pain. Associated symptoms, such as presyncope, dyspnea, diaphoresis, pain with inspiration, and association with eating meals, may be helpful. Ask the patient about risk factors for CAD (e.g., tobacco use, diabetes, hypertension, dyslipidemia, obesity, and family history of CAD). The BP (both arms), respiratory rate, and oxygen saturations should be assessed while recording the history. Elevated JVP, pulsus paradoxus, absence of breath sounds on one side, Hamman's crunch, friction rub, and signs of DVT may give clues to life-threatening etiologies.
2. ECG should be performed immediately in all patients with chest pain. CXR can be useful to assess for pneumothorax. Bedside POCUS can help evaluate cardiac tamponade. Troponin levels and CBC, CMP, D-dimer, and ABG (for patients in respiratory distress or with hypoxemia) should be drawn initially.
3. If the ECG shows a STEMI or concern for MI, nitroglycerin 0.04 mg and aspirin 324 mg should be administered. If the initial differential diagnosis highly suggests MI and/or PE, anticoagulation with heparin or enoxaparin should be considered.

FURTHER READING

- Morrow DA. Chest discomfort, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). McGraw Hill, 2025.

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7 Abdominal Pain

KEY POINTS

1. Abdominal pain has a broad differential diagnosis. Correctly diagnosing acute abdominal pain can be challenging because even the most catastrophic events may be heralded by the subtlest signs and symptoms.
2. A thorough history can help narrow the differential. Ask the patient about their pain: onset, characteristics, duration, location, and if the pain radiates. Ask about associated symptoms, such as nausea, emesis, or anorexia, diarrhea or constipation, and a menstrual history. Certain physical exam maneuvers (e.g., psoas and Murphy's signs) may help determine a specific etiology. High-pitched bowel sounds may indicate a bowel obstruction, while the absence of bowel sounds suggests an ileus. A pulsatile mass is observed with an abdominal aortic aneurysm.
3. Rule out life-threatening conditions first, including abdominal aortic aneurysm; bowel obstruction, rupture, perforation, or ischemia; acute MI; ascending cholangitis; acute appendicitis and cholecystitis; spontaneous bacterial peritonitis; neutropenic enterocolitis; diabetic ketoacidosis; acute adrenal crisis; and retroperitoneal hematoma. Once those have been ruled out, a broader investigation can continue toward identifying a non–life-threatening etiology of abdominal pain.
4. Patients with acute abdominal pain and hemodynamic instability need an urgent diagnostic workup and early empirical management. Diagnostic workup includes blood tests and imaging studies. Empirical treatment includes IV fluid boluses for patients with tachycardia and hypotension. Paracentesis should be performed in patients with ascites to rule out spontaneous bacterial peritonitis. When sepsis is suspected, IV antibiotics should be administered. If surgical intervention may be necessary, the patient should be made NPO.

CLINICAL VIGNETTE

A 64-year-old man with Crohn's disease (not currently on medications), hypertension, and hyperlipidemia was admitted 2 days ago to the general medical floor for a Crohn's disease flare. Prednisone, 40 mg daily, was initiated on admission with improving symptoms. As you see the patient this morning, he now describes severe, diffuse, crampy, aching, and steady abdominal pain that is different in character from the pain he was initially admitted with. He has also vomited twice this morning. The last reported bowel movement was 3 days ago. On exam, the patient is afebrile, he has new tachycardia, and BP is 96/74 mm Hg. He appears uncomfortable lying still in bed. The abdomen is distended, and there are high-pitched bowel sounds. Severe pain is accompanied by involuntary guarding with diffuse palpation. The morning lab data (CBC and CMP) have been collected, but the results are not available yet.

GUIDING QUESTIONS

1. What additional lab tests would you order? Would you order any imaging?
2. How would you manage this patient acutely?

INTRODUCTION

Abdominal pain is the leading GI symptom prompting ambulatory and ED visits in the United States. While understudied, its prevalence and characteristics cause a high disease burden in symptomatic patients. Any patient with abdominal pain of recent onset requires an early and thorough evaluation. While most patients admitted to the hospital have nonspecific abdominal pain that is not life-threatening, even the most catastrophic of events may be heralded by the subtlest signs and symptoms.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of abdominal pain can be assessed by location (Table 7-1) or by important causes of abdominal pain that need to be ruled out first (Table 7-2).

WHAT NOT TO MISS

- Vascular and intestinal
  - Abdominal aortic aneurysm rupture
  - Bowel obstruction, rupture, perforation, and ischemia from embolism or thrombosis

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TABLE 7-1 Differential Diagnoses of Abdominal Pain by Usual Location

LOCATION	DIFFERENTIAL DIAGNOSIS
Right upper quadrant	Cholecystitis Cholangitis Pancreatitis Pneumonia/empyema Pleurisy/pleurodynia Subdiaphragmatic abscess Hepatitis Budd-Chiari syndrome
Epigastric	Peptic ulcer disease Gastritis GERD Pancreatitis MI Pericarditis Ruptured aortic aneurysm Esophagitis
Left upper quadrant	Splenic infarct Splenic rupture Splenic abscess Gastritis Gastric ulcer Pancreatitis Subdiaphragmatic abscess
Right lower quadrant	Appendicitis Salpingitis Inguinal hernia Ectopic pregnancy Nephrolithiasis Inflammatory bowel disease (Fig. 7-1 A, B) Mesenteric lymphadenitis Neutropenic enterocolitis
Periumbilical	Early appendicitis Gastroenteritis Bowel obstruction Ruptured aortic aneurysm
Left lower quadrant	Diverticulitis Salpingitis Inguinal hernia Ectopic pregnancy Nephrolithiasis Irritable bowel syndrome Inflammatory bowel disease

(*Continued*)

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TABLE 7-1 Differential Diagnoses of Abdominal Pain by Usual Location (*Continued*)

LOCATION	DIFFERENTIAL DIAGNOSIS
Diffuse nonlocalized pain	Gastroenteritis
	Clostridioides difficile infection (Fig. 7-1 C)
	Mesenteric ischemia and ischemic colitis (Fig. 7-1 D)
	Bowel obstruction
	Irritable bowel syndrome
	Peritonitis
	Diabetes and diabetic ketoacidosis
	Malaria
	Familial Mediterranean fever
	Metabolic diseases
	Psychiatric disease

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TABLE 7-2 Some Important Causes of Abdominal Pain

CAUSES	DISEASES
Pain originating in the abdomen	Parietal peritoneal inflammation
	Bacterial contamination
	Perforated appendix or other perforated viscus
	Pelvic inflammatory disease
	Chemical irritation
	Perforated ulcer
	Pancreatitis
	Ovulation pain
	Mechanical obstruction of hollow viscera
	Obstruction of the small or large intestine
	Obstruction of the biliary tree
	Obstruction of the ureter
	Vascular disturbances
	Embolism or thrombosis
	Vascular rupture
	Pressure or torsional occlusion
	Sickle cell anemia
	Abdominal wall
	Distortion or traction of mesentery
	Trauma or infection of muscles
	Distention of visceral surfaces, e.g., by hemorrhage
	Hepatic or renal capsules
	Inflammation
	Appendicitis
	Typhoid fever
	Neutropenic enterocolitis
	Inflammatory bowel disease

(*Continued*)

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TABLE 7-2 Some Important Causes of Abdominal Pain (*Continued*)

CAUSES	DISEASES
Pain referred from extra-abdominal source	Cardiothoracic Acute MI Myocarditis, endocarditis, pericarditis HF Pneumonia (especially lower lobes) PE Pleurodynia Pneumothorax Empyema Esophageal disease, including spasm, rupture, or inflammation Genitalia Torsion of the testis
Metabolic causes	Diabetes and diabetic ketoacidosis Uremia Hyperlipidemia Hyperparathyroidism Acute adrenal insufficiency Familial Mediterranean fever Porphyria C1 esterase inhibitor deficiency (angioneurotic edema)
Neurologic/psychiatric causes	Herpes zoster Tabes dorsalis Causalgia Radiculitis from infection or arthritis Spinal cord or nerve root compression Functional disorders Psychiatric disorders
Toxic causes	Lead poisoning Insect or animal envenomation Black widow spider bites Snake bites
Uncertain mechanisms	Opiate withdrawal Heat stroke

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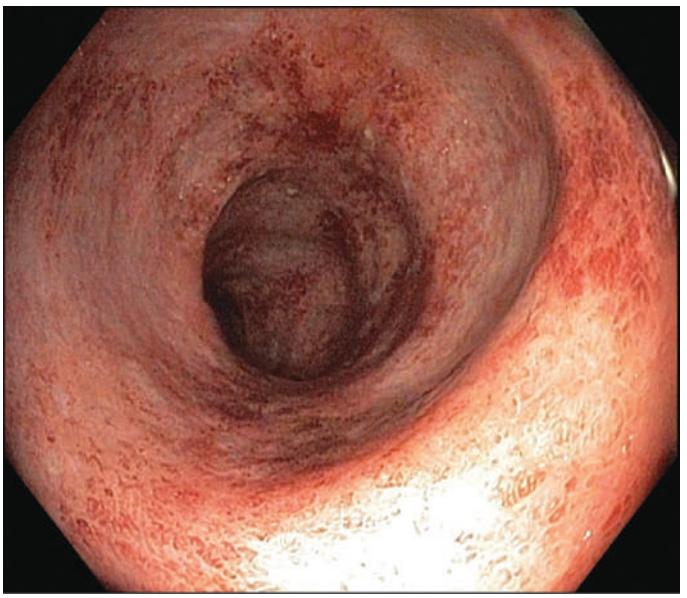

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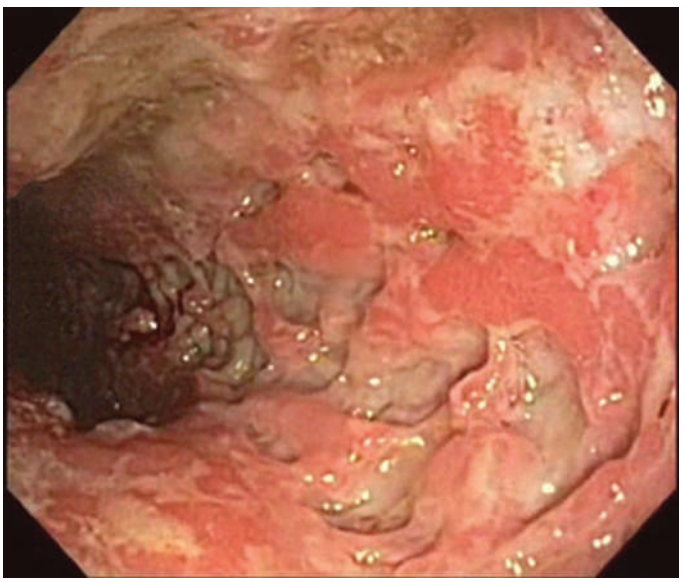

B

FIGURE 7-1 Causes of colitis. ***A.*** Chronic ulcerative colitis with diffuse inflammation. ***B.*** Severe Crohn's colitis with deep ulcers. ***C.*** Pseudomembranous colitis from *Clostridioides difficile* infection with yellow, adherent pseudomembranes. ***D.*** Ischemic colitis with patchy mucosal edema, subepithelial hemorrhage, superficial ulcerations, and cyanosis. (Used with permission from Song LMWK et al. Gastrointestinal endoscopy, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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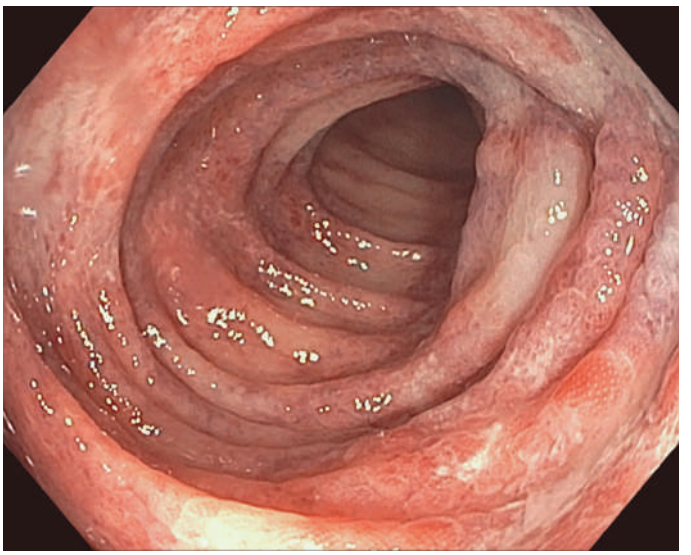
C



D

FIGURE 7-1 (*Continued*)

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    - Acute MI
    - Retroperitoneal hematoma
- Infectious
    - Ascending cholangitis
    - Acute appendicitis and cholecystitis
    - Spontaneous bacterial peritonitis
    - Neutropenic enterocolitis
- Endocrine
    - Diabetic ketoacidosis
    - Acute adrenal crisis

FOCUSED HISTORY

- Establish whether a life-threatening condition is causing the pain
- Decide whether patient needs to be seen immediately
    - Vital signs are stable: immediate workup not necessary
    - Sudden onset of pain despite normal vital signs: urgent evaluation required

QUESTIONS AT THE BEDSIDE

- How severe is the pain?
- How abruptly did the pain start?
    - If very abrupt, more likely to be from obstruction, acute vascular compromise, bowel perforation, nephrolithiasis, or torsion
- Is this a new or ongoing problem?
- What are the patient's vitals?
- What was the patient admitted for?
- Location of pain?
- Quality of pain?
    - Somatic pain is pinpoint
    - Visceral pain is vague
    - Neuropathic pain is burning or a pins-and-needles sensation
    - Inflammation of the parietal peritoneum is steady and aching in character
    - Colicky, burning, gnawing, or sharp pain can sometimes help determine an etiology
- Duration of pain?
- Radiation of pain?
- Pain that changes with respiration?
- Nausea or vomiting?
- Fever or chills?
- Last bowel movement?
- Hematemesis?
- Melena?
- Hematochezia?
- What makes the pain better or worse? Is it better leaning forward?
- Does eating affect the pain?
- If female, when was their last menstrual cycle?
- Prior surgeries?
- If history of AF and pain out of proportion to exam, think mesenteric ischemia
- Pain characteristics
    - Visceral pain localizes poorly and is often perceived in the midsection
    - Intestinal pain tends to be crampy (if appendix, it tends to localize above and around the umbilicus)
    - Pain from biliary or ureteral obstruction causes patients to writhe in discomfort
    - Somatic pain usually is sharper and more precisely localized to the diseased region, is exacerbated by movement, and causes patients to remain still
    - Patterns of radiation may be helpful: right shoulder (hepatobiliary), left shoulder (splenic), mid-back (pancreatic), flank (proximal urinary tract), and groin (genital or distal urinary tract)

FOCUSED EXAM

GENERAL

- Does the patient appear distressed or ill?
- Are they lying still in bed, or writhing in pain?

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VITALS
- Repeat now, especially the BP

HEENT
- Check for icterus

CHEST
- Check for skin lesions
- Listen for murmurs, rubs, or gallops
- Assess JVP

RESPIRATORY
- Listen for crackles, absent breath sounds on one side, and friction rubs

ABDOMEN
- Auscultate bowel sounds
  - High-pitched sounds occur with small bowel obstruction
  - Absent bowel sounds occur with ileus
- Percussion
  - Tympany
  - Shifting dullness is a sign of ascites
- Palpation
  - Guarding and rebound tenderness: signs of peritoneal inflammation and possibly a life-threatening condition
  - Murphy's sign: sign of acute cholecystitis
  - Psoas and obturator signs: signs of appendicitis
  - Costovertebral angle tenderness: sign of nephrolithiasis or pyelonephritis
  - Pulsatile mass: sign of an abdominal aortic aneurysm

RECTAL
- Assess for hemorrhoids and anal fissures
- Perform a digital rectal exam for melena and hematochezia evaluation

PELVIC
- Perform if indicated by the history

DIAGNOSTIC TESTS
- Consider the following in every patient
  - CBC
  - CMP
  - Lipase
  - Lactic acid
  - β–human chorionic gonadotropin, if female
  - UA
  - VBG (in the setting of possible mesenteric ischemia for which acidosis must be promptly identified)
- Paracentesis with cell count and cultures if concerned for spontaneous bacterial peritonitis
- Consider *Clostridioides difficile* stool toxin, ova and parasite stool studies, and/or stool PCR testing if diarrhea is present
- CXR if suspicious for an intrathoracic pathology
- ECG if suspicious for MI or pericarditis
- Abdominal CT (possibly with contrast), ultrasound, or both may be required
- Table 7-3 describes major causes of acute abdominal pain with their preferred diagnostic tests

MANAGEMENT
- *The initial goal is to determine if the patient has a life-threatening condition and needs surgical evaluation and treatment*
  - Rebound tenderness or guarding (especially involuntary) may herald life-threatening conditions
  - Ruptured viscus, abscess, hemorrhage, bowel obstruction, or acute ischemia have an abrupt onset of pain

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TABLE 7-3 Causes of Abdominal Pain and Preferred Diagnostic Tests

CAUSE OF ABDOMINAL PAIN	PREFERRED DIAGNOSTIC TEST
Acute appendicitis	CT scan
Acute cholecystitis or choledocholithiasis	Ultrasound
Acute diverticulitis	CT scan
Acute mesenteric ischemia	CT angiogram or MRI
Acute pancreatitis	Serum lipase, then possibly an ultrasound; some patients may need a CT scan
Biliary duct or pancreatic duct rupture	Magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP)
Bowel perforation	CT scan
Inflammatory bowel disease	Colonoscopy
Intestinal obstruction	Supine x-ray; CT scan
Ischemic colitis	Colonoscopy
Sigmoid volvulus	CT scan or barium enema

From Mitchell Edwards, DO.

- Other conditions can be managed using a more detailed approach to the underlying etiology after life-threatening conditions have been ruled out
- Keep the patient NPO if surgical intervention is a possibility
- Ensure IV access is present and consider IV fluids
- Correct any acid–base disturbances if present
- Use pain medications cautiously, as some abdominal pathologies may worsen over time with opiates, but recent evidence suggests giving opiates does not mask symptoms or a diagnosis
- Abdominal aortic aneurysm rupture
  - Vascular surgery consultation and transfer to the ICU
- Bowel obstruction, rupture, or perforation
  - Consult general surgery
  - NPO status and IV fluids
  - Likely needs a nasogastric tube set to low intermittent suction, and possible surgery
- Bowel ischemia from embolism or thrombosis
  - Anticoagulation and, if severe, vascular surgery consult
- Ascending cholangitis
  - Sepsis treatment with IV fluids, antibiotics (e.g., piperacillin-tazobactam), and GI consultation for an endoscopic retrograde cholangiopancreatography (ERCP)
- Acute appendicitis and cholecystitis
  - Sepsis treatment with IV fluids, antibiotics (e.g., ceftriaxone and metronidazole), and general surgery consultation
- Spontaneous bacterial peritonitis:
  - Albumin and antibiotics (e.g., ceftriaxone; see **Chap. 24**)
- Neutropenic enterocolitis
  - Sepsis treatment with IV fluids and antibiotics (e.g., cefepime and metronidazole)
- Acute MI
  - High-dose aspirin, heparin or enoxaparin, nitroglycerin, β blocker, anti-ischemic therapy, and cardiology consultation (see **Chap. 19**)
- Acute adrenal crisis
  - IV fluids and IV hydrocortisone 100 mg initial bolus
- Retroperitoneal hematoma
  - Pain control, reversal of anticoagulation, and surgery consultation

CASE ANSWERS

1. This patient has acute abdominal pain with signs of peritoneal inflammation on exam. Additional lab data that should be collected include lactic acid, lipase, and venous blood gas. Given the constellation of symptoms and history of Crohn's disease, a CT scan is a reasonable choice of imaging given the concern for an acute bowel obstruction. Other etiologies may be responsible for his symptoms, however, and CT will help delineate the underlying cause.

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2. With acute abdominal pain and hemodynamic instability, administering IV fluids and making the patient NPO are advisable first steps. If the patient continues to vomit, a nasogastric tube should be inserted and set to low-intermittent suction. After the CT scan is performed, surgical consultation may be necessary depending on the results.

FURTHER READING

- Jacobs DO. Abdominal pain, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). McGraw Hill, 2025.

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10 Dyspnea

KEY POINTS

1. Dyspnea is the subjective sensation of breathlessness or uncomfortable breathing. It typically results from cardiac, pulmonary, and neurologic conditions that cause an increased drive to breathe, increased work of breathing, and/or stimulation of specific receptors.
2. The onset of dyspnea (acute vs chronic) and the amount of respiratory distress the patient shows on exam (e.g., presence of hypoxemia, tachypnea, and accessory muscle use) help determine the urgency of further testing and management. Additional symptoms of chest pain, paroxysmal nocturnal dyspnea, orthopnea, or recent trauma can help narrow the differential diagnosis. Examination of the airway, JVP, and lung sounds, as well as the presence of edema, also can help identify an etiology.
3. Asthma, COPD, HF, anemia, deconditioning, and pneumonia are common etiologies of dyspnea.
4. Acute respiratory failure (hypoxemia and/or hypercapnia), inadequate tissue oxygenation (hypoxia), tension pneumothorax, airway obstruction, PE, MI, cardiac tamponade, unstable dysrhythmias, ARDS, and severe pneumonia are potentially life-threatening causes of dyspnea.
5. In patients with acute dyspnea, evaluate vitals and examine for signs of airway obstruction that might require emergent treatment. Quickly evaluate the tracheal position and lung fields to rule out a tension pneumothorax. Patients with hypoxemia need supplemental oxygen until an underlying etiology can be identified and managed. A bedside CXR, POCUS of the heart, and ECG can help quickly rule out life-threatening conditions (e.g., pneumothorax, cardiac tamponade, and MI).

CLINICAL VIGNETTE

A 72-year-old woman with HF and metastatic breast cancer was admitted 2 days ago from the ED to the general medical floor with pleuritic chest pain and diagnosed with acute pericarditis. High-dose aspirin and colchicine were started on admission. The bedside nurse pages you that the patient is having new-onset dyspnea, hypoxemia, tachycardia, and hypotension. As you examine the patient, there is the presence of JVD. The systolic BP drops by 14 mm Hg during inspiration. The heart sounds are muffled on cardiac auscultation. The breath sounds are clear bilaterally, and the trachea is midline. An ECG reveals sinus tachycardia with low voltages, electrical alternans, and PR-segment deviation.

GUIDING QUESTIONS

1. What is the cause of the patient's sudden dyspnea and hemodynamic instability?
2. What would be your initial management strategy for this patient?

INTRODUCTION

Dyspnea, a subjective experience of breathlessness or uncomfortable breathing, is a symptom that typically results from cardiac, pulmonary, and neurologic entities that cause an increased drive to breathe, increased work of breathing, and/or stimulation of specific receptors in the heart, lungs, or vasculature. It is perceived only by the person experiencing it, but signs of increased work of breathing, tachypnea, and accessory muscle use can be measured and observed by clinicians. Dyspnea is common and has been reported in up to one-half of inpatients and one-quarter of ambulatory patients. Its prevalence increases with age. Dyspnea accounts for 3–4 million ED visits each year.

DIFFERENTIAL DIAGNOSIS

In the acute setting, both acute causes of dyspnea and acute exacerbations of chronic conditions leading to dyspnea should be assessed. These can be divided generally into organ systems (Table 10-1).

WHAT NOT TO MISS

- Pulmonary
  - Airway obstruction
  - Acute respiratory failure (hypoxemia and/or hypercapnia) and inadequate tissue oxygenation (hypoxia)

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TABLE 10-1 Differential Diagnosis of Disease Processes Underlying Dyspnea

SYSTEM AND TYPE OF PROCESS	EXAMPLE OF DISEASE PROCESS	POSSIBLE PRESENTING DYSPNEA SYMPTOMS	POSSIBLE EXAM FINDINGS
Pulmonary			
Airways disease	Asthma, COPD, upper airway obstruction	Chest tightness, tachypnea, increased WOB, air hunger, inability to get a deep breath	Wheezing, accessory muscle use, exertional hypoxemia (especially with COPD)
Parenchymal disease	Interstitial lung disease[a]	Air hunger, inability to get a deep breath	Dry end-inspiratory crackles, clubbing, exertional hypoxemia
Infectious	Viral and bacterial pneumonia	Cough, increased WOB, pleuritic chest pain, fever, myalgia	Asymmetric chest expansion, fever, egophony, dullness to percussion
Chest wall disease	Kyphoscoliosis, neuromuscular weakness	Increased WOB, inability to get a deep breath	Decreased diaphragm excursion; atelectasis
Pleural disease	Pleural effusion	Tachypnea, increased WOB, dyspnea on exertion	Asymmetrical chest expansion, dullness to percussion
	Pneumothorax		Hyperresonance, unilateral absence of breath sounds, tracheal deviation
Pulmonary and Cardiac			
Pulmonary vasculature	Pulmonary hypertension	Tachypnea	Elevated right heart pressures, exertional hypoxemia
	PE	Tachypnea, sinus tachycardia, pleuritic chest pain, hemoptysis, syncope, cough	Crackles, S_4, loud P_2, left parasternal heave, JVD
Cardiac			
Left HF	CAD, cardiomyopathy[b]	Chest tightness, air hunger	Elevated left heart pressures; wet crackles on lung exam (left HF); pulsus paradoxus (pericardial disease)
Pericardial disease	Constrictive pericarditis; cardiac tamponade		
Myocardial ischemia	STEMI, NSTE-ACS	Chest pain, diaphoresis	Tachycardia, hypotension, S_3
Other			
Variable	Anemia	Exertional breathlessness	Variable
	Deconditioning	Poor fitness	
	Psychological	Anxiety	
	Metabolic disturbances		
	GI (e.g., GERD, aspiration pneumonitis)		
	Post-COVID syndrome		

[a]Differential diagnosis of interstitial lung disease includes idiopathic pulmonary fibrosis, collagen vascular disease, drug- or occupation-induced pneumonitis, and lymphangitic spread of malignancy; processes that are more alveolar rather than interstitial in nature also can less commonly contribute to parenchymal lung disease underlying chronic dyspnea and include entities such as hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, etc.
[b]Diastolic dysfunction in the setting of a stiff left ventricle is often seen and contributes significantly to insidious dyspnea that can be difficult to treat.
WOB, work of breathing.
Adapted with permission from Baron RM. Dyspnea, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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    - Tension pneumothorax
    - ARDS
    - Lung cancer
- Cardiac
    - PE
    - MI
    - Cardiac tamponade
    - Unstable dysrhythmias
- Infection
    - Severe pneumonia

FOCUSED HISTORY

Patients with dyspnea need to be seen urgently, especially if respiratory distress or hypoxemia are present.

QUESTIONS AT THE BEDSIDE

- What are the patient's vitals?
- Is the patient protecting their airway (e.g., is there airway obstruction of laryngeal edema)?
- When was the onset of dyspnea and what was the reason for admission?
- Does the patient have a history of lung disease, such as asthma or COPD?
- Is the patient receiving oxygen? If so, is this a new requirement?
- What does your dyspnea feel like?
- Do different positions make your dyspnea better or worse?
- Do you have chest tightness or pain?
- Do you wake up from sleep gasping for air? Are you short of breath when lying flat?
- Quickly examine the patient and then review the chart

FOCUSED EXAM

GENERAL

- Does the patient appear distressed or ill?
- Can they speak in full sentences?
- Are they pale or cyanotic?
- Are they protecting their airway (e.g., is there concern for laryngeal edema or airway obstruction)?
- Is the trachea midline or deviated (tension pneumothorax evaluation)?

VITALS

- Repeat now

CARDIOVASCULAR

- Assess for pulsus paradoxus (evaluation for cardiac tamponade)
- Examine the heart rhythm and JVP
- Assess for new murmurs or worsening of chronic murmurs
- S_3 or S_4 present?
- Evaluate skin temperature and color
- Evaluate capillary refill

RESPIRATORY

- Auscultate for
    - Crackles
    - Wheezing
    - Rhonchi
    - Diminished breath sounds
    - Absence of breath sounds
- Do they have a prolonged expiratory phase (suggests a COPD exacerbation)?
- Is hyperresonance (pneumothorax) or dullness to percussion (pleural effusion) present?
- Evidence of lobar consolidation (pneumonia)?
- Are they using accessory muscles or intercostal muscles for breathing?
- Are they sitting in a tripod position?

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ABDOMINAL

- Is there paradoxical movement of the abdomen (flail chest from multiple rib fractures)?

EXTREMITIES

- Assess for evidence of edema
- Evaluate for clubbing
- Assess for signs of Raynaud's disease of the fingers

NEUROLOGIC

- Evaluate the patient's mentation
- Test for asterixis (potential hypercapnia from carbon dioxide retention)

DIAGNOSTIC TESTS

- Consider the following in all patients
  - ABG (especially if hypoxemic)
  - Troponin
  - BNP
  - CBC
  - BMP
  - Lactic acid
  - D-dimer
  - ECG
  - CXR
  - POCUS exam
  - CT pulmonary angiography of the chest
    - If indicated by D-dimer and simplified Wells' criteria
  - Transthoracic echocardiogram
- If the patient is clinically stable, the following algorithm can be useful in the assessment of chronic dyspnea (**Fig. 10-1**)

MANAGEMENT

- *The first goal is to ensure the patient's airway is secure*
  - If it is not, consider an advanced airway
- Always treat the underlying etiology
- Administer supplemental oxygen to keep the Spo_2 > 92%
  - If patient has COPD and chronically retains $Paco_2$, target a Spo_2 between 88% and 92%
- Asthma or COPD
  - Albuterol-ipratropium by nebulizer q2–4h until stable
  - Consider IV methylprednisolone 60 mg IV q6h (or prednisone 40 mg daily), and antibiotics (for COPD) if needed
  - Consider BiPap if not improving
  - See **Chaps. 15** and **16** for further details
- HF
  - If the patient is volume overloaded, raise the head of the bed and administer IV diuretics
  - Consider nitroglycerin or morphine
  - Assess for adequate diuresis after administration of IV diuretics
  - Consider BiPap if not improving
  - See **Chap. 20** for further details
- If evidence of acute MI on ECG (ST elevation of ≥ 1 mm in at least two contiguous leads or new left bundle branch block)
  - Cardiology consultation for consideration of reperfusion therapy (angioplasty or thrombolytics)
  - Antiplatelet (aspirin 324 mg) and anticoagulation (either heparin or enoxaparin) therapy
  - Consider β blockers, nitrates, and morphine
  - See **Chap. 19** for further details
- For suspected cardiac tamponade
  - Examine for Beck's triad (hypotension, JVD, muffled heart sounds) and pulsus paradoxus
  - Perform POCUS or order an echocardiogram
  - If tamponade is confirmed
    - Administer IV fluid boluses
    - Consult cardiology for a pericardiocentesis

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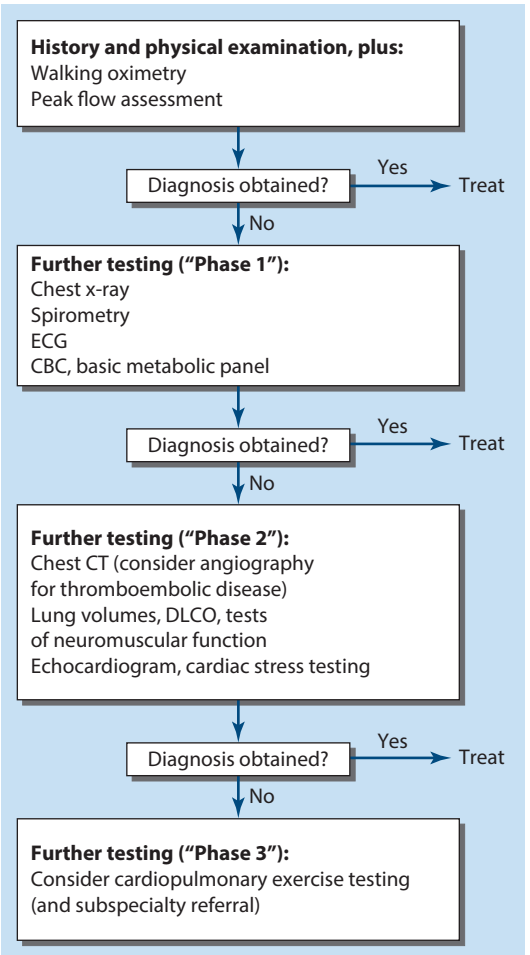

FIGURE 10-1 Possible algorithm for the evaluation of the patient with dyspnea. The approach should begin with a detailed history and physical exam, followed by progressive testing and ultimately more invasive testing and subspecialty referral as is indicated to determine the underlying cause of dyspnea. (Reproduced with permission from Baron RM. Dyspnea, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Pneumothorax
  - Tension pneumothorax requires immediate needle decompression in the second intercostal space in the midclavicular line, followed by chest tube placement
  - Other pneumothoraxes (not tension) involving > 20% of the lung require chest tube placement
  - Administer supplemental oxygen for small pneumothoraxes
- PE
  - If the suspicion is high, start heparin or enoxaparin
  - Obtain CT pulmonary angiography or a ventilation-perfusion (V/Q) scan to confirm the diagnosis
  - If massive PE, weigh options of fibrinolysis, catheter direct therapies, and surgical pulmonary embolectomy with a multidisciplinary team
  - See **Chap. 18** for further details
- Pneumonia
  - Determine if pneumonia is community-acquired (CAP) or hospital-acquired (HAP)
  - Start empirical antibiotics
    - Ceftriaxone and azithromycin for CAP
    - Vancomycin and cefepime for HAP
  - See **Chap. 39** for further details

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- Acute respiratory failure
  - Defined by ABG showing a Pao_2 < 60 mm Hg (hypoxemic respiratory failure) or $Paco_2$ > 50 mm Hg with a pH of < 7.3 (hypercapnic respiratory failure) with respiratory distress
  - Ensure the patient has not received opioids recently; if so, consider naloxone if the respiratory rate is < 6 breaths/min
  - Administer supplemental oxygen, with high-oxygen devices (e.g., high-flow nasal cannula or BiPap) if needed
  - Treat the underlying cause
  - If respiratory failure is associated with a pH < 7.2, intubation is usually required

CASE ANSWERS

1. This patient with a recent diagnosis of acute pericarditis and metastatic breast cancer has findings of cardiac tamponade as demonstrated by the presence of Beck's triad (hypotension, JVD, and muffled heart sounds), pulsus paradoxus (a > 10–mm Hg drop in the systolic BP with inspiration), and electrical alternans.
2. Patients with cardiac tamponade are preload dependent, making IV fluid boluses necessary as a temporizing measure. Pericardiocentesis is the definitive management to improve the patient's hemodynamics. Diagnostic testing of the pericardial fluid with cell count, culture, and cytology should be obtained to help identify the underlying cause of the excessive pericardial fluid.

FURTHER READING

- Baron RM. Dyspnea, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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12 Edema

KEY POINTS

1. Edema is soft tissue swelling due to abnormal expansion of interstitial fluid volume. Plasma transudate accumulates when fluid movement is favored from the vascular to the interstitial space.
2. Determining the duration of the edema and whether it is generalized or localized helps narrow the potential etiologies. The presence of dyspnea (and its associated characteristics), JVD, stigmata of cirrhosis, and whether the edema is pitting or nonpitting also help identify an etiology.
3. Common etiologies of edema include chronic HF, CKD, cirrhosis, DVT, adverse side effects of medication, lymphedema, venous stasis, and cellulitis.
4. Life-threatening causes of edema include myxedema coma, thyroid storm, nephrotic syndrome from rapidly progressive glomerulonephritis, HF exacerbation, decompensated cirrhosis, CKD progressing to dialysis, and eclampsia.
5. Patients with edema and respiratory distress (including pulmonary edema) should be assessed early to decide on a management strategy. A CMP, CBC, TSH, UA, BNP, D-dimer, CXR, and transthoracic echocardiogram are tests that can help identify the cause of the patient's edema depending on the history and exam.

CLINICAL VIGNETTE

A 62-year-old man with hypertension and alcohol use disorder presents to the ED with lower extremity swelling, abdominal distention, and confusion. He has not seen a doctor in 20 years. History is difficult to obtain due to alcohol intoxication. On physical exam, he is afebrile with a normal heart rate and BP. He is oriented to his name and the year but not to the location. Cardiovascular exam shows a normal JVP. Abdominal exam reveals a fluid wave and dilated tortuous veins around the umbilicus (caput medusae). Palmar erythema and scleral icterus are present. There is 2^+ pitting edema of the lower extremities. Asterixis is present.

GUIDING QUESTIONS

1. What diagnostic studies would you order for this patient?
2. What is the likely etiology of this patient's lower extremity edema?

INTRODUCTION

Edema is soft tissue swelling due to abnormal expansion of interstitial fluid volume. The fluid is a plasma transudate that accumulates when movement of fluid from the vascular to the interstitial space is favored. Detectable edema on exam occurs when ≥ 3 L of fluid accumulates, which requires renal retention of salt and water. The distribution of edema can be an important guide to its cause. There are several types of edema, including the following:

- Anasarca (generalized edema)
- Localized edema
- Ascites (fluid in the peritoneal cavity)
- Hydrothorax (fluid accumulation in the pleural cavities)

DIFFERENTIAL DIAGNOSIS

Generalized edema can be categorized as cardiac, hepatic, renal (both CKD and nephrotic syndrome), or related to malnutrition or the adverse side effects of medications (Table 12-1). Other forms of edema (localized, thyroid disease, hypercortisolism, and pregnancy) have unique characteristics.

WHAT NOT TO MISS

- Myxedema coma and thyroid storm
- Nephrotic syndrome resulting from rapidly progressive glomerulonephritis
- HF exacerbation

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TABLE 12-1 Causes of Edema and Their Classic History, Physical Exam, and Lab Findings

HISTORY	PHYSICAL EXAM FINDINGS	LAB FINDINGS
Cardiac		
Dyspnea with exertion is prominent—often associated with orthopnea or paroxysmal nocturnal dyspnea	JVD, S_3, occasionally a displaced or dyskinetic apical impulse; peripheral cyanosis, cool extremities, low pulse pressure when severe	Elevated BUN: SCr; hyponatremia; elevated BNP
Hepatic		
Dyspnea is uncommon except if associated with a significant degree of ascites or hepatic hydrothorax; most often a history of extensive alcohol use	Frequently associated with ascites; JVP is normal or low; BP lower than in renal or cardiac disease; one or more of the following signs of cirrhosis: jaundice, palmar erythema, Dupuytren's contracture, spider angiomata, caput medusae, gynecomastia; asterixis, and other signs of encephalopathy	If severe, reduction in serum albumin, cholesterol, other hepatic proteins (transferrin, fibrinogen); elevated liver enzymes depending on cause and acuity of liver injury; tendency toward hypokalemia, respiratory alkalosis; macrocytosis from folate deficiency; thrombocytopenia; elevated PT/INR
Chronic Kidney Disease		
Usually chronic edema; may be associated with uremic signs and symptoms, including decreased appetite, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating, restless legs, or myoclonus; dyspnea can be present, but generally less prominent than in HF	Elevated BP; hypertensive retinopathy; uremic fetor; pericardial friction rub in advanced uremia	Elevation of SCr and cystatin C; albuminuria; hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, anemia (usually normocytic)
Nephrotic Syndrome		
Childhood diabetes; plasma cell dyscrasias	Periorbital edema; hypertension	Proteinuria (≥ 3.5 g/d); hypoalbuminemia; hypercholesterolemia; microscopic hematuria
Malnutrition		
Low BMI; malignancy or other immunocompromised states	Temporal wasting	Hypoalbuminemia, low prealbumin, hypophosphatemia
Medication-Induced[a]		
Edema that started after initiation of a new medication	Either edema in the lower extremities or generalized edema	Mostly normal or related to adverse effects of the specific medication
Localized Edema (Thrombophlebitis, Venous Thromboembolism, Varicose Veins, Venous Insufficiency, Lymphedema, Cellulitis)		
Edema localized at the site of disease	Red and associated with ulcers (venous insufficiency, venous thromboembolism, cellulitis); prominent superficial veins; grainy appearance (lymphedema)	Elevated D-dimer (venous thromboembolism); elevated inflammatory markers (cellulitis)
Thyroid Disease		
Either signs of hypothyroidism (fatigue, weight gain, cold intolerance) or hyperthyroidism (nervousness, heat intolerance, sweating, palpitations, fatigue and weakness, weight loss, frequent bowel movements)	For hypothyroidism: bradycardia, dry hair and skin, hair loss, periorbital puffiness, prolongation of the relaxation phase of deep tendon reflexes; for hyperthyroidism: pretibial myxedema, warm and moist skin, eyelid retraction, lid lag, tachycardia, AF, hypertension, fine tremor, and hyperreflexia	Abnormal thyroid studies

(*Continued*)

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TABLE 12-1 Causes of Edema and Their Classic History, Physical Exam, and Lab Findings (*Continued*)

HISTORY	PHYSICAL EXAM FINDINGS	LAB FINDINGS
Hypercortisolism		
Psychological disturbances, fatigue, diabetes, and weakness	Central obesity, hypertension, acne, hirsutism, easy bruising, purple striae, fat deposition in the face and nuchal areas	Hypokalemia, metabolic acidosis, and hyperglycemia
Pregnancy		
Edema can occur anytime in pregnancy, but is more common after 5 months	Edema usually occurs in the hands, ankles, and feet	Positive β-hCG; proteinuria if associated with pre-eclampsia

[a]Medications causing edema include NSAIDs; antihypertensive agents (arterial vasodilators, hydralazine, clonidine, methyldopa, guanethidine, minoxidil, calcium channel antagonists); α-adrenergic antagonists, thiazolidinediones, steroids (glucocorticoids, anabolic steroids, estrogens, progestins); cyclosporine; growth hormone; and immunotherapies (interleukin 2, OKT3 monoclonal antibody).
β-hCG, beta-human chorionic gonadotropin; SCr, serum creatinine.
Modified with permission from D Longo et al (eds). *Harrison's Principles of Internal Medicine*, 22nd ed. McGraw Hill; 2024.

- Decompensated cirrhosis
- CKD progressing to an urgent need for dialysis
- Pre-eclampsia and eclampsia

FOCUSED HISTORY

An important first question is whether the edema is localized or generalized (Fig. 12-1). If it is localized, search for the underlying condition. If it is generalized, determine if there is hypoalbuminemia; if so, the history, exam, and other lab data can help you evaluate the patient for cirrhosis, malnutrition, or nephrotic syndrome. If hypoalbuminemia is absent, determine if HF is the cause. *Patients with associated respiratory distress, severe hypertension, or hypotension should be seen urgently.*

QUESTIONS AT THE BEDSIDE

- When did the swelling begin?
- Is it in one spot or all over?
- Any shortness of breath? If so, is it worse with lying flat?
- Any fever?
- Is the area around the swelling painful or red?
- Recent long travel? Recent surgeries?
- Any recent fatigue?
- Cold intolerance? Heat intolerance? Loss or gain of hair?
- Any new medications?
- When was the last menstrual period, and is there a possibility of pregnancy? If pregnant, where are they in their pregnancy course?

FOCUSED EXAM

GENERAL

- Does the patient appear distressed or ill?
- Evaluate for signs of thyroid disease, malnutrition, and hypercortisolism

VITALS

- What is their BP?
- Do they have a fever?
- Are they tachy- or bradycardic?

CARDIOVASCULAR

- Measure JVP
- Is the rhythm regular or irregular?
- Auscultate for extra heart sounds (S_3 or S_4), murmurs, and friction rubs

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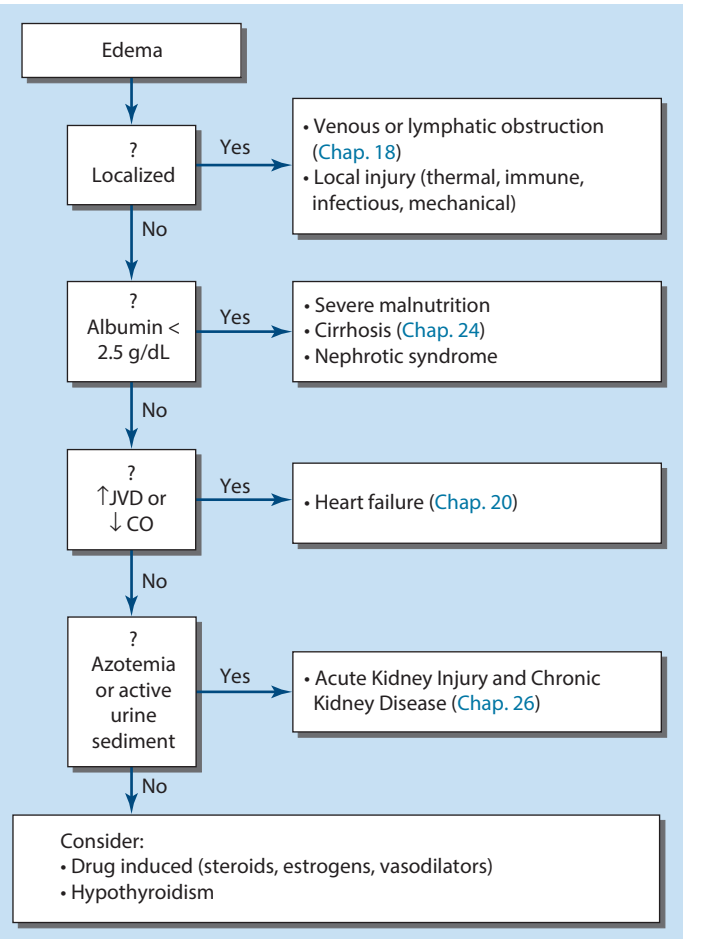

FIGURE 12-1 Diagnostic approach to edema. (Modified with permission from *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). New York, McGraw-Hill Education, 2020.)

RESPIRATORY

- Crackles in the bases?
- Dullness to percussion?

ABDOMINAL

- Examine for caput medusae and an abdominal fluid wave
- Signs of pregnancy?

EXTREMITIES

- Determine whether the edema is localized or generalized
- Is the edema pitting or nonpitting?
- Is there redness, warmth, or tenderness around the edema?
- Are there varicose veins present?
- Any ulcers within the edema?
- Are there spider angiomata or jaundice?

NEUROLOGIC

- Examine for asterixis

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DIAGNOSTIC TESTS

- Consider the following in all patients
  - CBC
  - CMP
  - Albumin
  - BNP
  - UA
- CXR and transthoracic echocardiogram are ordered for patients with signs of HF and/or associated dyspnea
- Other studies depend on your differential from the history and exam (e.g., if the patient recently had a long car ride and has unilateral pain and swelling to the right calf, consider D-dimer testing and lower extremity venous duplex ultrasound for DVT evaluation; see Table 12-1 for other diagnostic studies to consider)

MANAGEMENT

- *Management depends entirely on the underlying etiology*
- HF: Treat the underlying cause of the exacerbation and administer diuretics (see **Chap. 20**)
- Cirrhosis: Treat the cause of decompensation, consider paracentesis if ascites is present, and administer furosemide and spironolactone (see **Chap. 24**)
- CKD: Treat risk factors and comorbidities, administer diuretics, and consider dialysis if indicated
- Nephrotic syndrome: Treatment is complex based on the underlying cause; nephrology consultation is recommended
- DVT: Administer anticoagulation (e.g., apixaban 10 mg bid; see **Chap. 18**)
- Cellulitis: Treat with appropriate antibiotics (see **Chap. 43**)
- Malnutrition: Provide nutritional support (use caution in refeeding syndrome) and treat the underlying cause of malnutrition
- Medication-induced: Stop the offending medication
- Venous insufficiency: Care for local wound(s), control edema with diuretics if indicated, and use compression stockings as tolerated
- Thyroid disease: Treat the underlying hyper- or hypothyroidism, especially if myxedema coma or thyroid storm is present
- Hypercortisolism: Excise adrenal gland

CASE ANSWERS

1. The differential diagnosis for bilateral nonpitting edema in a man includes HF, CKD, nephrotic syndrome, and cirrhosis. In this patient, a CBC, CMP (including serum albumin), BNP, and UA can help identify an underlying etiology.
2. Given the patient's alcohol use disorder and exam findings of scleral icterus, normal JVP, abdominal fluid wave, dilated tortuous veins around the umbilicus (caput medusae), palmar erythema, and asterixis, this patient likely has cirrhosis due to alcohol use. In decompensated cirrhosis, bilateral lower extremity edema is often present. This patient also likely has hepatic encephalopathy given the presence of encephalopathy and asterixis.

FURTHER READING

- Loscalzo J. Edema, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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13 Nausea & Vomiting

KEY POINTS

1. Nausea is the feeling of needing to vomit. Vomiting (emesis) is the oral expulsion of GI contents resulting from gut and thoracoabdominal wall contractions.
2. Both the acuity and associated circumstances of nausea and vomiting are important in establishing an etiology. Acute nausea is more commonly from infections, toxins, and intracranial or intraperitoneal abnormalities. Temporal association with food intake also can be helpful (e.g., in gastroparesis the nausea is within an hour of eating; in bowel obstruction it occurs later). The presence of blood in the emesis (hematemesis) also suggests certain etiologies (e.g., peptic ulcer disease, esophageal varices). The physical exam complements the history and may provide clues to the underlying etiology (e.g., high-pitched bowel sounds are present in bowel obstruction, whereas the absence of bowel sounds indicates an ileus).
3. Life-threatening causes of nausea and vomiting should be ruled out first. These include bowel obstruction; superior mesenteric artery syndrome; sepsis from cholecystitis, appendicitis, ascending cholangitis; severe pancreatitis; MI; increased intracranial pressure from malignancy, hemorrhage, abscess, hydrocephalus; severe uremia; diabetic ketoacidosis; adrenal crisis; liver failure; and severe alcohol withdrawal.
4. Nausea and vomiting associated with headache, hematemesis, melena, chest pain, severe abdominal pain, or hemodynamic instability should be assessed urgently. In all patients with acute nausea and emesis, a CBC, electrolytes, BUN/SCr, liver function tests, lactic acid, lipase, troponin, UA, and abdominal x-ray should be considered. In patients with hypovolemia, IV fluids can be administered. Antiemetics, such as ondansetron, offer symptomatic therapy.

CLINICAL VIGNETTE

A 54-year-old woman with cholelithiasis presents to the ED with nausea, vomiting, and abdominal pain that has progressively worsened over the last 12 h. The nausea has worsened over the past 6 h. The emesis showed no gross blood. She denies diarrhea or blood in the stool. On physical exam, her temperature is 38.4°C (101.2°F), heart rate is 108 beats/min, respiratory rate is 18 breaths/min, BP is 124/82 mm Hg, and Spo_2 is 98% on room air. The patient has subungual and scleral icterus. On abdominal exam, the right upper quadrant is tender to palpation. The psoas sign is negative. Lab data reveal a WBC count of 13,400 cells/μL with a neutrophil percentage of 78%. A CMP shows an elevated bilirubin (4.4 mg/dL). A UA, lactic acid, and β-human chorionic gonadotropin are normal. A right upper quadrant ultrasound reveals bile duct dilation and biliary ductal stones.

GUIDING QUESTIONS

1. What is the most likely diagnosis causing this patient's nausea and vomiting?
2. How would you manage this patient?

INTRODUCTION

Nausea is the feeling of needing to vomit. Vomiting (emesis) is the oral expulsion of GI contents resulting from gut and thoracoabdominal wall contractions. Vomiting is controlled by two brainstem areas: the vomiting center (brainstem nuclei—including the nucleus tractus solitarius) and the chemoreceptor trigger zone. Activation of the chemoreceptor trigger zone results in impulses to the vomiting center, which controls the physical act of vomiting. Regurgitation is the effortless passage of gastric contents into the mouth. Rumination is the repeated regurgitation of food residue. In contrast with emesis, regurgitation and rumination exhibit volitional control. Nausea alone at least weekly is reported by 1.9% of the general population, while nausea plus vomiting is noted by 1.1%.

DIFFERENTIAL DIAGNOSIS

Conditions within and outside the peritoneum, medications, and circulating toxins are general categories that cause nausea and vomiting (Table 13-1).

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TABLE 13-1 Causes of Nausea and Vomiting

INTRAPERITONEAL	EXTRAPERITONEAL	MEDICATIONS/METABOLIC DISORDERS
Obstructing disorders	Cardiopulmonary disease	Drugs
Pyloric obstruction	Cardiomyopathy	Cancer chemotherapy
Small-bowel obstruction	MI	Opioids
Colonic obstruction	Labyrinthine disease	Analgesics
Superior mesenteric artery syndrome	Motion sickness	GLP-1 receptor agonists
Enteric infections	Labyrinthitis	Oral hypoglycemics
Viral	Malignancy	Parkinson's disease/restless legs therapies
Bacterial	Intracerebral disorders	Antidepressants
Inflammatory diseases	Malignancy	Smoking cessation agents
Cholecystitis	Hemorrhage	Antibiotics
Pancreatitis	Abscess	Cardiac antiarrhythmics/ antihypertensives
Appendicitis	Hydrocephalus	Oral contraceptives
Hepatitis	Psychiatric illness	Endocrine/metabolic disease
Altered sensorimotor function	Anorexia and bulimia nervosa	Pregnancy
Gastroparesis	Depression	Uremia
Intestinal pseudo-obstruction	Postoperative vomiting	Ketoacidosis
Gastroesophageal reflux		Thyroid and parathyroid disease
Chronic nausea vomiting syndrome		Adrenal insufficiency
Gastroparesis-like symptoms		Toxins
Cyclic vomiting syndrome		Liver failure
Cannabinoid hyperemesis syndrome		Ethanol
Rumination syndrome		
Mesenteric insufficiency		
Celiac artery stenosis		
Median arcuate ligament syndrome		
Biliary colic		
Abdominal irradiation		

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WHAT NOT TO MISS

- Small or large bowel obstruction
- Superior mesenteric artery syndrome
- Sepsis associated with cholecystitis, appendicitis, or ascending cholangitis
- Severe pancreatitis
- MI
- Intracerebral disorders, including malignancy, hemorrhage, abscess, and hydrocephalus
- Severe uremia
- Diabetic ketoacidosis
- Adrenal crisis
- Liver failure (from any cause, including hepatitis)
- Severe alcohol withdrawal

FOCUSED HISTORY

The history helps identify the etiology. Drugs, toxins, and infections often cause acute symptoms. Gastroparesis and pyloric obstruction elicit vomiting within an hour of eating, while emesis from intestinal obstruction occurs later after eating. Vomiting minutes after eating characterizes rumination. Hematemesis raises suspicion of an ulcer, esophageal varices, malignancy, or Mallory-Weiss tear. *Patients with nausea and vomiting associated with headache, hematemesis, melena, chest pain, severe abdominal pain, or hemodynamic instability need to be seen urgently.*

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QUESTIONS AT THE BEDSIDE

- Is this a new problem or an old one? If old, is it worse than usual?
- Is it associated with eating? If so, how long after eating does it occur?
- What color is the emesis? Is there blood?
- Any blood in the stool? Any diarrhea?
- Do you have any abdominal or chest pain? If so, what does it feel like? Does it radiate anywhere?
- Any fever or chills?
- Spinning of the room?
- Any unintentional weight loss?
- Headache, blurry vision, hiccups, or weakness?
- Any new diet changes?
- Recent excessive alcohol use or cessation of chronic alcohol use?
- Any prior abdominal surgeries?
- History of diabetes, adrenal insufficiency, cancer, or liver disease?
- Any new medications?
- Cannabis or opiate use?

FOCUSED EXAM

The physical exam complements the history. Orthostatic hypotension and reduced skin turgor indicate fluid loss. Pulmonary abnormalities indicate aspiration. Involuntary guarding raises suspicion of inflammation. Bowel sounds are absent with ileus, while high-pitched rushes suggest bowel obstruction. A succussion splash is found with gastroparesis or pyloric obstruction. Neurologic disease presents with papilledema or focal neural abnormalities. Palpable masses or adenopathy suggest a neoplasm.

GENERAL

- Does the patient appear distressed or ill?
- Does the patient have characteristic smells of certain etiologies?
  - Alcohol and ketosis?
  - Cannabinoids?
  - Ammonia-like breath (uremia)?
  - Musty sweet breath (fetor hepaticus of liver disease)?

VITALS

- Repeat now with orthostatic vital sign measurement

HEENT

- Examine for papilledema, mydriasis, miosis, and nystagmus

CARDIAC

- Auscultate for new murmurs or rubs

RESPIRATORY

- Evaluate for crackles or rhonchi for signs of aspiration

ABDOMINAL

- Palpate for tenderness and evaluate for involuntary guarding
- Absent bowel sounds suggest ileus
- High-pitched sounds suggest obstruction
- Succussion splash suggests gastroparesis or pyloric obstruction

SKIN

- Evaluate skin turgor

NEUROLOGIC

- Perform full neurologic evaluation if elevated intracranial pressure is a concern
- Evaluate for asterixis (hepatic encephalopathy and uremia evaluation)

INTERPRETATION OF THE HISTORY & PHYSICAL EXAM LINKED TO SPECIFIC DISORDERS

- Vomiting in patients with encephalopathy, intractable hiccups, or focal neurologic abnormalities (e.g., cranial nerve abnormalities) suggests elevated intracranial pressure
- Headaches may indicate migraine-associated vomiting
- Vestibular neuritis has a rapid onset of vertigo, nausea, vomiting, and nystagmus

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- Abdominal pain with vomiting often indicates an organic pathology (e.g., appendicitis)
- Abdominal distention and tenderness suggest bowel obstruction
- Feculent emesis suggests intestinal obstruction
- Vomiting blood or coffee-ground material indicates an upper GI bleed
- Heartburn with nausea often indicates GERD

DIAGNOSTIC TESTS

- Consider the following in all patients
  - CBC
  - CMP
  - Lactic acid
  - Lipase
  - Troponin
  - UA
  - Kidney, ureter, and bladder (KUB) x-ray
- Obtain blood cultures if patient is septic and infection is a concern
- If diarrhea is present, consider
  - *Clostridioides difficile* stool toxin
  - Ova and parasite stool studies
  - Stool PCR testing
- Further testing for endocrine, rheumatologic, or paraneoplastic etiologies depends on clinical suspicion (such as a TSH for thyroid disease or cosyntropin stimulation test for adrenal insufficiency)
- Consider further imaging when appropriate
  - KUB then a CT scan for small or large bowel obstruction
  - Ultrasound or CT scan for pancreatitis
  - Ultrasound and/or CT scan for appendicitis, cholecystitis, or ascending cholangitis
  - CT scan for evaluation of intra-abdominal malignancy
  - CT or MRI of the brain if concerned for intracranial pathology
- If initial work-up is nonrevealing, consider
  - Endoscopy
  - Endoscopic retrograde cholangiopancreatography
  - Abdominal MRI

MANAGEMENT

- *Always treat the underlying cause of nausea and vomiting*
- Patients with severe dehydration should be hospitalized if oral replenishment is unobtainable
- Start a low-fat liquid diet when able to take food by mouth again
- Glycemic control (e.g., for nausea and vomiting caused by gastroparesis)
- Symptomatic relief with antiemetics (e.g., ondansetron 4 mg IV q4h prn) while also managing the underlying cause (**Table 13-2**)
- Appendicitis and cholecystitis
  - Treat with antibiotics (e.g., ceftriaxone and metronidazole), IV fluids, and surgery consultation
- Ascending cholangitis
  - Treat with antibiotics (e.g., piperacillin-tazobactam), IV fluids, and gastroenterology consultation for endoscopic retrograde cholangiopancreatography
- Small or large bowel obstruction
  - Make NPO
  - Administer IV fluids
  - Place nasogastric tube to low-intermittent suction
  - Surgery consultation
- Pancreatitis
  - Treat with IV fluids, pain control, and oral intake as tolerated (see **Chap. 25**)
- MI
  - High-dose aspirin, heparin or enoxaparin, nitroglycerin, β blocker
  - Consider morphine administration
  - Cardiology consultation (see **Chap. 19**)
- Severe uremia
  - Consideration of dialysis with nephrology consultation

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TABLE 13-2 Treatment of Nausea and Vomiting

MECHANISM	EXAMPLES	CLINICAL INDICATIONS
Antiemetic Agents		
Antihistaminergics	Dimenhydrinate, meclizine	Motion sickness, inner ear disease
Anticholinergics	Scopolamine	Motion sickness, inner ear disease
Antidopaminergics	Prochlorperazine, thiethylperazine, haloperidol	Medication-, toxin-, or metabolic-induced emesis, chemotherapy-induced emesis, cannabinoid hyperemesis syndrome
5-HT_3 antagonists	Ondansetron, granisetron	Chemotherapy- and radiation-induced emesis, postoperative emesis, opioid-induced nausea and vomiting
Cannabinoids	Tetrahydrocannabinol, cannabidiol	Chemotherapy-induced emesis, gastroparesis
Tricyclic antidepressants	Amitriptyline, nortriptyline	Chronic nausea vomiting syndrome, cyclic vomiting syndrome, gastroparesis
Other antidepressant/atypical antipsychotics	Mirtazapine, olanzapine	Functional dyspepsia, chemotherapy-induced emesis, gastroparesis
Neuropathic modulators	Gabapentin	Chemotherapy-induced emesis
Neurokinin (NK_1) receptor antagonists	Aprepitant, fosaprepitant, netupitant, rolapitant	Chemotherapy-induced emesis
Prokinetic Agents		
5-HT_4 agonist and antidopaminergics	Metoclopramide	Gastroparesis
Motilin agonists	Erythromycin	Gastroparesis, intestinal pseudo-obstruction
Peripheral antidopaminergics	Domperidone	Gastroparesis
Pure 5-HT_4 agonists	Prucalopride	Idiopathic gastroparesis
Somatostatin analogues	Octreotide	Intestinal pseudo-obstruction
Acetylcholinesterase inhibitors	Pyridostigmine	Small-intestinal dysmotility/ pseudo-obstruction
Special Settings		
Benzodiazepines	Lorazepam	Anticipatory nausea and vomiting with chemotherapy, cyclic vomiting syndrome
5-HT_{1A} agonists	Buspirone, tandospirone	Functional dyspepsia
Glucocorticoids	Methylprednisolone, dexamethasone	Chemotherapy-induced emesis
Anticonvulsants	Topiramate, zonisamide, levetiracetam	Cyclic vomiting syndrome
Antimigraine agents	Sumatriptan	Cyclic vomiting syndrome
Topical analgesics	Capsaicin cream	Cannabinoid hyperemesis syndrome

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- Diabetic ketoacidosis
  - IV fluids
  - IV insulin infusion
  - Electrolyte repletion
  - Management of the underlying precipitant
- Acute adrenal crisis
  - IV fluid boluses and IV hydrocortisone 100-mg initial bolus
- Liver failure
  - Gastroenterology consultation
  - Treat the underlying etiology of liver failure
  - Liver transplant if indicated
- Alcohol withdrawal
  - Benzodiazepines and/or phenobarbital
  - Thiamine
  - Supportive care (see Chap. 54)

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- Intracerebral disorders
  - Depends on the underlying etiology
  - Neurosurgery or oncology consult

CASE ANSWERS

1. The clinical findings of nausea, vomiting, abdominal pain, fever, tachycardia, jaundice, leukocytosis, and an ultrasound revealing biliary stones causing ductal dilation strongly suggest sepsis secondary to ascending cholangitis. Charcot's triad (fever, abdominal pain, and jaundice) is present in 50–75% of patients with ascending cholangitis.
2. Treatment of sepsis from ascending cholangitis consists of
   a. Fluids (30 mL/kg IV crystalloid fluid in the first 3 h)
   b. IV antibiotics
      i. Either monotherapy with piperacillin-tazobactam *or*
      ii. Dual therapy with metronidazole plus ceftriaxone, cefazolin, cefuroxime, cefotaxime, ciprofloxacin, or levofloxacin
   c. Gastroenterology consultation for endoscopic retrograde cholangiopancreatography to remove source of infection

FURTHER READING

- Hasler WL. Nausea, vomiting, and indigestion, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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14 Diarrhea

KEY POINTS

1. Diarrhea is defined as the passage of abnormally liquid or unformed stools at an increased frequency. Diarrhea can be categorized as acute, persistent, or chronic.
2. For acute diarrhea (the focus of this chapter), five high-risk groups are recognized: (1) travelers, (2) consumers of certain foods, (3) immunodeficient persons, (4) daycare attendees and their family members, and (5) institutionalized persons. The presence of fever, melena, and/or hematochezia may help identify certain etiologies. A recent dietary history and full medication review should be performed. On physical exam, signs of severe dehydration should be assessed.
3. Acute diarrhea is caused by infectious agents in > 90% of cases. The remaining 10% stems from medications, toxin ingestions, ischemia, food indiscretions, and other conditions.
4. Life-threatening causes of acute diarrhea include any infectious agent leading to severe dehydration, toxic megacolon from *Clostridioides difficile* infection, *Shigella* with hemolytic-uremic syndrome, acute mesenteric ischemia, and diarrhea from ingested toxins.
5. A thorough history and physical exam are vital to triage how sick or dehydrated the patient is. In patients with severe dehydration, IV fluids and electrolyte replacement should be administered. Otherwise, patients should be encouraged to ingest fluids with electrolytes by mouth. Specific patient populations should have stool microbiological studies sent (PCR or culture) with management of the underlying infectious etiology. The treatment of *C. difficile* infection depends on the severity of infection and whether the infection is the first or recurrent.

CLINICAL VIGNETTE

A 74-year-old man with multiple myeloma recently treated with chemotherapy presented to the ED 1 day ago and was admitted for chest pain. His ECG and troponins were normal on serial evaluations. When talking with the bedside nurse before seeing the patient prior to discharge, the nurse mentions the patient had four loose, nonbloody stools in the past 6 h. The patient states it has been present for the last 3 days and has progressively worsened. On physical exam, the temperature is 37.4°C (99.3°F), BP is 100/64 mm Hg, and heart rate is 92 beats/min. Orthostatic vital signs reveal a significant rise in the patient's heart rate, a reduction in the systolic BP, and symptoms of dizziness. There is decreased skin turgor. Palpation of the abdomen reveals mild diffuse tenderness. The bowel sounds are normal on auscultation. The patient states he also feels nauseous with mild abdominal pain and is concerned about not being able to drink enough fluids if discharged home.

GUIDING QUESTIONS

1. What blood tests would you order for this patient?
2. Are stool studies indicated in this patient?

INTRODUCTION

Diarrhea is exceedingly common and has a large toll in terms of mortality, morbidity, loss of work productivity, and consumption of medical resources. It is defined loosely as the passage of abnormally liquid or unformed stools at an increased frequency. Diarrhea can be categorized as acute if lasting < 2 weeks, persistent if 2–4 weeks, and chronic if > 4 weeks' duration. Worldwide, > 1 billion individuals suffer one or more episodes of acute diarrhea each year. Nearly half of the 100 million patients with acute diarrhea in the United States must restrict their activities, 10% consult physicians, ~250,000 require hospitalization, and ~5000 die (primarily older adults). This chapter will focus on *acute diarrhea*.

DIFFERENTIAL DIAGNOSIS

- Infectious agents cause > 90% of acute diarrhea cases
- The remaining 10% stem from medications, toxin ingestions, ischemia, food indiscretions, and other conditions
- Table 14-1 describes infectious etiologies in acute diarrhea and their clinical features

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TABLE 14-1 Causes of Acute Infectious Diarrhea

NONINFLAMMATORY DIARRHEA	INFLAMMATORY DIARRHEA
Viral	**Viral**
Noroviruses, astrovirus, adenovirus, rotavirus, sapovirus, SARS-CoV-2	Cytomegalovirus
Protozoal	**Protozoal**
Giardia lamblia	*Entamoeba histolytica*
Cryptosporidium	**Bacterial**
Cyclospora	Cytotoxin production
Bacterial	Shiga toxin–producing *E. coli* (STEC)
Preformed enterotoxin production	*Vibrio parahaemolyticus*
Staphylococcus aureus	*Clostridioides difficile*
Bacillus cereus	Mucosal invasion
Clostridium perfringens	*Shigella*
Enterotoxin production	*Campylobacter jejuni*
Enterotoxigenic *Escherichia coli* (ETEC)	*Salmonella*
Vibrio cholerae, *Vibrio vulnificus*	Enteroinvasive *E. coli* (EIEC)
	Listeria monocytogenes
	Aeromonas
	Yersinia enterocolitica
	Infectious proctitis
	Chlamydia
	Neisseria gonorrhoeae

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- Medications that cause diarrhea
  - Antibiotics
  - Cardiac antiarrhythmics
  - Antihypertensives
  - NSAIDs
  - Certain antidepressants
  - Weight loss agents
  - Chemotherapeutic agents
  - Bronchodilators
  - Antacids
  - Laxatives
- Occlusive or nonocclusive ischemic colitis
- Ingestion of toxins
  - Organophosphate insecticides
  - *Amanita*
  - Arsenic
  - Preformed toxins in ciguatera
  - Scombroid
- Acute allergic reactions from food ingestion, including galactose alpha-1,3-galactose

WHAT NOT TO MISS

- Any infectious diarrhea leading to severe dehydration and end-organ damage
- Toxic megacolon from *Clostridioides difficile* infection
- *Shigella* with hemolytic-uremic syndrome
- Acute mesenteric ischemia
- Diarrhea from ingested toxins

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FOCUSED HISTORY

In the United States, five high-risk groups are recognized in diarrhea: (1) travelers, (2) consumers of certain foods, (3) immunodeficient persons, (4) daycare attendees and their family members, and (5) institutionalized persons. Figure 14-1 shows an approach to the patient with acute diarrhea. *Patients with hemodynamic instability with acute diarrhea need to be seen urgently.*

QUESTIONS AT THE BEDSIDE

- When did the diarrhea begin?
- Has it worsened or improved since it began?
- How many episodes per day are you having?
- Is the stool bloody?
- Do you have a fever?
- Do you have any abdominal pain, nausea, or vomiting?
- Do you feel dizzy with standing or have you lost consciousness?
- Any recent travel?
- Any recent antibiotics or new medications?
- Any recent new foods, or foods consumed left out and nonrefrigerated?
- Do you have an immunocompromising condition (e.g., cancer on chemotherapy, HIV/AIDS, organ or stem cell transplant)?
- Do you have AF (as a potential embolization event causing acute mesenteric ischemia)?

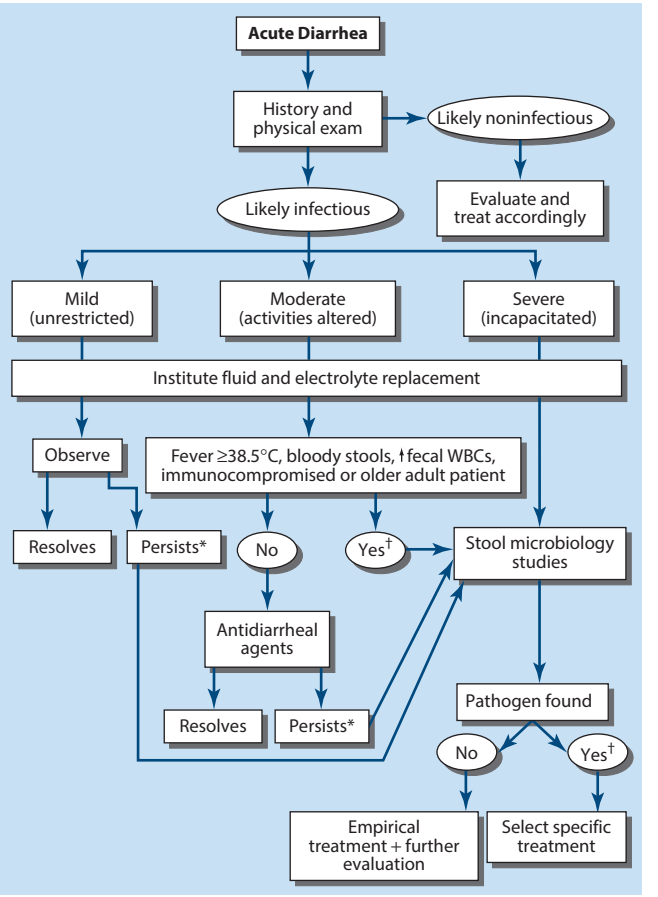

FIGURE 14-1 Algorithm for the management of acute diarrhea. Consider empirical treatment before evaluation with (*) metronidazole and with (†) quinolone. WBCs, white blood cells. (Reproduced with permission from Camilleri M, Murray JA. Diarrhea and constipation. In: D Longo D et al (eds). *Harrison's Principles of Internal Medicine*, 22nd ed. McGraw Hill; 2025.)

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FOCUSED EXAM

GENERAL
- Does the patient appear distressed or ill?

VITALS
- Is fever present?
- Are they hypotensive and tachycardic?

ABDOMINAL EXAM
- Palpate for tenderness and evaluate for involuntary guarding (in case toxic megacolon is present)
- Absent bowel sounds suggest ileus

SKIN EXAM
- Evaluate skin turgor

DIAGNOSTIC TESTS

- Consider the following in all patients
  - CBC
  - CMP
  - Lactate
  - Fecal leukocytes
  - Calprotectin
- Indications for stool microbiological studies (*C. difficile* PCR, stool PCR, ova and parasites) include
  - Profuse diarrhea with dehydration
  - Overtly bloody stools
  - Fever ≥ 38.3°C (101°F)
  - Diarrhea duration > 48 h without improvement
  - Recent antibiotic use
  - New community outbreaks
  - Associated with severe abdominal pain in patients aged > 50 years
  - Older adults (≥ 70 years)
  - Immunocompromised patients
- Because colonization of *C. difficile* in the community is common, many hospitals have a protocol for when it is appropriate to order *C. difficile* testing
  - Follow your local hospital's protocol if suspecting *C. difficile*
- Consider testing for vitamin B_{12} and folate deficiency, eosinophilia and anemia (CBC with diff), and malnutrition (serum albumin)
  - These tests are mostly used in the evaluation of chronic diarrhea and malabsorption
- Consider imaging (such as abdominal X-ray or CT) if there is concern for an associated ileus, mesenteric ischemia, or toxic megacolon

MANAGEMENT

- *Most episodes of acute diarrhea are mild and self-limited and do not justify the cost and potential morbidity rate of diagnostic or pharmacologic interventions*
- Fluid and electrolyte replacement are of central importance to all forms of acute diarrhea
  - Start oral sugar–electrolyte solutions (iso-osmolar sport drinks or designed formulations) promptly in older or vulnerable patients with severe diarrhea to limit dehydration
  - IV hydration is required for profoundly dehydrated patients, especially older adults and infants
- Antimotility and antisecretory agents
  - Can be useful adjuncts to control moderately severe nonfebrile and nonbloody diarrhea
  - Avoid loperamide in febrile dysentery (may prolong illness) and use with caution with drugs that increase levels of cardiac dysrhythmias
  - Bismuth subsalicylate
    - May reduce symptoms
    - Avoid in immunocompromised patients or those with renal impairment (because of the risk of bismuth encephalopathy)
- Antibiotics
  - Azithromycin (500 mg single dose) or ciprofloxacin (500 mg bid for 3–5 days)
    - Used empirically to treat moderately to severely ill patients with febrile diarrheal illness

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    - Metronidazole (250 mg qid for 7 days)
        - Consider empirical treatment if suspecting giardiasis
    - Selection of antibiotics and dosages are dictated by
        - Specific pathogens
        - Geographic resistance patterns
        - Conditions
    - Do not delay treatment in the following persons while awaiting identification of causative organism
        - Immunocompromised patients
        - Older adults
        - Persons with mechanical heart valves or recent vascular grafts
- *C. difficile* infection
    - Ask about previous infections (i.e., how many and how severe)
    - Prescribe fidaxomicin 200 mg bid ×10 days for the first nonsevere occurrence
    - Fulminant *C. difficile* (presence of hypotension or shock, ileus, or megacolon) is managed with a combination of
        - Oral vancomycin
        - IV metronidazole
        - Rectal vancomycin via retention enema (if an ileus is present)
    - See Chap. 40 for further details
- Stop potential offending medications causing diarrhea

CASE ANSWERS

1. In this older immunocompromised patient with acute diarrhea, CBC, CMP, fecal leukocytes, calprotectin, and lactic acid should be ordered to determine if any of the following are present.
    a. Infectious etiology (e.g., presence of leukocytosis)
    b. End-organ damage from hypovolemia (e.g., AKI)
    c. Electrolyte derangements (e.g., hypokalemia)
    d. Evidence of inadequate tissue oxygenation

    The test results will help determine the severity of illness.
2. This patient has two indications to support ordering stool studies: age ≥ 70 years and the presence of an immunocompromising state (malignancy and recent chemotherapy). Therefore, stool studies (stool PCR, *C. difficile* PCR, etc.) are indicated.

FURTHER READING

- Camilleri M, Murray JA. Diarrhea and constipation, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). McGraw Hill, 2025.
- McQuaid KR. Diarrhea, in *Current Medical Diagnosis & Treatment 2026*, Papadakis MA, Rabow MW, McQuaid KR, Nadler PL, Price E (eds). McGraw Hill, 2027.

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15 Chronic Obstructive Pulmonary Disease

KEY POINTS

1. COPD is defined as a disease state characterized by persistent respiratory symptoms and airflow obstruction. COPD includes *emphysema*, an anatomically defined condition characterized by destruction of the lung alveoli with air space enlargement; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and/or *small airway disease*, a condition in which small bronchioles are narrowed and reduced in number.
2. Cough, sputum production, and dyspnea on exertion are the three most common symptoms of COPD. In exacerbations, these symptoms are worsened from the patient's baseline. Exacerbations may present acutely, or there may be a gradual decline over months. The history should attempt to identify an underlying precipitant of the exacerbation. Examination findings that suggest a COPD exacerbation include accessory muscle use, hyperresonance, early inspiratory crackles, and a prolonged expiratory phase. Encephalopathy and asterixis may be signs of hypercapnia and a severe exacerbation.
3. COPD is suspected on clinical history and exam, then confirmed on spirometry. Spirometry is performed on stable outpatients. A CBC with differential (including an eosinophil count), ABG, CXR, and a CT of the chest all may have findings that suggest underlying COPD and potentially a COPD exacerbation. In acute exacerbations, a sputum Gram stain, respiratory viral panel, D-dimer, and, if indicated, CT pulmonary angiography may be useful to help identify a precipitating cause of the exacerbation.
4. In patients hospitalized for exacerbations, supplemental oxygen (target Spo_2 of 88–92%), short-acting bronchodilators, steroids, and antibiotics are the mainstay of treatment. Once the patient improves, long-acting bronchodilators are prescribed. Which inhalers are prescribed to each patient depends on their GOLD group and the eosinophil count. Adjunct therapies, including chronic azithromycin and monoclonal antibody (dupilumab) therapy, are patient-specific. Continuous oxygen therapy (if indicated) and smoking cessation are interventions that improve patient mortality.
5. Acute hypoxemic and hypercapnic respiratory failure are the most common and life-threatening complications of COPD exacerbation. Over time, pulmonary hypertension, cor pulmonale, HF, and AF may develop. Lung cancer is a concern in patients who are long-time smokers. In patients hospitalized for COPD, the mortality rate is 20% in the following year. Hospital mortality rates for mechanically ventilated patients vary between 17% and 49%.

EPIDEMIOLOGY & DEFINITIONS

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, affecting > 15 million people, and an estimated 480 million in the world. The risk of eventual mortality from COPD is closely associated with reduced levels of FEV_1. Economic analysis has shown that > 70% of COPD-related health care expenditures are due to ED visits and hospital care for COPD exacerbations, which translates to > $10 billion annually in the United States. In the outpatient setting, the diagnosis of COPD is usually a clinical suspicion in a person who has smoked for many years and has had dyspnea with a chronic cough; spirometry establishes the diagnosis. In the inpatient setting, a COPD exacerbation occurs with either an increase in cough or sputum production, or increased dyspnea on exertion from their baseline over the course of fewer than 14 days. History of prior exacerbations is important, as well as their baseline level of activity.

COPD is a disease state characterized by persistent respiratory symptoms and airflow obstruction that is not fully reversible.

Chronic bronchitis is a clinical diagnosis: productive cough > 3 months per year for ≥ 2 years.

Small airway disease is a condition in which small bronchioles are narrowed and reduced in number.

Emphysema is a pathologic/anatomic diagnosis: dilation and destruction of lung parenchyma.

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CLINICAL VIGNETTE

A 68-year-old man presents to the ED with 3 days of worsening dyspnea on exertion and productive cough. He reports being able to garden for 20 minutes before feeling dyspneic. Now, the dyspnea onset is within 5 minutes. COPD was diagnosed 6 years ago, and the patient reports adherence to their tiotropium, salmeterol, and fluticasone combination inhaler. He has increased the amount of prn albuterol from 0 to 1 time per day to 2 to 3 times per day. He does not use oxygen at home. The patient's daughter left for a vacation last weekend, and his daycare-attending granddaughter stayed at his house for 4 days with a mild cough and runny nose. He is a current smoker with a 70-pack-year history. In the last 2 years, two hospitalizations for COPD exacerbations have required mechanical ventilation. On physical exam he is afebrile, he is tachycardic at 104 beats/min with an irregularly irregular rhythm, respiratory rate is 18 breaths/min, and Spo_2 is 86% on room air. You note accessory muscle use for breathing and staining on the second and third digits of the patient's right hand without clubbing. On respiratory exam, early inspiratory crackles, wheezing, and a prolonged expiratory phase are present. The JVP is normal, and no edema is noted in the lower extremities. Previous spirometry data show the FEV_1 is 29% of predicted.

GUIDING QUESTIONS

1. What GOLD classification is this patient?
2. What diagnostic tests would you order?
3. Assuming this patient does not have an indication for management in the ICU, how would you manage this patient's acute COPD exacerbation?

HISTORY

COPD exacerbations classically present with a worsening of the patient's baseline cough, sputum production, and exertional dyspnea. Some patients have an acute triggering event causing rapid symptoms, while others' symptoms worsen over several weeks to months before presentation. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious. Dyspnea evaluation should include quantification of the degree and change in dyspnea by asking about breathlessness during activities of daily living and typical activities for the patient. Fever, myalgias, and sore throat also may be present. A careful history to assess the patient's severity of symptoms, as well as to identify the cause of the exacerbation (see Etiology section), is important and may change management. Prior exacerbations and their severity should be explored. Recent PFTs (specifically the FEV_1) should be reviewed to establish the severity of COPD.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - A patient with known lung disease who has increased sputum production, worsening dyspnea, wheezing, and is an active smoker
  - The three most common symptoms of COPD exacerbations are worsening cough, sputum production, and exertional dyspnea from baseline
- Cough? Worsening?
  - Common symptom of COPD exacerbation
- Change in sputum production and quality?
  - May suggest a viral or bacterial etiology, especially if fever is present
- Increased dyspnea on exertion?
  - Avoidance of exertion may be the first sign
  - Ask about breathlessness during activities of daily living and typical activities for the patient
  - COPD patients in exacerbation have difficulty with significant arm work, especially with over-the-shoulder movements
  - Activities that allow them to use accessory muscles, such as using a shopping cart or walking on a treadmill, are more tolerated
- Baseline of activity?
  - A worsening of activity from baseline level is a sign of exacerbation
- Home oxygen use?
  - Have oxygen requirements increased recently?
- History of exacerbations?
  - What happened during previous admissions?
  - History of intubations?

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    - How is this similar or different?
    - The single greatest risk factor for hospitalization with an exacerbation is a history of prior hospitalization for an exacerbation
- Fever or chills?
    - Potential signs of co-existing viral or bacterial pneumonia
- Ill contacts?
    - Potential source of viral illness or bacterial pneumonia causing the exacerbation
- Nausea and vomiting?
    - Can they tolerate oral medications or not?
    - Is there another potential etiology of the patient's symptoms?
- Diarrhea?
    - Could be a sign of *Legionella* infection and volume depletion
- Myalgias?
    - Possible viral or bacterial infection etiology
- Wheezing?
    - Common sign/symptom of exacerbation
- Chest pain? Hemoptysis?
    - Possible PE or myocardial ischemia that needs to be ruled out
- Edema?
    - HF should be considered in the differential

PAST MEDICAL HISTORY

- History of COPD?
    - How severe?
        - Known pulmonary function tests?
    - Exacerbation history (as in History of Present Illness section)?
    - Home oxygen use?
- History of HF?
    - Can mimic a COPD exacerbation
- History of asthma?
    - Risk factor for asthma-COPD overlap syndrome
- History of cystic fibrosis?
    - Changes management and antibiotic coverage
- History of AF and/or multifocal atrial tachycardia?
    - COPD is a risk factor for AF and multifocal atrial tachycardia
- History of lung cancer?
    - Previous radiation therapy?
    - Pneumonitis?
    - Worsening symptoms?
- History of diabetes?
    - Risk factor for *Pseudomonas* pneumonia and need to manage hyperglycemia

SOCIAL HISTORY

- Alcohol, smoking, recreational drugs
    - Continued smoking can precipitate an exacerbation
- Occupation (and exposures)
- Living situation
- Sexual history

FAMILY HISTORY

- History of COPD?
- History of heart disease?
- History of asthma?
- History of α_1-antitrypsin deficiency?

ALLERGIES

- Seasonal allergies?

MEDICATIONS

- What medications they are taking, especially maintenance inhalers, and the adherence to use and technique
- Home oxygen?

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PHYSICAL EXAM

In the early stages of COPD, the physical exam is usually entirely normal. Many physical exam abnormalities become apparent as the disease progresses. When a patient comes to the hospital with an exacerbation, specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete sentences, and the patient's mental status. Altered mental status can be a sign of an impending need for intubation from hypercapnia. The classic "blue bloaters" and "pink puffers" are generally not seen individually, but rather, a combination of the two. The chest exam should establish the presence or absence of focal findings, degree of air movement, presence or absence of wheezing, asymmetry (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and presence or absence of paradoxical motion of the abdominal wall.

Likelihood ratios for individual positive or negative findings on physical exam can be clinically useful in determining whether COPD exists. When a finding can be either positive or negative, then the likelihood ratios are called the *positive likelihood ratio* (PLR) or the *negative likelihood ratio* (NLR), respectively. A finding that has a PLR > 1 indicates that the positive finding is associated with the presence of COPD; a finding that has an NLR of < 1 indicates that the finding is associated with the absence of COPD. The further either ratio is from 1, the more likely COPD is either present or absent. For example, a PLR of 3 = 20% probability patient has condition, a PLR of 4 = 25% probability patient has condition, a PLR of 5 = 30% probability patient has condition, and a PLR of 10 = 45% probability patient has condition.

- Vital signs
  - Assess the patient's vital signs for tachypnea, tachycardia, hypotension, hypoxemia, and fever
- General appearance
  - Ability to speak in complete or not complete sentences
  - Accessory muscle use (PLR 3.3)
  - Cyanosis of lips and nail bed
  - Pursed lips
  - Tripod position
  - Barrel chest
  - Cachexia and bitemporal wasting (a poor prognostic sign)
  - Cigarette odor
- Cardiac
  - Subxiphoid cardiac impulse (PLR 7.4)
  - JVD and an S_3, in the presence of edema, could indicate an HF exacerbation
- Respiratory
  - Hyperresonance (PLR 5.1)
  - Early inspiratory crackles (PLR 14.6)
  - Prolonged expiratory phase (PLR 4.1)
  - Expiratory wheezing
  - Decreased breath sounds (PLR 3.2)
  - Asymmetry in chest exam (suggesting large airway obstruction or pneumothorax mimicking an exacerbation)
  - Hoover's sign (PLR 4.2)
    - Paradoxical inward movement of rib cage with inspiration due to chronic hyperinflation of lungs
- Abdominal
  - Hepatomegaly could indicate right HF from cor pulmonale
- Skin and extremities
  - Evaluate for dermatitis of hands from tripod position and nicotine stains on fingers and nails
  - Lower extremity edema is also visible with pulmonary hypertension from cor pulmonale
  - Digital clubbing raises the possibility of lung cancer (it is not a finding from COPD)
  - Lymph node exam, especially in smokers
- Neurologic
  - Asterixis can be present in the setting of hypercapnia
  - Mental status exam

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Pneumonia
  - Could co-exist with COPD exacerbations
  - Fever, myalgias, productive cough, leukocytosis, lobar consolidation on CXR

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- HF
  - Left HF causes vascular congestion and can mimic COPD exacerbations
  - Usually, the patient has a cardiac history and elevated JVP with lower extremity edema
- Asthma
  - Primarily a younger patient with a known diagnosis of asthma
- Bronchiectasis
  - Chronic cough
  - Foul-smelling sputum
  - Recurrent or chronic pneumonia
  - Hemoptysis
- Cystic fibrosis
  - Younger person with a known diagnosis
- PE (approximately 20% of COPD exacerbations may have an underlying PE)
  - Can be subtle
  - Needs to be risk-stratified and possibly investigated
- Pneumothorax
  - Respiratory distress, unilateral hyperresonance, and absence of breath sounds
  - Tension pneumothorax will have tracheal deviation
- α_1-Antitrypsin deficiency
  - Younger patients who do not smoke and who have COPD symptoms
- Pleural effusion
  - Can be asymptomatic or dyspneic and have dullness on percussion
  - Effusion identified on CXR
- Lung cancer
  - Risk factors of malignancy with dyspnea and CXR/CT findings of a mass

ETIOLOGY OF ACUTE COPD EXACERBATIONS

- Smoking
- Previous exacerbations: the strongest predictor of future exacerbations
- Nonadherence with inhaler therapy
- Infectious pathogens in acute exacerbations
  - Respiratory viruses
    - Data suggest that most COPD exacerbations from infections are viral in origin
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *Chlamydia pneumoniae*
  - *Pseudomonas*
- Air pollution and allergen exposure
- PE
  - Recent studies have shown that the prevalence of PE in patients hospitalized with a COPD exacerbation varies from 5.9% to 29%

DIAGNOSTIC TESTS

LABS

- CBC with differential
  - Leukocytosis may be present with infectious etiologies; additionally, look for polycythemia as secondary polycythemia may occur from COPD
  - Elevated hematocrit suggests chronic hypoxemia
  - An eosinophil count can help determine whether specific therapies are needed to decrease the risk of exacerbation
- BMP
  - Look for any electrolyte abnormalities and hyperglycemia
- BNP
  - Helps rule out HF as a potential etiology
- D-dimer if clinical suspicion for PE
  - Use simplified Wells' criteria to determine whether PE risk is high or low

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- Troponins
  - Rule out MI causing pulmonary congestion as a cause of dyspnea
- ABG
  - Indications to obtain in acute COPD exacerbations
    - Patients with advanced COPD (FEV_1 < 50%)
    - A history of hypercapnia
    - Mental status changes
    - Patients in significant distress
    - Patients with an unclear diagnosis of COPD
  - The classic pattern on ABG reveals an increase in $Paco_2$ and a decrease in $Paco_2$
  - In the acute setting, there is decreased pH, indicating an acute respiratory acidosis
    - In chronic respiratory acidosis, a compensatory metabolic alkalosis (increased HCO_3^-) occurs
    - The change in pH with $Paco_2$ is 0.08 units/10 mm Hg acutely and 0.03 units/10 mm Hg in the chronic state, allowing you to know if the elevated $Paco_2$ is acute, acute on chronic, or chronic
- Sputum culture with Gram stain
  - Order to help determine if a specific antibiotic is required
  - In most infectious causes of COPD exacerbations, an etiology is not found
- Respiratory viral panel
  - Most infectious causes of COPD exacerbations are from viruses
- Serum α_1-antitrypsin level
  - Reasonable to obtain in patients with COPD or asthma who have chronic airflow obstruction
  - If the α_1-antitrypsin level is low, then order a protease inhibitor (PI) type determination for definitive diagnosis

IMAGING

- ECG
  - Helps identify other potential causes of the patient's dyspnea
    - Acute MI
    - PE (sinus tachycardia and/or $S_1Q_3T_3$)
  - Multifocal atrial tachycardia and AF are common in patients with COPD
- CXR
  - Hyperinflation, flattened diaphragm, enlarged retrosternal space
  - Emphysema is suggested by the presence of
    - Bullae
    - Paucity of parenchymal markings
    - Hyperlucency
- CT chest
  - Definitive test to diagnose emphysema and the pattern of emphysema
  - Can also help look for interstitial lung disease and bronchiectasis, which are common complications of COPD
  - In advanced stages, a CT scan can help determine the possibility of surgical lung resection planning
  - In patients with high-risk of malignancy, CT can help identify lung cancer
- CT pulmonary angiography
  - Evaluates for a PE
  - Use the D-dimer and Wells' criteria to aid decision making for the necessity of this study
- Transthoracic echocardiogram
  - Most useful to rule out other conditions that may mimic a COPD exacerbation (e.g., HF)
  - Elevated pulmonary artery pressure may suggest long-standing COPD
- Outpatient spirometry shows a reduction in the FEV_1 and FEV_1/FVC

MANAGEMENT

ACUTE EXACERBATIONS

TRIAGING THE LEVEL OF CARE

- General floor admission indications
  - Any patient the ED calls to admit
    - If the patient is not at baseline after a few inhaler treatments, they need to be admitted
  - Marked increase in the patients' baseline symptoms
  - Respiratory acidosis and hypercapnia
  - Severe underlying COPD

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- Significant comorbidities
- Outpatient treatment failure of COPD exacerbation
- Change in mental status
- Poor home support
- Older age (> 65 years)

- ICU admission indications
  - Rising $Paco_2$ and the need for BiPap or intubation
  - Change in mental status with concern that the patient cannot protect their airway
  - Severe dyspnea
  - Poor response to initial therapy
  - Worsening hypoxemia (Pao_2 < 40 mm Hg)
  - Severe hypercapnia ($Paco_2$ > 60 mm Hg) with severe acidosis (pH < 7.25)
    - A $Paco_2$ > 60 mm Hg is not strict criteria; some patients may chronically have levels > 60 mm Hg
  - Mechanical ventilation
  - Vasopressor requirements

QUICK TREATMENT REFERENCE FOR COPD EXACERBATIONS REQUIRING HOSPITALIZATION

- Supplemental oxygen to keep Spo_2 between 88% and 92%
- Noninvasive positive pressure ventilation (e.g., BiPap) in severe respiratory acidosis
- Albuterol-ipratropium q2–4h
- Steroids (IV methylprednisolone 125 mg followed by prednisone 40 mg for 5 total day course)
- Antibiotics (azithromycin if uncomplicated exacerbation and no risk factors for *Pseudomonas*)
- Manage precipitating etiologies if they require specific therapy (e.g., anticoagulation for a PE)

INPATIENT MANAGEMENT OF COPD EXACERBATIONS

- Supplemental oxygen with continuous pulse oximetry to keep the Spo_2 between 88% and 92%
  - Overcorrecting hypoxemia (e.g., to an Spo_2 of 100%) can decrease the patient's respiratory drive, increasing $Paco_2$ levels further
- Albuterol-ipratropium, an inhaled short-acting muscarinic agonist (SAMA) and short-acting β-agonist (SABA)
  - The main pharmacologic treatment in exacerbations
  - Administer q2–4h via nebulizer depending on severity of the exacerbation
    - Transitioning to a metered-dose inhaler (MDI) with proper oversight is just as effective as nebulizers and makes the transition to outpatient therapy easier
    - MDIs also cost significantly less than nebulizer therapy
  - As the patient improves, switch to long-acting inhalers
    - See Outpatient COPD Treatment section for details
  - Notice that long-acting β-agonists (LABA; e.g., salmeterol) and inhaled corticosteroids (ICS; e.g., fluticasone) are *not* indicated in acute exacerbations
- Antibiotics
  - Administer to hospitalized patients (unless a noninfectious cause is obvious) (Table 15-1)

TABLE 15-1 Choice of Empirical Antibiotics Based on if the Patient Has an Uncomplicated or Complicated Exacerbation and the Risk of *Pseudomonas*

TYPE OF EXACERBATION	ANTIBIOTIC SELECTION (CHOOSE ONE OF THE FOLLOWING AGENTS)
Uncomplicated with no *Pseudomonas* risk factors	• Azithromycin or clarithromycin • Cefuroxime, cefpodoxime, or cefdinir • Doxycycline • Trimethoprim-sulfamethoxazole
Complicated with no *Pseudomonas* risk factors	• Levofloxacin or moxifloxacin • Amoxicillin/clavulanate
Uncomplicated or complicated with *Pseudomonas* risk factors	• Obtain a sputum sample • Levofloxacin • Cefepime • Ceftazidime • Piperacillin-tazobactam

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- To determine appropriate antibiotic choice, ask the following:
  - Is COPD exacerbation uncomplicated or complicated?
  - Does the patient have *Pseudomonas* risk factors?
- Patients have a complicated COPD exacerbation if any of the following are present
  - Age > 65 years
  - FEV_1 < 50% predicted
  - ≥ 2 exacerbations per year
  - Cardiac disease
- Patients have *Pseudomonas* risk factors if any of the following are present
  - Advanced COPD
  - Previous isolation of *Pseudomonas* from sputum
  - Bronchiectasis
  - Frequent administration of antibiotics
  - Frequent hospital admissions
  - Systemic glucocorticoid use
- Treatment duration is typically 5–7 days

- Steroids
  - IV methylprednisolone 125 mg ×1 (usually administered in the ED)
    - Then 60 mg q6h if still severe exacerbation or cannot tolerate oral pills
  - Prednisone 40 mg daily for 5 days if not severe
    - A 5-day course of glucocorticoids is noninferior to a 14-day course for the treatment of acute COPD exacerbations in the prevention of re-exacerbations at 180 days [1]
  - Steroids decrease length of stay, hasten recovery, and reduce the chance of subsequent exacerbation or relapse
  - Most common adverse side effect is hyperglycemia
- IV magnesium 2 g
  - Consider for patients with severe exacerbation not responding promptly to inhaled bronchodilators
  - Has bronchodilator activity from inhibition of calcium influx into airway smooth muscle
- Incentive spirometer
- Noninvasive positive pressure ventilation (NIPPV) in patients with
  - Acute respiratory acidosis ($PaCO_2$ > 60 mm Hg or values significantly higher than their baseline) *and*
  - pH ≤ 7.30 *or*
  - Severe tachypnea
- BiPap is contraindicated if any of the following are present
  - Cardiovascular instability
  - Markedly impaired mental status
  - Inability to cooperate
  - Copious secretions or the inability to clear secretions
  - Craniofacial abnormalities or trauma preventing the fitting of the mask
  - Extreme obesity
  - Significant burns

OUTPATIENT COPD TREATMENT

- Two major goals are to
  - Provide symptomatic relief of symptoms
    - Reduce respiratory symptoms
    - Improve exercise tolerance
    - Improve health status
  - Reduce future risk of progression and exacerbations to reduce mortality
- Treatment is based on COPD GOLD groups A, B, or E (based on spirometry, symptoms, and hospitalizations) and risk of exacerbations
- Smoking cessation **(improves survival)**
  - Counsel about the benefits of smoking cessation
  - Bupropion, nicotine replacement, and varenicline help with cessation
  - Behavioral support for all patients
  - There is some evidence now that the use of e-cigarettes to help aid smoking cessation is better than the above measures when used with behavioral support, but its use remains controversial
  - If a smoker quits, the rate of decline of FEV_1 slows to that of someone of the same age who has never smoked
  - However, quitting does not result in a complete reversal of lung function loss

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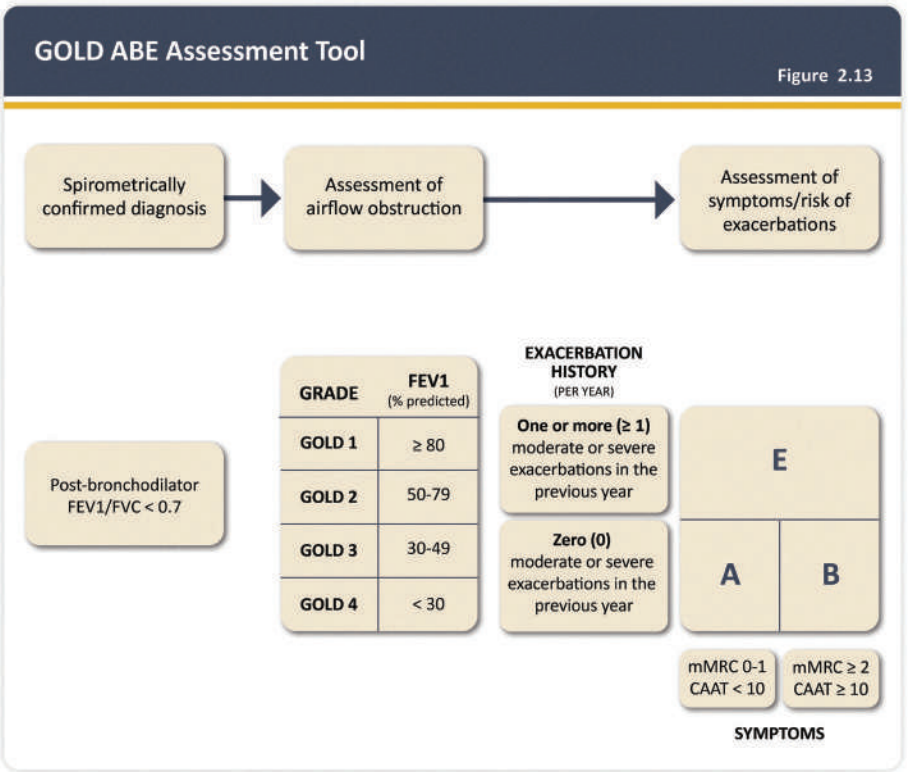

FIGURE 15-1 COPD severity assessment. COPD severity categories are defined using respiratory symptoms (based on the Modified Medical Research Council Dyspnea Scale [mMRC] or COPD Assessment Test [CAT]) and annual frequency of COPD exacerbations. The mMRC provides a single number for degree of breathlessness: 0—only with strenuous activity; 1—hurrying on level ground or walking up a slight hill; 2—walk slower than peers or stop walking at their own pace; 3—walking about 100 yards or after a few minutes on level ground; 4—too breathless to leave the house or when dressing. The CAT is an eight-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea after climbing one flight of stairs, limitation in home activities, confidence in leaving the home, sleep, and energy. Range of total score is 0–40. Both mMRC and CAT are available from Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024. (Reproduced with permission from 2026 GOLD Report-Global initiative for chronic obstructive lung disease; 2026.)

- Bronchodilators
  - In symptomatic patients, prescribe a scheduled long-acting agent (LAMA; e.g., tiotropium) and prn SABA (e.g., albuterol)
  - As disease severity increases (GOLD group), more agents can be added (Figs. 15-1 and 15-2)
    - Long-acting muscarinic antagonists (LAMA; e.g., tiotropium, aclidinium, glycopyrrolate, umeclidinium)
      - Improve symptoms and reduce exacerbations
    - LAMA + long-acting β-agonists (LABA; e.g., salmeterol, indacaterol, arformoterol, formoterol, olodaterol, vilanterol)
      - Reduce exacerbations and hospitalizations
    - LAMA + LABA + ICS (e.g., fluticasone, budesonide)
      - Reduce exacerbations and hospitalizations
  - Trial evidence of bronchodilator treatments (Table 15-2)
- Azithromycin prophylaxis
  - Azithromycin taken for 1 year, when added to usual treatment, decreased the frequency of exacerbations and improved quality of life but caused hearing decrements in a small percentage of patients [8]
  - Avoid in the setting of a prolonged QT_c interval

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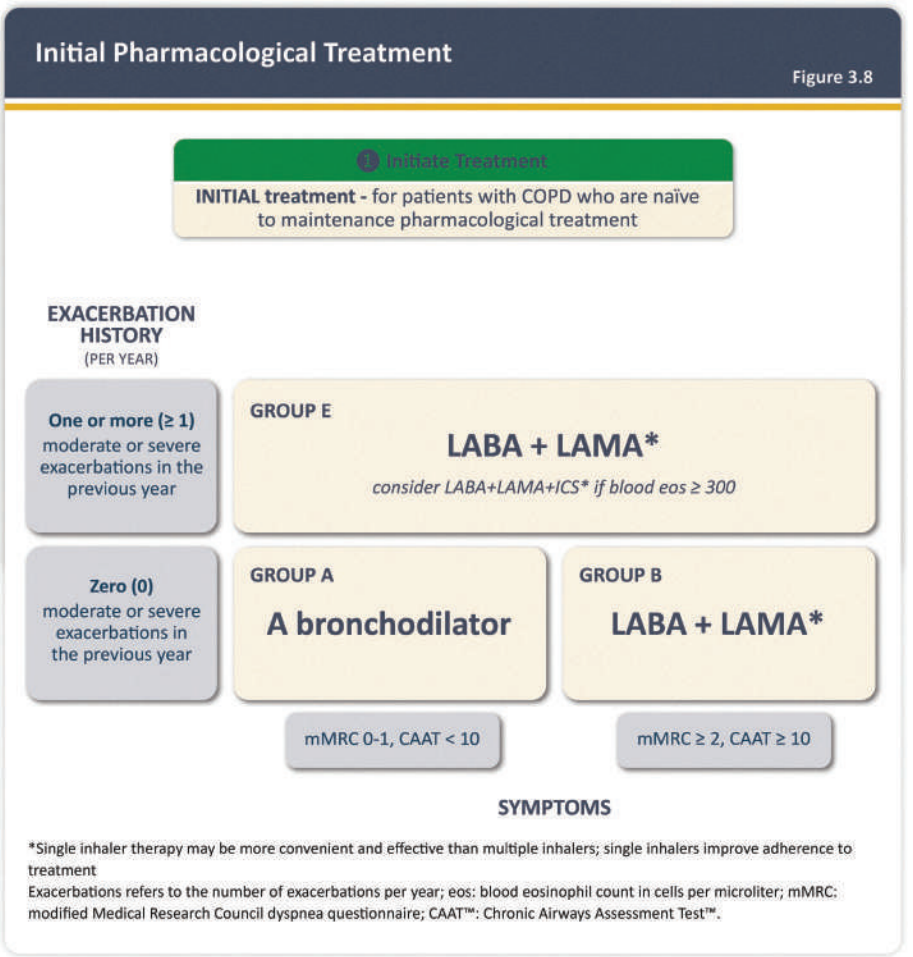

FIGURE 15-2 Medication therapy for stable COPD. Initial pharmacologic therapy (***A***) is based on both COPD exacerbations and respiratory symptoms (assessed through the Modified Medical Research Council Dyspnea Scale [mMRC] or the COPD Assessment Test [CAT]). Follow-up pharmacologic therapy (***B***) is based on response to treatment initiation and reassessment of symptoms and exacerbations. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2024. *For ***B***: Single-inhaler therapy may be more convenient and effective than multiple inhalers. **Consider deescalation of ICS if pneumonia or other side effects occur. Eos, blood eosinophil count in cells per microliter; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist. (Reproduced with permission from 2026 GOLD Report-Global initiative for chronic obstructive lung disease; 2026.)

- Continuous supplemental oxygen **(improves survival)**
  - Indications
    - Resting $Spo_2 \leq 88\%$
    - Resting $Spo_2 \leq 89\%$ with pulmonary hypertension, right HF, or erythrocytosis
  - In patients with COPD and hypoxemia, continuous oxygen therapy significantly reduces mortality when compared with nocturnal oxygen therapy [9]
  - There is a greater mortality benefit with greater hours of daily oxygen use
- Consider the phosphodiesterase inhibitors roflumilast or ensifentrine in patients with continued dyspnea while receiving LABA + LAMA therapy
  - A pulmonologist should help with this decision

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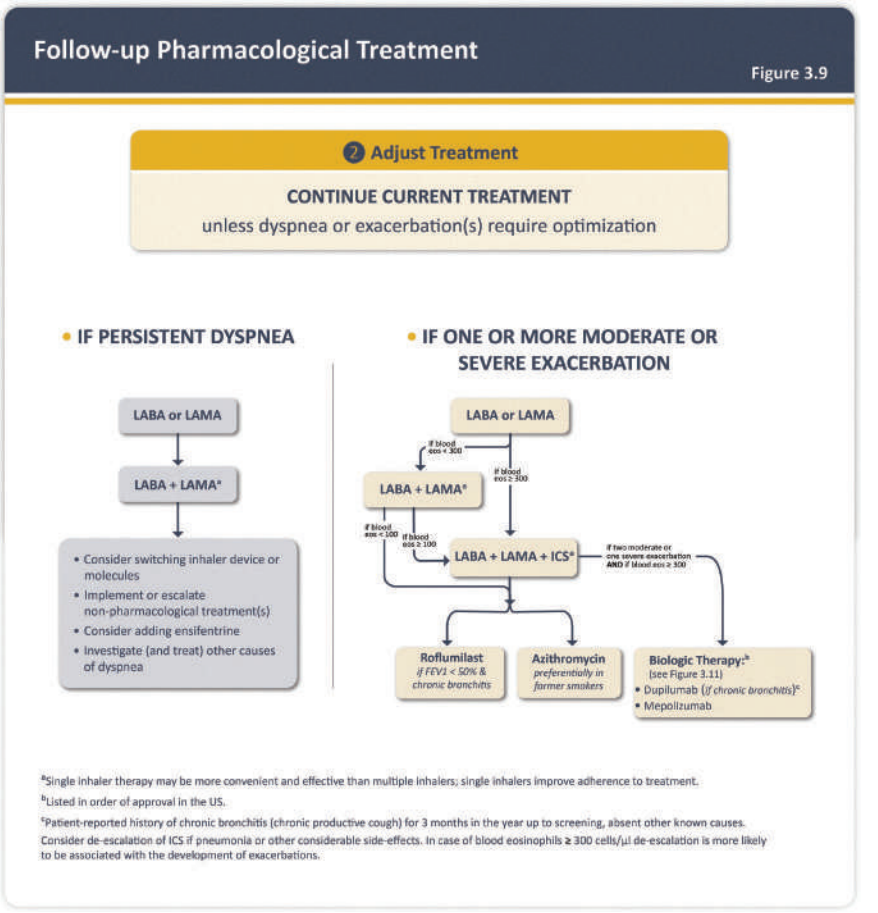

FIGURE 15-2 (*Continued*)

- Monoclonal antibody therapy
  - Consider dupilumab, a monoclonal antibody of interleukin (IL)-3 and -4, in patients with a blood eosinophil count > 300 cells/µL
  - Dupilumab and mepolizumab reduce the exacerbation rates of symptomatic patients when added to triple therapy [10]
- Pulmonary rehab
  - Improves health-related quality of life, dyspnea, exercise capacity
  - Reduces rates of hospitalization over a 6- to 12-month period
- Lung volume reduction surgery (improves survival in select patients)
  - Lung volume reduction surgery in patients with severe bilateral emphysema does not improve survival but is associated with improved exercise tolerance when compared with medical therapy alone
  - A survival benefit may be present for low- and moderate-risk patients with upper lobe emphysema and low exercise capacity
- Lung transplantation
  - COPD is currently the second leading indication for a lung transplant
  - Candidates must have very severe airflow limitation, have severe disability despite maximal medical therapy, and be free of significant comorbid conditions
- Endobronchial valves
  - Some evidence suggests that bronchoscopically placed valves in regions with severe emphysema can make air exit the area but not re-enter
  - Requires specialized training and equipment and has a high risk of pneumothorax

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TABLE 15-2 Trial Evidence of Bronchodilator Treatments

TRIALS	DRUG (CLASS)	EVIDENCE
UPLIFT [2] INVIGORATE [3] POET-COPD [4]	Tiotropium (LAMA)	• Tiotropium did not significantly slow the decline of FEV_1, but it did reduce the incidence of COPD exacerbations among individuals with moderate to severe COPD and showed a trend toward improved survival • Tiotropium had fewer exacerbations per year than indacaterol (LABA) or salmeterol (LABA)
FLAME (COPD) [5] EMAX trial [6]	Indacaterol (LABA) + Glycopyrronium (LAMA)	• Among patients with COPD and mMRC dyspnea grade ≥ 2 symptoms, indacaterol + glycopyrronium is associated with a reduction in the annual rate of COPD exacerbations when compared with salmeterol + fluticasone (LABA + ICS) • Combined LABA-LAMA therapy was associated with improved lung function, and 55% had sustained improvement in symptom scores compared with a LABA alone or a LAMA alone • Combination LABA + LAMA improves lung function and reduces exacerbations more so than either agent alone
IMPACT [7]	Vilanterol (LABA) + Umeclidinium (LAMA) + Fluticasone or Budesonide (ICS)	• Triple therapy with vilanterol, umeclidinium, and fluticasone resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone-vilanterol or umeclidinium-vilanterol; triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium-vilanterol • Guidelines recommend adding an ICS to LAMA + LABA combination therapy in patients with GOLD group E and blood eosinophil count ≥ 100 cells/μL

GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council.

- *Do not prescribe long-term oral corticosteroids*
  - They have an unfavorable benefit/risk ratio because of their side effects
- Treatment of α_1-antitrypsin deficiency, if present
- Pneumococcal, influenza, COVID-19, and respiratory syncytial virus (RSV) vaccines
- Regular physical activity
- Annual low-dose chest CTs for malignancy screening in selected current and former smokers
- *In summary, only three interventions reduce mortality*
  - Smoking cessation
  - Continuous oxygen therapy for chronically hypoxemic patients
  - Lung volume reduction surgery in selected patients with emphysema

COMPLICATIONS

- Pulmonary
  - Bronchiectasis
  - Interstitial lung disease
  - Pulmonary hypertension
  - Respiratory failure
- Cardiac
  - AF
  - CAD
  - Cor pulmonale
  - HF
  - Multifocal atrial tachycardia
- Hematologic/oncologic
  - Anemia
  - Secondary polycythemia
  - Lung cancer
- General
  - Cachexia and weakness
  - Depression

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- Disability
- Infections

PROGNOSIS

- Following a hospitalization for COPD, about 20% of patients are rehospitalized within 30 days, and 45% are rehospitalized within 1 year
  - Mortality is ~20% in the year following hospital discharge
- ICU admission doubles the mortality rate for patients aged > 65 to ~60% in the following year, regardless if intubation is necessary
- Hospital mortality rates for mechanically ventilated patients vary between 17% and 49%
- BODE index
  - BMI ≤ 21 (+1)
  - Obstruction (FEV_1): 50–64% (+1), 36–49% (+2), < 35% (+3)
  - Dyspnea: walking (+1), after 100 yards (+2), with activities of daily living (+3)
  - Exercise capacity (6-min walk): 250–349 m (+1), 150–249 m (+2), < 149 m (+3)
  - The 4-year survival rate is 18% with 7–10 points
- Global Initial of COPD (GOLD) groups A, B, and E
  - Determined based on either Modified Medical Research Council (mMRC) grade or COPD Assessment Test (CAT) score, and how many exacerbations/hospitalizations they had in the last year
  - The mMRC and CAT are used on stable outpatients
  - See how to determine the patient's GOLD group in Fig. 15-1

PATHOPHYSIOLOGY

- Lung structural changes in emphysema
  - Destruction and fibrosis of lung parenchyma (Fig. 15-3) → ↓ diffusion capacity, ↓ gas exchange
  - Formation of large emphysematous air spaces
  - CD8+ T cells prominent in smokers
- Types of emphysema
  - *Centrilobular*: smoking-related, primarily affects upper lobes/superior lower lobes
  - *Panlobular*: α_1-antitrypsin deficiency, diffuse but predominates in lower lobes
  - *Paraseptal*: along pleura, sparing central lung regions
- Four stages of the pathogenesis of emphysema (Fig. 15-4)
  - Chronic inhaled irritants (e.g., smoke) → inflammatory/immune recruitment
  - Inflammatory cells release proteinases → extracellular matrix (ECM) and alveolar damage
  - Oxidative injury, cellular senescence, and proteolytic loss of structure → airway/alveolar destruction
  - Abnormal ECM repair (elastin degradation) → airspace enlargement

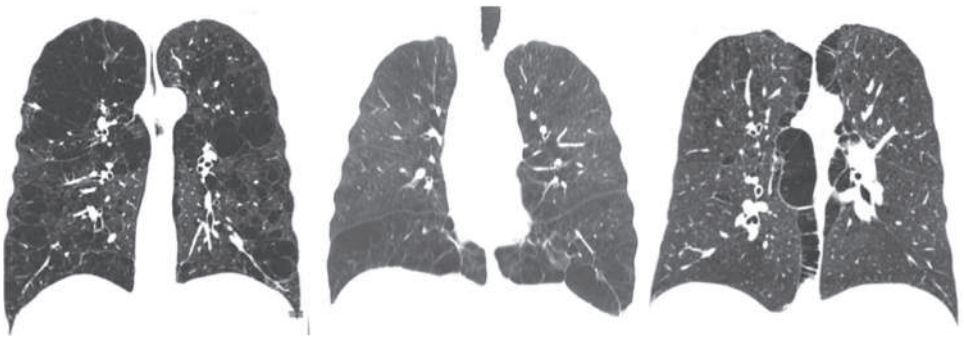

FIGURE 15-3 CT patterns of emphysema. *A.* Centrilobular emphysema with severe upper lobe involvement in a 68-year-old man with a 70-pack-year smoking history but forced expiratory volume in 1 s (FEV_1) 81% predicted (Global Initiative for Chronic Obstructive Lung Disease [GOLD] spirometry grade 1). ***B.*** Panlobular emphysema with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α_1-antitrypsin (α_1AT) deficiency. ***C.*** Paraseptal emphysema with marked airway inflammation in a 52-year-old woman with a 37-pack-year smoking history and FEV_1 40% predicted. (Used with permission from Hersh CP et al. Chronic obstructive pulmonary disease, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). McGraw Hill, 2025.)

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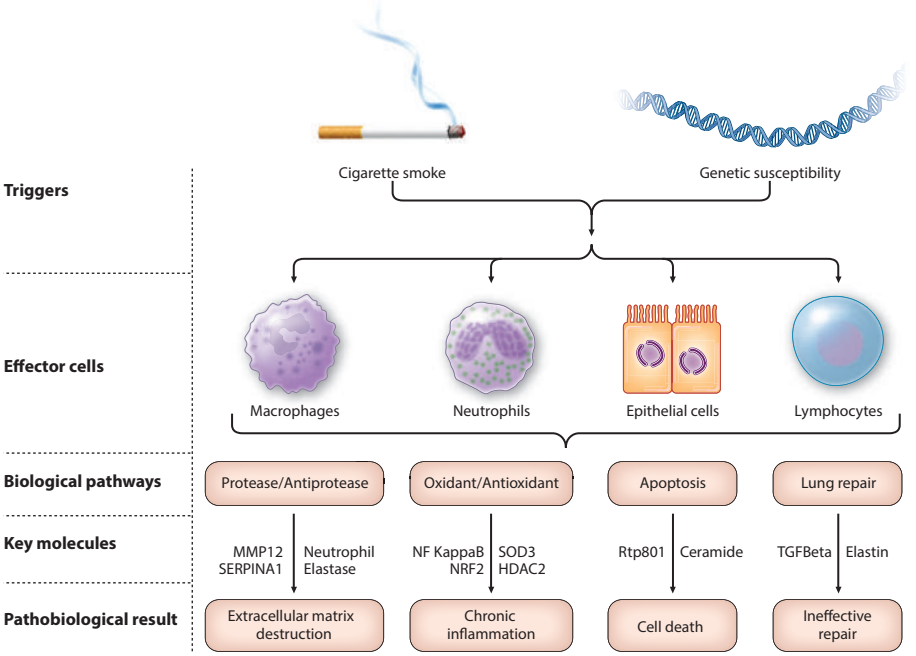

FIGURE 15-4 Pathogenesis of emphysema. Upon long-term exposure to cigarette smoke in genetically susceptible individuals, lung epithelial cells and T and B lymphocytes recruit inflammatory cells to the lung. Biologic pathways of protease-antiprotease imbalance, oxidant/antioxidant imbalance, apoptosis, and lung repair lead to extracellular matrix destruction, cell death, chronic inflammation, and ineffective repair. Although most of these biologic pathways influence multiple pathobiologic results, only a single relationship between pathways and results is shown. A subset of key molecules related to these biologic pathways is listed. (Reproduced with permission from D Longo et al (eds). *Harrison's Principles of Internal Medicine*, 22nd ed. McGraw Hill; 2025.)

- Inflammation and proteolysis
  - Elastase–antielastase imbalance → elastin degradation and airspace dilation
  - Activated macrophages/epithelial cells release proteinases, interleukin 8, tumor necrosis factor α, and matrix metalloproteinases (MMPs)
  - CD8+ T cells release chemokines (IP-10, CXCL-7) → macrophage MMP12 production
  - Oxidative stress pathways are implicated via the transcription factors NRF2 and SOD3
  - Autoimmune activity is possible (IgG vs elastin; T_H1/T_H17-driven chronic inflammation)
  - Smoking → ciliary loss, impaired macrophage clearance → bacterial infection and neutrophilia
- Airflow limitation and air trapping
  - ↓ FEV_1 and FVC → ↓ FEV1/FVC ratio (nonreversible)
  - ↑ residual volume (RV) and total lung capacity (TLC) → hyperinflation
  - Flattened diaphragm → inefficient inspiration, reduced muscle tension for tidal breathing
- Gas exchange impairment
  - Normal Pao_2 until FEV_1 < 50% → hypercapnia (↑ $Paco_2$) when FEV_1 < 25%
  - Severe hypoxemia (Pao_2 < 55 mm Hg) → pulmonary hypertension and cor pulmonale
  - Hypoxemia due to ventilation-perfusion mismatch (not shunt); modest oxygen therapy is effective
- Airway remodeling
  - Goblet cell metaplasia replaces surfactant-producing club cells → ↓ surfactant, ↑ surface tension
  - Small airway fibrosis and collapse → main site of airway resistance
  - Smooth muscle hypertrophy and squamous metaplasia → bronchial hyperreactivity and cancer risk

RISK FACTORS

- Smoking (specifically cigarettes, less evidence for cigars and pipes, e-cigarette use as a risk factor is currently unknown)
  - Number of pack years is the best predictor of the decline in FEV_1

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- Low FEV_1 as a predictor of COPD exacerbations
  - The frequency of exacerbations increases as airflow obstruction worsens
  - Patients with severe (FEV_1 < 50%) or very severe (FEV_1 < 25%) on average have 1 to 3 exacerbations per year
- Genetic predisposition
  - Only 15% of the variability of FEV_1 decline is explained by smoking, and some smokers never get COPD
- Airway hyperresponsiveness
  - More clearly linked to asthma, but it has some overlap with COPD, and is particularly true for persons who had asthma in childhood who become chronic smokers
- α_1-Antitrypsin deficiency
- Occupational exposures
  - Vapors, gas, dust, or fumes (VGDF), coal and gold mining, cotton textile dust
- Indoor and outdoor air pollution
- Impaired lung growth/development
- Recurrent infections
- Passive and second-hand smoke exposure

ADMITTING ORDERS

- Admit to floor or ICU
- Diagnosis: COPD exacerbation
- Condition: stable, guarded, or critical
- Vital signs: routine or ICU routine
- Diet: tailored to the patients' comorbidities
- Nursing: oxygen to maintain Spo_2 of 88–92%, incentive spirometer administration and education
- Fluids: only if indicated
- Diagnostic tests
  - CBC with differential
  - BMP
  - Sputum, blood, and urine cultures (if indicated)
  - BNP
  - Troponin
  - ABG
  - ECG
  - CXR
  - D-dimer
  - CT pulmonary angiography if indicated
- Medications:
  - IV methylprednisolone 125 mg IV ×1 then prednisone 40 mg daily for 5 days
  - Albuterol-ipratropium q2–4h
  - Antibiotics
    - Azithromycin or clarithromycin
    - Levofloxacin, piperacillin-tazobactam, or cefepime if suspect *Pseudomonas* based on risk factors
  - Nicotine patch 21 mg daily if they smoke a pack per day

DISCHARGE INFORMATION

- Assess for home oxygen needs (see Management section)
- Education of outpatient medications (proper administration of metered dose inhaler)
- Smoking cessation education and medications if indicated
- Avoidance of exacerbation triggers
- Follow up with their primary care physician and pulmonologist
  - Pulmonary consult if age < 40, ≥ 2 episodes/year, rapidly worsening disease, severe disease (FEV_1 < 50%), and/or need for home oxygen

CASE ANSWERS

1. The GOLD classification is based on FEV_1 value, symptom severity, and recent history of exacerbations and hospital admissions. This patient has a severe reduction in their FEV_1 and has had two hospital admissions for exacerbations requiring mechanical ventilation. Therefore, this categorizes the patient as GOLD group E (see Figs. 15-1 and 15-2).

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2. For patients in whom a COPD exacerbation is a concern, it is important to rule out other possible diagnoses, identify potential precipitants, and establish illness severity. A CBC with differential (including eosinophil count), BMP, BNP, D-dimer, troponin, ABG, sputum culture with Gram stain, ECG, and a CXR are initial diagnostic tests.
3. Management for a hospitalized patient with a COPD exacerbation includes adequate oxygen supplementation (target a goal Spo_2 of 88–92%), short-acting bronchodilators (albuterol-ipratropium), steroids (prednisone 40 mg for 5 days), and antibiotics (e.g., azithromycin). If a treatable precipitant is identified (e.g., a PE), additional management is required. As the patient improves, transition the short-acting bronchodilators to appropriate long-acting agents.

LANDMARK TRIALS

[1] Leuppi JD et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: The REDUCE randomized clinical trial. JAMA 309:2223, 2013. [PMID: 23695200]
- *Summary:* The REDUCE trial found that a 5-day course of glucocorticoids is noninferior to a 14-day course for treatment of acute COPD exacerbations in prevention of re-exacerbations at 180 days.

[2] Tashkin DP et al. A 4 year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 359:1543, 2008. [PMID: 18836213]
- *Summary:* The UPLIFT trial showed that tiotropium did not significantly slow the decline of FEV_1, but it did reduce the incidence of COPD exacerbations among individuals with moderate to severe COPD, and it showed a trend toward improved survival.

[3] Decramer ML et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): A randomised, blinded, parallel-group study. Lancet Respir Med 1:524, 2013. [PMID: 24461613]
- *Summary:* The INVIGORATE trial showed that tiotropium (LAMA) had fewer exacerbations per year compared with those randomized to indacaterol (LABA).

[4] Vogelmeier C et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 364:1093, 2011. [PMID: 21428765]
- *Summary:* The POET-COPD trial showed that patients randomized to the LAMA tiotropium had fewer exacerbations per year compared with the LABA salmeterol.

[5] Wedzicha JA et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med 374:2222, 2016. [PMID: 27181606]
- *Summary:* The FLAME trial showed that among patients with COPD and mMRC dyspnea grade ≥ 2 symptoms, indacaterol + glycopyrronium (LABA + LAMA) is associated with a reduction in the annual rate of COPD exacerbations when compared with salmeterol + fluticasone (LABA + ICS).

[6] Maltais F et al. Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: The EMAX randomised trial. Respir Res 20:238, 2019. [PMID: 31666084]
- *Summary:* Results from the EMAX trial showed that combined LABA-LAMA therapy was associated with improved lung function, and 55% had sustained improvement in symptom scores versus a LABA alone or a LAMA alone.

[7] Lipson DA et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med 378:1671, 2018. [PMID: 29668352]
- *Summary:* The IMPACT trial showed that triple therapy with vilanterol, umeclidinium, and fluticasone resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone-vilanterol or umeclidinium-vilanterol. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium-vilanterol.

[8] Albert RK et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 365:689, 2011. [PMID: 21864166]
- *Summary:* Among selected subjects with COPD, azithromycin taken daily for 1 year, when added to usual treatment, decreased the frequency of exacerbations and improved quality of life but caused hearing decrements in a small percentage of subjects. Although this intervention could change microbial resistance patterns, the effect of this change is not known.

[9] Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 93:391, 1980. [PMID: 6776858]
- *Summary:* The NOTT trial showed that in patients with COPD and hypoxemia, continuous oxygen therapy significantly reduces mortality when compared to nocturnal oxygen therapy.

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[10] Bhatt SP et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. N Engl J Med 390:2274, 2024. [PMID: 38767614]
    - *Summary:* The NOTUS trial showed that among patients with elevated blood eosinophils of at least 300 cells/μL, dupilumab, a monoclonal antibody targeting IL-4 and IL-3, reduced the exacerbation rates of symptomatic patients when added to triple therapy.

FURTHER READING

- Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. N Engl J Med 381:1257, 2019. [PMID: 31553837]
- Hersh CP et al. Chronic obstructive pulmonary disease, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- McGee S. COPD, in *Evidence-Based Physical Diagnosis*, 6th ed. Amsterdam, Elsevier, 2026.
- Stoller JK, Hatipoğlu U. COPD exacerbations: Management. UpToDate. https://www.uptodate.com/contents/copd-exacerbations-management. Accessed December 20, 2025.

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16 Asthma

KEY POINTS

1. Asthma is a disease defined by episodic airway obstruction and airway hyperresponsiveness, usually accompanied by airway inflammation.
2. Asthma is a clinical diagnosis suggested by dyspnea, cough, wheezing, and mucus production in relation to common bronchoconstrictor precipitants. Physical exam is often normal in mild compensated disease but can reveal wheezing, a prolonged expiratory phase, and hyperinflated lungs when in exacerbation. Pale nasal mucous membranes are found in asthma related to allergic rhinitis. Nasal polyps can be found in aspirin-induced asthma.
3. A thorough history, including symptoms related to precipitating airway narrowing triggers (e.g., allergens, irritants, exercise, dry cold air, air pollution, occupational exposures), and a thorough physical exam support a clinical diagnosis of asthma. The diagnosis is confirmed with PFTs.
4. In patients with asthma exacerbation, repeated nebulized albuterol therapy is the mainstay of treatment. IV methylprednisolone 40–60 mg and IV magnesium sulfate 2 g are administered in severe exacerbations. Step-up therapy guides which inhalers to use for long-term management and prevention of asthma. Adjunctive medications (such as leukotriene modifiers, cromolyn sodium, oral corticosteroids, anti-IgE, interleukin 4/5/13 agents, and azithromycin) can be prescribed to specific patients. Patients with exercise-induced asthma should use on-demand budesonide-formoterol prior to exercise.
5. Complications of asthma include permanent narrowing of the bronchial tubes, symptoms interfering with daily activities, repeated ED visits and hospitalizations, and death. Asthma mortality has decreased with the increased use of inhaled corticosteroids. However, patients with repeated admissions to the hospital, ICU admissions, intubations, depression, and severe psychosocial problems have an increased mortality risk from asthma.

EPIDEMIOLOGY & DEFINITIONS

Asthma is a disease defined by episodic airway obstruction and airway hyperresponsiveness, usually accompanied by airway inflammation. Most of the time, the obstruction is reversible. In a large proportion of patients, the airway inflammation is eosinophilic, but some patients may present with different types of airway inflammation.

Asthma is the most common chronic disease associated with significant morbidity and mortality, with ~262 million people affected globally. In the United States, 7.9% of the population has asthma, and prevalence continues to increase, associated with a transition from rural to urban living. Asthma is more prevalent among children (8.4%) than adults (7.7%), favoring boys, with a trend toward greater prevalence in women in adulthood.

Prior to the effects of the COVID-19 pandemic, 1.8 million people visited an ED in the United States for asthma, and 189,000 were hospitalized. In 2013, the United States estimated the total economic cost at $82 billion. Prevalence is higher in persons who are exposed to such triggers as molds, pests, and air pollution as well as those who may not have access to healthcare.

CLINICAL VIGNETTE

A 32-year-old woman with a history of asthma receiving step 2 inhaler therapy with maintenance budesonide and rescue albuterol presents to the ED with increased cough, wheezing, and dyspnea over the past 2 days with increased use of her rescue inhaler. In the last 2 weeks, she joined an adult soccer league, and the temperature at the night games has been in the mid-forties. She recently started taking aspirin to help with muscle soreness from exercise. She has never been hospitalized for an asthma exacerbation, but she went to the ED twice in the last 2 years after exposure to her neighbor's cat. On examination, she is afebrile, her respiratory rate is 30 breaths/min, her heart rate is 100 beats/min, and her oxygen saturation on room air is 94%. She is tripoding but able to speak in complete sentences. Lung examination reveals wheezing in all lung fields, with a prolonged expiratory phase of 5 s and good air movement. She has pale nasal mucous membranes and nasal polyps. Her pharyngeal mucosa is not erythematous. Her peak expiratory flow is measured at 325 L/min, with a home baseline of 400 L/min.

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GUIDING QUESTIONS

1. What diagnostic tests would you order, and what medication(s) would you start/consider in the ED?
2. The patient's CBC does not reveal a leukocytosis, and her sputum sample is normal. Would you administer antibiotics to this patient?
3. Given the patient's presentation, what on-demand medication would you suggest she use in the future? What medication should this patient avoid in the future?

HISTORY

When determining if someone has asthma, the history is used to determine whether the person has asthma or if there is another condition for the person's chronic or intermittent cough. After evaluating an appropriate differential, asthma can be presumptively diagnosed based on a history of recurrent wheezing, dyspnea, chest tightness, cough, and mucus production related to common bronchoconstrictor precipitants. These symptoms can occur in combination or separately and can resolve spontaneously or with therapy. Symptoms may be worse in the morning. In some patients, wheezing and/or dyspnea can be persistent. If the patient has known asthma and is presenting to the hospital with an exacerbation, it is important to inquire about

- A history of exacerbations
- Medications they take and inhalers they use
- How often they take those medications/inhalers
- Their baseline peak expiratory flow measurement
- If they are adherent with their medications and inhalers

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Patient with dyspnea, chest tightness, wheezing, and exposure to a trigger (cold air, allergens)
- Have they had symptoms like this before, and if so, are they intermittent?
- Chest tightness and/or wheezing?
  - Most common symptom of asthma exacerbations
- Dyspnea? Dyspnea on exertion?
  - How does it compare with their baseline?
  - Is it worsening?
- Relief with rescue inhalers?
  - If so, as much relief as usual? Or is there less relief?
- Baseline asthma status?
  - How often do you use your relief inhaler normally?
  - Nighttime use of relief inhaler?
- Allergies?
  - Can cause asthma or asthma exacerbation because of inflammation
- Prior exacerbations and outcomes?
  - Will help you know whether you need to admit the patient, and where their disposition may be (e.g., medical floor vs ICU)
  - Ask about
    - Prior intubations
    - History of labile asthma
    - Frequent hospitalizations or ED visits in the past 12 months for asthma
    - Adherence to inhaled corticosteroids
- Change in mental status?
  - May be an indication for intubation and mechanical ventilation
- Recent illness?
  - Can be a cause of asthma exacerbation, or could indicate a pneumonia, bronchitis, or upper respiratory tract infection
- Ask about triggers of airway narrowing
  - Allergens
  - Irritants
  - Viral infections
  - Exercise and cold, dry air

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- Air pollution
- Drugs
- Occupational exposures
- Hormonal changes
- Pregnancy

PAST MEDICAL HISTORY

- History of COPD or restrictive lung diseases?
  - May be the reason for the dyspnea and wheezing
- History of allergies?
  - May cause an asthma exacerbation
- History of cystic fibrosis?
  - Can present similarly, but more likely has an associated bacterial infection in exacerbations

SOCIAL HISTORY

- Use of alcohol or recreational drugs, smoking
- Occupation (and exposures)
- Living situation
- Sexual history

FAMILY HISTORY

- History of asthma?
  - How severe?

MEDICATIONS

- Adherence with medications/inhalers?
- Are they using their rescue inhaler more often?
- β-blockers, aspirin (aspirin-associated asthma), NSAIDs, or ACE-I use?
  - These medications can worsen asthma symptoms

PHYSICAL EXAM

The physical exam in an asthma exacerbation focuses on its severity. Mental status is important, as are signs of respiratory fatigue that could be a sign of impending respiratory failure.

- Vital signs
  - Presents with tachypnea and tachycardia during exacerbations
  - Fever could indicate a viral infection or another source of dyspnea such as bacterial pneumonia
- HEENT
  - Evaluate the oral mucosa for moisture, dryness, and pharyngeal erythema
    - Pharyngeal erythema may indicate asthma or GERD as the cause of wheezing
    - Many patients have pale nasal mucous membranes consistent with allergic rhinitis
  - Nasal polyps
    - Cystic fibrosis or aspirin-induced asthma may cause nasal polyps
- Cardiac
  - Pulsus paradoxus may be present (> 10–mm Hg drop in BP with inspiration) in asthma exacerbations
  - Measure JVP to rule out HF as a cause of symptoms
- Respiratory
  - Can they speak in full sentences?
  - Evaluate for tracheal deviation and asymmetric breath sounds, which could indicate tension pneumothorax
  - Wheezing is a classic sign with an increased expiratory phase
  - Decreased breath sounds can be a sign of increased severity of exacerbation
  - Hyperresonance with percussion may be present
  - Accessory muscle use indicates a more severe exacerbation
- Dermatologic
  - Evaluate for signs of atopic dermatitis (may indicate atopic asthma)
  - Evaluate for cyanosis
- Neurologic
  - A mental status exam is indicated to assess severity of exacerbation

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DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- COPD
  - Patient is usually an older adult with a chronic cough and dyspnea and a history of smoking
  - Asthma is a risk factor for asthma–COPD overlap
- Pneumonia
  - Sudden onset of chills, fever, productive cough (rather than dry), myalgias
  - Will have findings of pneumonia on CXR
- Pneumothorax
  - Asymmetric breath sounds and tracheal deviation
- PE
  - May have hemoptysis and pleuritic chest pain but can present similarly to asthma
- Panic attack
  - Dyspnea after a traumatic or emotional event; may have a psychiatric history
- HF
  - Edema of the airways and congestion of the bronchial mucosa can cause wheezing in HF exacerbations
  - The patient usually is older and has a cardiac history with JVD and edema on exam
- GERD
  - History of reflux pain and wheezing after meals
  - May be a cause of uncontrolled asthma if not treated appropriately
- Bronchiectasis
  - Chronic foul-smelling cough, recurrent or chronic pneumonia, and hemoptysis
- Allergic bronchopulmonary aspergillosis
  - An allergic reaction that causes wheezing and has an infectious component
- Cystic fibrosis
  - Previous diagnosis with recurrent pneumonia and chronic cough
- Eosinophilic pneumonia
  - Rapid onset of cough, fever, increasing breathlessness, and night sweats
- Bronchiolitis obliterans
  - Shortness of breath and a dry cough
  - Associated with a normal peak expiratory flow
- Foreign body aspiration
  - Generally, the diagnosis is clear from the history
- Vocal cord paralysis/dysfunction
  - Can cause wheezing but with an absence of dyspnea and changes in speech
- Laryngotracheal mass
  - Stridor is a predominant feature
- Tracheal stenosis
  - Gradually worsening dyspnea, particularly dyspnea on exertion, and usually has stridor, which can be mistaken for wheezing
- Tracheomalacia
  - Usually has stridor
- Angioedema
  - Throat swelling, possible ACE-I use

ETIOLOGY

- Genetic and environmental factors (see Pathophysiology section)
- Acute exacerbation etiologies
  - Allergens
  - Upper respiratory infections
  - Exercise and hyperventilation
  - Cold air exposure
  - Sulfur dioxide exposure
  - Irritant gases exposure
  - Drugs: Use of β-blockers, aspirin (especially in aspirin-induced asthma), ACE-Is
  - Stress
  - GERD
  - Hormones (premenstrual asthma)

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    - Pregnancy
    - Smoking
- Exercise-induced asthma
- Aspirin-exacerbated respiratory disease

DIAGNOSTIC TESTS

LABS

- ABG if severe exacerbation
    - Hypocarbia is common from tachypnea
    - If the $PaCO_2$ levels increase or go back to normal, this may be a sign of impending respiratory failure and the necessity for intubation
    - Hypoxemia may be present with an increased A-a gradient
- CBC with differential
    - May show elevated eosinophils (which may guide management)
    - Evaluate for leukocytosis, as this may show an infectious process is present
- BMP to evaluate for electrolyte abnormalities
- D-dimer based on simplified Wells' score for PE assessment
- Sputum culture: may help determine whether an infectious etiology is present
- Respiratory viral panel: viral etiologies of asthma exacerbations are common
- Blood cultures if there is concern about a bacterial infection

IMAGING

- Peak expiratory flow (PEF)
    - Perform this at the beginning of the ED visit, then intermittently throughout the ED and hospital stay
    - Measure their baseline PEF in the office setting to compare to when having an exacerbation
    - Normal PEF values: 450–650 L/min (men), 350–500 L/min (women)
        - Varies based on the patient's age and height
    - Mild exacerbation: > 300 L/min
    - Moderate to severe exacerbation: 100–300 L/min
    - Severe exacerbation: < 100 L/min
- CXR
    - Perform to exclude other conditions (pneumonia, pneumothorax, pneumomediastinum, foreign body aspiration)
    - May show hyperinflation in severe asthma; normal in nonsevere asthma
- CT chest can evaluate for bronchiectasis and mucus plugging
- CT pulmonary angiography for PE if indicated from simplified Wells' criteria and D-dimer testing
- PFTs are required for diagnosis and are usually performed in the outpatient setting
    - Typical findings of asthma on PFTs include
        - Decreased FEV_1, decreased FVC, decreased FEV_1/FVC ratio
        - Increase in FEV_1 > 12% with albuterol
        - Decrease in FEV_1 > 20% with methacholine or histamine
        - Increase in the diffusion capacity of the lung for CO_2

MANAGEMENT

SEVERITY OF ACUTE ASTHMA EXACERBATIONS

- Treatment strategies, admission criteria, and level of care depend on the severity of the asthma exacerbation
    - Clinical findings of a severe asthma exacerbation
        - Tachypnea (> 30 breaths/min)
        - Tachycardia (> 120 beats/min)
        - Use of accessory muscles of inspiration and flaring of the nares
        - Diaphoresis
        - Inability to speak in full sentences
        - Inability to lie supine due to breathlessness and/or tripoding
        - Presence of pulsus paradoxus
        - Peak expiratory flow < 25% of predicted and/or improving < 10% with initial treatment
- Quadrupling the dose of inhaled glucocorticoids at the start of an exacerbation has been shown to result in fewer severe asthma exacerbations

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- Adults and adolescents with asthma who performed a personalized self-management plan that included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate experienced fewer severe asthma exacerbations than those with a plan in which the dose was not increased

ED MANAGEMENT

- Supplemental oxygen to maintain Spo_2 > 92%
- Measure an initial peak expiratory flow (PEF) and repeat 1–2 h after initial treatment
- Albuterol nebulizer 2.5–5 mg every 20 min × 3 initially (*mainstay of treatment*)
  - Add ipratropium 500 μg with albuterol if presenting with a severe exacerbation
- If PEF is not > 60% of predicted after 1–2 h of treatment and/or not improving by > 10% from the initial PEF measurement, administer IV methylprednisolone 40–60 mg (or oral prednisone 40–60 mg)
  - When comparable doses are administered, the effects of PO and IV routes of glucocorticoids are identical
- Magnesium sulfate 2 g IV for patients with life-threatening exacerbation
  - Administer if the exacerbation remains severe after 1 h of intensive conventional therapy
- Antibiotic administration only if bacterial infection is suspected
  - Antibiotic therapy may be associated with
    - A longer hospital length of stay
    - Higher hospital costs
    - Similar risk of treatment failure in patients who receive corticosteroids
  - These results highlight the need to reduce inappropriate antibiotic prescribing among patients hospitalized for asthma exacerbation [1]
- Intubation for respiratory failure
  - Patients usually present with respiratory alkalosis from tachypnea
  - If repeat $Paco_2$ is rising after initial treatment, this is a sign of impending respiratory failure, and intubation should be considered
  - Worsening mental status despite treatment also warrants intubation consideration
- Disposition from the ED
  - Based on the patient's clinical response to initial therapy, Spo_2, and PEF improvement
  - Patients can generally be discharged from the ED with PO prednisone, 40–60 mg for 5–7 days, if
    - The initial PEF is > 70% of expected without hypoxemia and with improvement of symptoms
    - The initial PEF is 40–69% with > 10% improvement and mild to moderate symptoms, with minimal comorbidities, and without concerns for nonadherence
    - Ensure patients have a rescue inhaler, maintenance inhalers, and close follow-up with their primary care clinician
  - Admit patient to the medical floor if
    - The initial PEF is 40–69% with < 10% improvement
    - Complex medical comorbidities
    - Recent visits to the ED for asthma exacerbation
    - Concern for inhaler adherence
  - Admit patient to the ICU if the patient has
    - Status asthmaticus requiring intubation
    - Prior intubations
    - Severe exacerbation criteria and initial PEF < 40% of predicted or improving < 10% with initial treatment
    - Signs of impending respiratory failure
      - Change in mental status
      - Worsening fatigue
      - $Paco_2$ > 42 mm Hg (or well above baseline) or rising on repeat testing

ICU MANAGEMENT

- Intubation if indicated
  - There is little evidence for administering noninvasive positive pressure ventilation (e.g., BiPap) in asthma exacerbations
- Continue therapies started in the ED
- Nonstandard therapies that may provide benefits include
  - Anesthetic agents (ketamine, isoflurane)
  - Helium-oxygen
  - Extracorporeal membrane oxygenation (ECMO) may be helpful in individual patients but cannot be recommended for routine use because of insufficient data

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INPATIENT (NON-ICU) MANAGEMENT

- In general, inpatient management is a continuation of ED or ICU management, followed by a transition to a discharge regimen
- Continue albuterol ± ipratropium
  - Taper to q4–6h and transition to a metered-dose inhaler (MDI) format based on clinical improvement
- Continue prednisone 40–60 mg daily for a total of 5–7 days
  - In a systematic review, there is not strong enough evidence to reveal whether shorter or lower-dose regimens are generally less effective than longer or higher-dose regimens, or that the latter are associated with more adverse events
- Begin (or resume) inhaled corticosteroids (ICS—e.g., budesonide) when patients can tolerate MDIs or dry-powder inhalers
- Depending on their step therapy (see Management of Chronic Asthma and Prevention section), may require
  - ICS/LABA (e.g., budesonide/formoterol)
  - ICS/SABA (budesonide/albuterol)
  - Leukotriene modifier (e.g., montelukast), *or*
  - Advanced therapies
- If a new inhaler will be used after discharge, start the new inhaler prior to discharge to ensure proper instruction on technique
- If a patient is not improving with typical management, consider
  - Viral bronchitis and bronchiolitis
  - Bronchiectasis
  - Underlying COPD
  - Untreated GERD
  - Cardiac dysfunction with volume overload
- Smoking cessation counseling

MANAGEMENT OF CHRONIC ASTHMA & PREVENTION

- Reduce exposure to triggers
- Smoking cessation
- Every patient should have an asthma action plan (such as the National Heart, Lung, and Blood Institute Asthma Action Plan), which describes what the patient should do at home if an exacerbation is beginning
- The overall goals of asthma management are to reduce symptoms and exacerbations, to improve quality of life, and to optimize lung function (**Table 16-1**)
- Reassessment of these goals and symptom control determines if you need to move up or down step therapy (**Table 16-2**)
- Regular use of low-dose ICS is associated with a decreased risk of death from asthma
  - LABAs without use of ICS increases the risk of respiratory death
- Combination therapy with an ICS (budesonide) plus LABA (formoterol)
  - Results in significantly fewer asthma exacerbations [5]
  - Does not result in a significantly higher risk of serious asthma-related events than treatment with an ICS alone
- Adjunct medications (a pulmonologist may guide use of these therapies)
  - Leukotriene modifiers (LTMs): montelukast 10 mg PO qhs or zileuton 1.2 g PO bid
  - Cromones: cromolyn sodium 200 mg inhaled daily (usually used in children)
  - Oral corticosteroids: at lowest possible dose only if other options are not controlling symptoms

TABLE 16-1 Goals of Asthma Therapy

1. Reduction in symptom frequency to ≤ 2 times/week
2. Reduction of nighttime awakenings to ≤ 2 times/month
3. Reduction of reliever use to ≤ 2 times a week (except before exercise)
4. No more than 1 exacerbation/year
5. Optimization of lung function
6. Maintenance of normal daily activities
7. Satisfaction with asthma care with minimal or no side effects of treatment

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TABLE 16-2 Step Therapy in Personalized Asthma Management Plan

	PREFERRED	ALTERNATIVE
Steps 1 and 2	Low-dose ICS-formoterol as needed *or* Low-dose ICS daily and SABA as needed *or* Concomitant ICS and SABA as needed	LTM daily and SABA as needed *or* Cromolyn *or* Theophylline and SABA as needed
Step 3	Combination low-dose ICS plus formoterol daily and as needed	Medium-dose ICS daily and SABA as needed *or* Low-dose ICS-LABA daily *or* Low-dose ICS *plus* LAMA daily *or* Low-dose ICS *plus* LTM and SABA as needed *or* Low-dose ICS daily *plus* theophylline or zileuton and SABA as needed
Step 4	Combination medium-dose ICS-formoterol daily and as needed	Medium-dose ICS-LABA daily *or* Medium-dose ICS *plus* LAMA daily and SABA as needed *or* Medium-dose ICS *plus* LTM daily *or* Medium-dose ICS *plus* zileuton daily and SABA as needed *or* Medium-dose ICS *plus* theophylline daily
Step 5	Medium- to high-dose ICS-LABA plus LAMA and SABA as needed	Medium- to high-dose ICS-LABA daily *or* High-dose ICS *plus* LTM and SABA as needed
Step 6	High-dose ICS-LABA plus oral systemic corticosteroids plus SABA as needed	

Data support as-needed reliever therapy recommendations for Step 1. For as-needed ICS/formoterol: The regular use of low-dose inhaled corticosteroids is associated with a decreased risk of death from asthma [2], and both monocomponents of budesonide-formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance [3]. For the alternative, as-needed ICS/SABA: As-needed use of albuterol-budesonide resulted in a lower risk of a severe asthma exacerbation than as-needed use of albuterol alone among participants with disease that was uncontrolled despite treatment for mild asthma [4].
ICS, inhaled corticosteroid (e.g., budesonide); LTM, leukotriene modifier (e.g., montelukast).
Reproduced with permission from Abbas R et al. Pulmonary disorders. In Papadakis MA, Rabow MR, McQuaid KR, Nadler P (eds). *CURRENT Diagnosis & Treatment 2026*. McGraw Hill, 2026.

- Anti-IgE: omalizumab subcutaneous every 2–4 weeks
  - The IgE level must be in a specific range (30–700 IU/mL)
  - Patient must be ≥ 6 years with moderate to severe classification uncontrolled with high doses of ICS therapy
- Interleukin (IL)-5 active drugs: mepolizumab, reslizumab, or benralizumab (for severe disease with elevated eosinophils)
- Anti–IL-4/13: dupilumab (for severe disease with FeNO of 20-25 ppb)
- Anti–thymic stromal lymphopoietin (TSLP): tezepelumab binds TSLP, a proximal alarmin in the epithelial response cascade, decreasing blood eosinophils, fractional exhaled nitric oxide, and IgE levels
- Azithromycin: may be effective in a subset of persons with asthma who respond poorly to other therapies
- Theophylline 300–600 mg/day: rarely used now because of
  - Narrow therapeutic window
  - Drug–drug interactions
  - Reduced bronchodilation compared to other agents

- Special considerations
  - Exercise-induced asthma
    - Budesonide-formoterol on demand prior to exercise
      - The combination of budesonide and formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction in the same order of magnitude as regular budesonide treatment despite a substantially lower total steroid dose
    - LTMs if the patient exercises regularly
    - Use a mask that covers the mouth and nose while exercising in cold weather
  - Pregnancy: treatment is essentially the same, but asthma can be harder to control
  - Aspirin-exacerbated respiratory disease: avoid aspirin and NSAIDs, and prescribe LTMs

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- Control morbidities that may make asthma difficult to control
  - Chronic rhinosinusitis ± nasal polyposis
  - Obesity
  - GERD
  - Inducible laryngeal obstruction (vocal cord dysfunction)
  - COPD
  - Anxiety/depression
  - Obstructive sleep apnea
- Administer annual influenza vaccine
- Avoid sedative medications (e.g., benzodiazepines, opiates)

COMPLICATIONS

- Symptoms interfering with activities of daily living
- Permanent narrowing of bronchial tubes
- ED visits and hospitalizations
- Side effects from medications
- COPD
- Death

PROGNOSIS

- Asthma mortality increased worldwide in the 1960s, apparently related to overuse of inhaled β_2 agonists
- Reduction in mortality since then has been attributed to increased use of inhaled corticosteroids
- Asthma mortality declined globally from 0.44 per 100,000 people in 1993 to 0.19 in 2006, but further reduction in mortality has not occurred since that time
- Table 16-3 lists patients at greater risk for asthma mortality

PATHOPHYSIOLOGY

- Asthma is an inflammatory process in genetically susceptible individuals with environmental exposures (Fig. 16-1), and the pathway to developing asthma can be varied
- *Asthma pathophysiology triad*
  - Airway hyperresponsiveness (AHR)
  - Airway inflammation
  - Reversible airflow obstruction
- AHR
  - The pathobiologic processes in the airways that lead to episodic and chronic airway obstruction of asthma are highlighted in Fig. 16-2
  - Acute airway narrowing in response to stimuli that do not affect healthy individuals
  - Triggered by direct smooth muscle–acting agents (e.g., histamine, methacholine)
  - Inflammatory cell activation releases bronchoconstrictors → airway edema + mucus secretion
  - Sensory nerve stimulation affects smooth muscle and inflammatory cells

TABLE 16-3 Patients at Greater Risk for Asthma Mortality

1. History of ICU admission for asthma
2. History of intubation for asthma
3. Illicit drug use
4. Depression
5. New diagnosis within past year
6. ≥ 2 ED visits in past 6 months
7. Severe psychosocial problems
8. Lower socioeconomic status
9. On daily prednisone prior to admission
10. Black race

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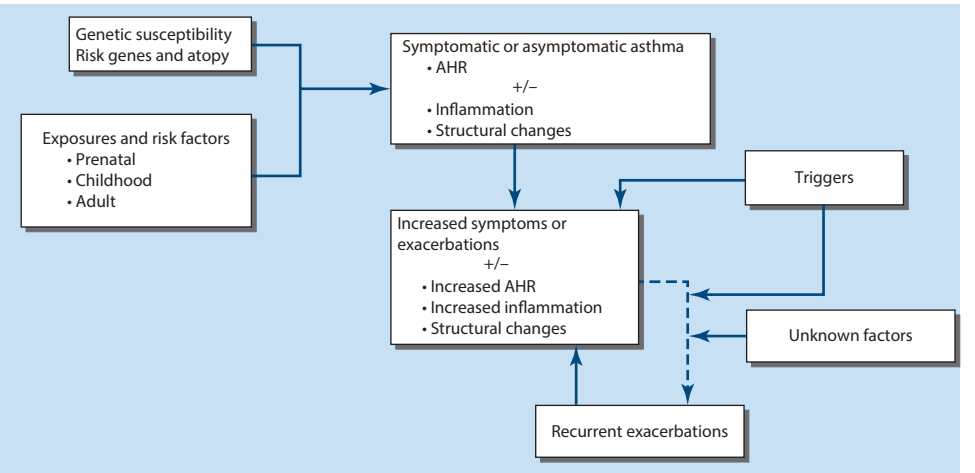

FIGURE 16-1 Asthma development pathway. Illustration of how genetic susceptibility, development, and exposure during the life span interact to produce a disease that can vary in intensity and chronicity. Disease expression is characterized by airway hyperresponsiveness with varying degrees of airway inflammation and airway structural changes accompanied by varying degrees of symptoms that can be influenced by exposure to triggers that can cause acute deterioration as well as chronic symptoms. AHR, airway hyperresponsiveness. (Reproduced with permission from Israel E. Asthma, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Chronic/severe asthma → airway wall thickening from smooth muscle hypertrophy, subepithelial collagen, edema, and inflammation
    - Therapeutic goal: reduce AHR
- Airway inflammation
    - Arises from acute events; may persist chronically
    - Commonly *eosinophilic* but can be neutrophilic (especially in severe asthma)
    - Mast cells become increasingly present in airway tissues
    - Classified as type 2 or non–type 2 inflammation (**Fig. 16-3**)
    - Type 2 inflammation
        - Involves both innate and adaptive immunity (CD4+ T_H2 cells)
        - Cytokines—interleukin (IL)-4, IL-5, IL-13—are key
        - IL-4 → B cells produce IgE, leading to mast cell/basophil activation via IgE cross-linking
        - Causes bronchoconstriction, edema, mucus hypersecretion, and goblet cell metaplasia
        - Nonallergic triggers (via innate lymphoid type 2 cells [ILC2 cells]) can also induce IL-5 and IL-13 release
    - Non–type 2 inflammation
        - May coexist with or occur independently of type 2 inflammation
        - Triggered by irritants, pollutants, microbes, and viruses
        - Activates IL-6, transforming growth factor (TGF)-β, IL-23, IL-33, CXC motif chemokine ligand 8 (CXCL8), granulocyte-macrophage colony-stimulating factor (GM-CSF)
        - Leads to neutrophilic inflammation
        - Common in severe, steroid-resistant asthma
        - Sometimes associated with chronic infection (e.g., *Mycoplasma*)
    - Other inflammatory mediators
        - Leukotrienes, prostaglandins, nitric oxide, reactive oxygen species, and chemokines contribute to airway inflammation

RISK FACTORS

- Allergen exposure during vulnerable developmental periods is believed to increase the risk of development of allergic sensitization in those with a tendency toward atopy
- Some research suggests that early, varied microbiome exposure (bacteria and bacterial products) may reduce the development of atopy

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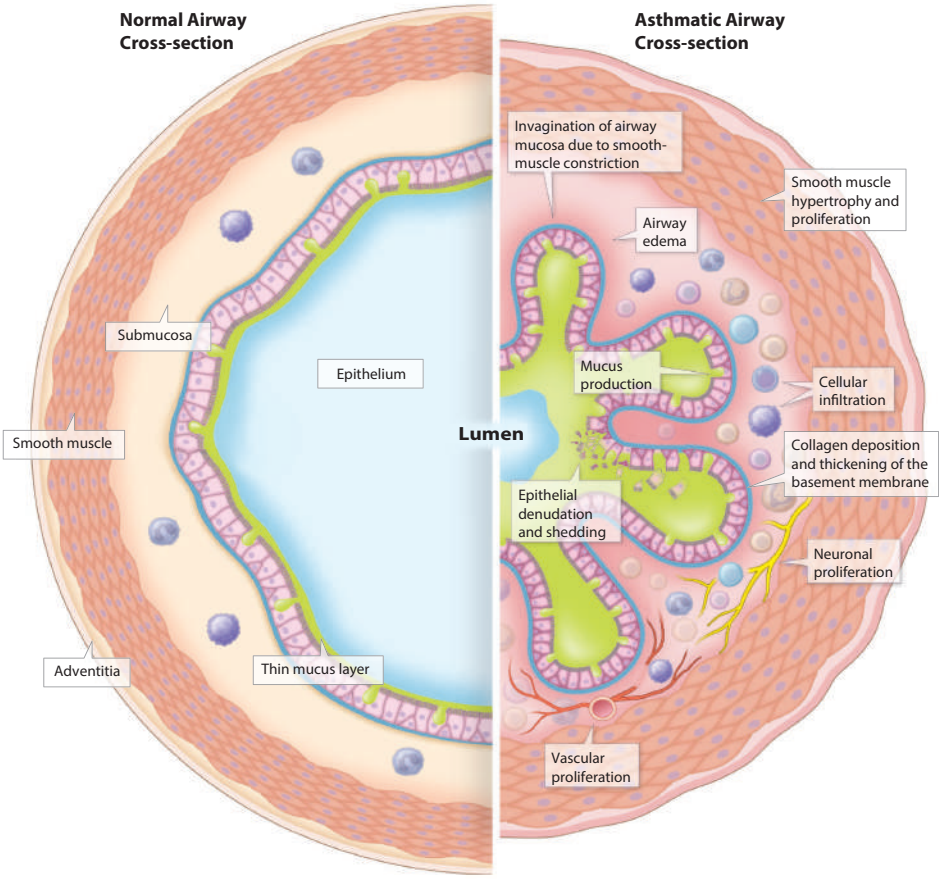

FIGURE 16-2 Pathologic changes that can be seen in asthmatic airways. Illustrated is a cross-sectional lumen of a bronchus. The left-hand side represents the normal airway, and the right represents an asthmatic airway highlighting the pathologic changes that can be seen in asthma. The asthmatic airway lumen is reduced by smooth-muscle contraction and hypertrophy, mucus in the airway lumen, and thickening of the submucosa due to edema and cellular infiltration. In addition, the ability of the lumen to increase in size with smooth-muscle relaxation may be impaired by deposition of collagen. The epithelium is disrupted, and there is evidence of vascular and neuronal proliferation. All these changes may not be present in one individual, and certain patients may have normal-appearing airways. (Reproduced with permission from Israel E. Asthma, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Exposures that can lead to the development of asthma
  - Tobacco
  - Air pollution
  - Infections (respiratory, rhinoviruses, respiratory syncytial virus, *Mycoplasma*)
  - Occupational exposures (e.g., in adult-onset asthma)
    - Immunologic stimulants (proteins, flour, formaldehyde, and diisocyanate)
    - Irritative stimulants (oxidizing and reducing agents in aerosols)
  - Diet (vitamin D deficiency)
  - Obesity
  - Medications
    - Use of proton pump inhibitors and H_2 blockers in pregnancy increases risk of asthma in the child
    - Use of acetaminophen in early childhood: conflicting data
  - Preeclampsia, prematurity, and delivery via cesarean section

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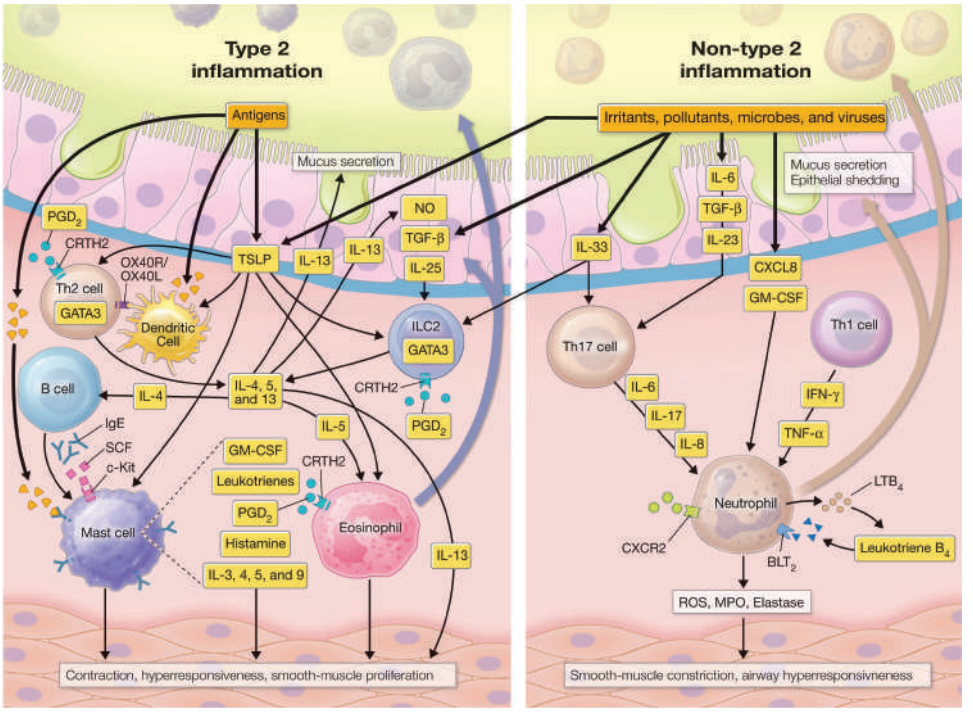

FIGURE 16-3 Inflammatory cells and mediators involved in type 2 and non–type 2 inflammation. Allergens and nonallergic stimuli can trigger activation of multiple inflammatory cells and release of mediators that are responsible for recruiting and activating these cells. The mediators can affect airway smooth-muscle proliferation and hyperresponsiveness and fibroblast proliferation and matrix deposition. BLT2, leukotriene B_4 receptor 2; CRTH2, chemoattractant receptor-homologous molecule (PGD2 receptor); CXCL8, CXC motif chemokine ligand 8; CXCR2, CXC chemokine receptor 2; GATA3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; ILC2, innate lymphoid type 2 cells; c-Kit, mast/stem cell growth factor receptor; LTB4, leukotriene B4; MPO, myeloperoxidase; NO, nitric oxide; OX40L/OX40R, OX40 ligand/OX40 receptor; PGD2, prostaglandin D2; ROS, reactive oxygen species; SCF, stem cell factor; TGF-β, transforming growth factor β; Th, T helper; TNF-α, tumor necrosis factor α; TSLP, thymic stromal lymphopoietin. (Reproduced with permission from Israel E. Asthma, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Fungi and allergic airway mycoses (*Aspergillus*)
    - Exercise-induced symptoms in elite athletes (asthma in swimmers with no asthma risk factors or airway hyperresponsiveness [possible exposure to chlorinated pools])
- Triggers for airway inflammation
    - Allergens
    - Upper respiratory infections
    - Exercise and hyperventilation
    - Cold air
    - Sulfur dioxide
    - Irritant gases
    - β-blockers
    - Aspirin
    - Stress
    - GERD
    - Hormones (premenstrual asthma)

ADMITTING ORDERS

- Admit to floor or ICU
- Diagnosis: asthma exacerbation
- Condition: stable, guarded, or critical

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- Vital signs: routine or ICU routine
- Activity: as tolerated
- Nursing: check peak expiratory flow at least daily and educate the patient in performing at home; oxygen supplementation to maintain oxygen saturations > 92%
- Diet: regular or modified for other medical conditions
- Fluids: order if needed
- Diagnostic tests
    - ABG (if indicated)
    - CBC
    - CMP
    - D-dimer based on simplified Wells' criteria for PE
    - Sputum culture
    - Respiratory viral panel
    - Blood cultures
    - CXR
- Medications
    - Albuterol
        - Albuterol nebulizer q4h
        - Albuterol q2h prn for shortness of breath or wheezing
    - Methylprednisolone if severe exacerbation
        - 125 mg IV upon admission
        - Followed by prednisone 60 mg daily

DISCHARGE INFORMATION

- Ensure adequate medications and inhalers are prescribed with education on how to use them
- Use step approach to decide what inhalers to prescribe
- Provide a peak expiratory flow monitor
- Educate about trigger avoidance and smoking cessation
- Develop an asthma action plan, such as the National Heart, Lung, and Blood Institute Asthma Action Plan
- Follow up in 7 days with primary care clinician and/or asthma specialist

CASE ANSWERS

1. This patient is presenting with a primary concern of an asthma exacerbation. A CBC with differential, BMP, sputum culture, respiratory viral panel, and CXR should be ordered for this patient. While you await the results of bloodwork and imaging, administer nebulized albuterol 2.5–5 mg every 20 min × 3. IV methylprednisolone and magnesium should be considered if initial therapy does not improve symptoms. An ABG may be considered early in the initial presentation but especially should be obtained if the patient does not respond well to initial therapy.
2. Unlike in COPD exacerbations, antibiotics are not indicated in asthma exacerbations unless there is an obvious bacterial infection. This patient is afebrile, has no specific infectious findings (such as leukocytosis), and presents with a history of worsening symptoms after exercising in cold air and new aspirin use. Therefore, antibiotics are not indicated for this patient.
3. This patient should use on-demand budesonide-formoterol prior to exercise. This combination improves asthma control by reducing exercise-induced bronchoconstriction. Aspirin should be avoided given the patient's recent use of aspirin and the finding of nasal polyps on exam.

LANDMARK TRIALS

[1] Stefan MS et al. Association of antibiotic treatment with outcomes in patients hospitalized for an asthma exacerbation treated with systemic corticosteroids. JAMA Intern Med 179:333, 2019. [PMID: 30688986]
    - *Summary:* Antibiotic therapy may be associated with a longer hospital length of stay, higher hospital cost, and similar risk of treatment failure in patients who receive corticosteroids. These results highlight the need to reduce inappropriate antibiotic prescribing among patients hospitalized for asthma.

[2] Suissa S et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 343:332, 2000. [PMID: 10922423]
    - *Summary:* The regular use of low-dose inhaled corticosteroids is associated with a decreased risk of death from asthma.

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[3] LaForce C et al. As-needed albuterol-budesonide in mild asthma. N Engl J Med 393:113, 2025. [PMID: 40388330]
- *Summary:* As-needed use of albuterol-budesonide resulted in a lower risk of a severe asthma exacerbation than as-needed use of albuterol alone among participants with disease that was uncontrolled despite treatment for mild asthma.

[4] Rabe KF et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: A randomized controlled, double-blind study. Lancet 368:744, 2006. [PMID: 16935685]
- *Summary:* Both monocomponents of budesonide-formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance.

[5] Busse WW et al. Combined analysis of asthma safety trials of long-acting β_2 agonists. N Engl J Med 378:2497, 2018. [PMID: 29949492]
- *Summary:* Combination therapy with a long-acting β_2 agonist plus an inhaled corticosteroid did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma exacerbations.

FURTHER READING

- Cahill KN. Acute exacerbations of asthma in adults: Emergency department and inpatient management. UpToDate. https://www.uptodate.com/contents/acute-exacerbations-of-asthma-in-adults-emergency-department-and-inpatient-management. Accessed January 4, 2026.
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18 Venous Thromboembolism

KEY POINTS

1. VTE encompasses DVT and PE. Patients with risk factors of Virchow's triad (venous stasis, endothelial injury, and hypercoagulability) have a higher probability of developing a VTE.
2. Patients presenting with PE commonly have dyspnea, pleuritic chest pain, and cough. More severely ill patients may have hypoxemia, hemoptysis, and obstructive shock with findings of crackles, S_4 heart sound, and JVD on exam. DVTs commonly present with unilateral leg swelling, pain, and erythema on exam. A thorough medical history, including recent surgery, periods of immobilization, and medications, is important in understanding risk factors.
3. The simplified Wells' criteria help guide the initial workup in the evaluation of PE and DVT. An age-adjusted D-dimer should be ordered in patients with a low to intermediate risk of VTE. If the D-dimer is elevated, Doppler ultrasound of the leg and CT angiography of the chest are first-line imaging studies to diagnose DVT and PE, respectively. ECG and cardiac biomarkers (troponin, BNP) help evaluate if RV strain is present in PE.
4. In patients with a high probability of PE or DVT using the simplified Wells' criteria, anticoagulation should be administered as imaging studies are pursued. DOACs are the preferred agents for VTE management except in select patient populations. In patients with massive PE, systemic fibrinolysis, catheter-directed fibrinolysis or thrombectomy, and embolectomy are treatment options that require a multidisciplinary team.
5. PE can lead to dysrhythmias, pulmonary infarction, shock, cardiac arrest, post-PE syndrome, and chronic thromboembolic pulmonary hypertension. DVT can cause a PE, an ischemic stroke from a paradoxical embolus, postthrombotic syndrome, phlegmasia alba dolens, and phlegmasia cerulean dolens. Treatment with anticoagulation can cause bleeding, including intracranial hemorrhage. The prognosis of PE has improved but plateaued over the last decades. PE-related mortality is increasing among young and middle-aged adults.

EPIDEMIOLOGY & DEFINITIONS

VTE encompasses DVT and PE and causes death, chronic disability, and emotional distress. While hospitalizations in the United States have decreased for acute MI, HF, and stroke, PE hospitalizations have increased. Additionally, readmission rates are high, estimated at 11% at 30 days and 15% at 90 days. Since 2020, the COVID-19 pandemic led to increased rates of VTE in patients infected with COVID-19, and ~25% of patients who died from COVID-19 had both macrovascular and microvascular PE on autopsy.

Low-risk PE is associated with the absence of RV strain, elevated cardiac biomarkers, and hypotension.

Submassive PE is associated with RV strain, elevated cardiac biomarkers, and the absence of hypotension.

Massive PE has extensive thrombosis affecting at least half of the pulmonary vasculature, with the above signs of submassive PE and hypotension or obstructive shock.

Lower extremity DVT is thrombosis of the deep veins of the leg (popliteal, femoral, and/or iliac veins).

Superficial venous thrombosis is a thrombosis of superficial veins, usually in the lower extremities (associated with varicose veins), and presents as a palpable cord.

The terms *provoked* and *unprovoked* should no longer be used to classify VTEs given that many types of provoked VTEs have a similar recurrence rate to unprovoked VTEs once anticoagulation is discontinued. Enduring risk factors (such as HF, chronic lung disease, and inflammatory bowel disease) need to be assessed for indefinite anticoagulation, as they heighten the risk of recurrence.

CLINICAL VIGNETTE

A 64-year-old man presents to the ED complaining of an enlarging left calf for the past 6 days and progressively worsening cramping sensations and shortness of breath since yesterday. His medical history includes hypertension, type 2 diabetes mellitus, obesity, peripheral vascular disease, and pancreatic cancer for which he is receiving immunotherapy. On exam, he is afebrile, respiratory rate is 20 breaths/min, heart rate is 112 beats/min, BP is 130/82 mm Hg (his baseline BP is 130s/80s mm Hg), and Spo_2 is 92% on room air. His heart rate is regular and tachycardic; the rest of the cardiac

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exam is normal. Crackles are present in the right lower lobe. Both of his lower legs have an erythematous appearance, but the left is swollen (4 cm larger than the right) with pitting edema and is warm to the touch. There are collateral superficial veins present on the left leg. An ECG reveals sinus tachycardia. A Doppler ultrasound of the left leg reveals a DVT. A CT angiography of the chest is ordered and pending.

GUIDING QUESTIONS

1. What other diagnostic tests would you order?
2. Cardiac troponin and BNP levels are mildly elevated, and CT angiography of the chest reveals a right-sided segmental PE without evidence of right heart strain. Should this patient be admitted to the hospital?
3. How would you manage this patient?

HISTORY

The presentation of DVT and PE can be subtle (PEs are "the great masquerader") and easily missed if the health care provider does not have a clinical suspicion. This can be a life-threatening process, requiring it to be ruled out in many clinical situations. There are ~100,000–180,000 deaths annually from PE, and the U.S. Surgeon General has declared that PE is the most common preventable cause of death among hospitalized patients. When occult PE occurs concomitantly with HF or pneumonia, clinical improvement often fails to ensue despite standard medical treatment of the concomitant illness, providing a clinical clue to the possible coexistence of PE. Long-term effects are seen from these conditions as well: nearly half of patients with PE after 1 year had exercise limitations, decreased walking distance, or dyspnea, as well as lowered quality of life. It is important to know and ask about risk factors for VTE, which are listed in the Risk Factors section.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - A patient with dyspnea, hemoptysis, pleuritic chest pain, tachycardia, tachypnea and unilateral leg swelling that is painful and erythematous who has cancer or a recent surgery
- PE
  - Dyspnea?
    - Present in 61–83% of PEs
  - Pleuritic chest pain?
    - Present in 40–48% of PEs
  - Cough?
    - Present in 37% of PEs
  - Hemoptysis?
    - Present in 13% of PEs; usually associated with pulmonary infarction
  - Palpitations?
    - PE may present with sinus tachycardia or dysrhythmias (e.g., AF)
  - Syncope?
    - In patients admitted for first episode of syncope, 17% were found to have PE after a standardized, guideline-based inpatient evaluation
    - PE was identified in 12.7% of patients with an alternative etiology for syncope and 25.4% of patients who did not have an alternative etiology
    - PE was identified in 25% of patients without typical signs or symptoms
  - Recent major surgery? Active cancer/treatment of cancer in the last 6 months?
    - Risk factors for hypercoagulability
- DVT
  - Leg swelling/pain? Unilateral or bilateral?
    - Presents as worse with dependency/walking and better with elevation/rest
    - The most common complaint is a leg cramp that persists and intensifies over several days
    - Bilateral symptoms could indicate bilateral DVTs but are more likely from another clinical entity (e.g., venous stasis)
  - Recent long travel or immobilization? Recent major surgery? Active cancer/treatment of cancer in last 6 months?
    - Risk factors for hypercoagulability
  - Fever/chills?
    - Presence of fever/chills may indicate another clinical entity (e.g., cellulitis)

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PAST MEDICAL HISTORY

- History of HF?
  - Lower extremity swelling of HF may mimic DVT, and tachypnea/dyspnea may mimic PE
- History of cancer?
  - A hypercoagulable state
- History of COPD?
  - Can mimic PE symptoms
- History of chronic kidney disease?
  - A hypercoagulable state making patients susceptible to DVT
  - Edema from CKD may mimic or mask the edema of a DVT
- History of SLE or inflammatory bowel disease?
  - Hypercoagulable states

SURGICAL HISTORY

- Any recent surgery?
  - Especially orthopedic surgery of long bones/pelvis can lead to either thrombotic or nonthrombotic (i.e., fat or bony/cement embolus) VTE

SOCIAL HISTORY

- Use of alcohol and recreational drugs, smoking (increases hypercoagulability)
- Occupation
- Living situation
- Sexual history

FAMILY HISTORY

- History of blood clots?
  - A family history of blood clots can lead you to investigate genetic causes of clots (e.g., factor V Leiden mutation, prothrombin mutation)

MEDICATIONS

- Birth control? Hormone therapy (estrogen)?
  - Increased estrogen states are hypercoagulable
- Taking anticoagulants (warfarin, apixaban, rivaroxaban, etc.)?
  - If patient is receiving an anticoagulant and is still clotting, then further investigation and intervention are needed (have they been compliant with all doses?)

PHYSICAL EXAM

Vital signs can range from normal to hemodynamically unstable. A full lung exam and an exam for lower extremity pain/swelling are important. It is important to assess for JVD, which could indicate a massive PE. Cyanosis may be present.

- Vital signs
  - Tachypnea (70% of PEs) is the most common sign/symptom of PE
  - Tachycardia (30% of PEs)
  - Hypoxemia may be present in submassive and massive PEs
  - Fever can be present in either PE or DVT
  - Hypotension may be a sign of a massive PE
- Pulmonary
  - Crackles (51% of PEs)
- Cardiac
  - S_4 (24% of PEs)
  - Loud P_2 may be present (23% of PEs)
  - Left parasternal heave (positive likelihood ratio of 2.4 for PE)
  - Evaluate for JVD (sign of hemodynamic abnormalities of the heart in PE)
- Skin
  - Edema (to calf and/or thigh) and erythema
  - Leg pain/swelling/palpable cord
    - Homan's sign may be positive in DVT, but it is a low-specificity test
  - Presence of venous stasis
    - May present similarly to a DVT

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DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Differential of PE
  - Acute coronary syndrome
    - Can lead to dyspnea, tachypnea, and edema (from acute HF), associated with typical angina and elevated troponins with ECG changes of ischemia
  - Pneumonia
    - Fever, dyspnea, tachypnea, productive cough, and pleuritic chest pain
    - CXR and/or CT reveals a consolidation
  - Asthma exacerbation
    - Dyspnea, cough, and wheezing
  - COPD exacerbation
    - Dyspnea, cough, wheezing
    - Smoking history
    - Elevated $Paco_2$ levels
  - HF
    - Dyspnea from vascular congestion, edema, and elevated JVP
  - Pericarditis
    - Pleuritic chest pain better with leaning forward, radiating to the trapezius ridge, presence of a friction rub, and diffuse ST-segment elevation and PR-segment depression
  - Cardiac tamponade
    - Hypotension, JVD, decreased heart sounds (Beck's triad), pulsus paradoxus, and narrowed pulse pressure
  - Pleurisy, costochondritis, and musculoskeletal discomfort
    - Long-time smokers with lung disease, cough or pleuritic chest pain, and musculoskeletal discomfort
  - Pleural effusion
    - Dyspnea with possible associated cough
    - Seen on CXR
    - PE can cause an exudative pleural effusion
  - Pneumothorax
    - Respiratory distress with unilateral hyperresonance and absence of breath sounds
  - Rib fracture
    - Point tenderness at the site of fractures, usually associated with trauma
    - CXR or chest CT reveals fractures
  - Anxiety
    - Dyspnea in a patient with an acute stressor or an acute exacerbation of a chronic mental health condition
  - Vasovagal syncope
    - PE can cause syncope, but vasovagal usually has prodromal symptoms of lightheadedness and dizziness with standing without associated chest pain, dyspnea, or cough
- Differential of DVT
  - Muscular strain
    - Trauma or exercise-induced pain in the leg with associated bruising
  - Baker's cyst
    - Sudden severe calf pain, felt on physical exam
    - Ultrasound reveals the cyst
  - Achilles tendon rupture
    - Positive Thompson test; unable to plantar flex the foot
  - Cellulitis
    - Signs of fever/chills, presence of a wound, and erythema
    - Soft tissue edema without thrombosis on ultrasound
  - Superficial thrombophlebitis
    - More superficial and along veins; a palpable cord is present
  - Venous insufficiency
    - Bilateral chronic leg swelling and redness with associated ulcers
  - Lymphatic obstruction (e.g., pelvic tumor) or lymphedema
    - Nonpitting edema of the entire leg
  - Reflex sympathetic dystrophy
    - Swelling, redness with vasomotor instability, hyperhidrosis, coolness to the touch

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- May-Thurner syndrome
  - Recurrent left thigh edema caused by right proximal iliac artery compression of the left proximal iliac vein
  - Can also induce a DVT of the left leg

ETIOLOGY

- Factor V Leiden mutation (autosomal dominant inheritance, resistance to activated protein C which normally inactivates clotting factors V and VIII)
- Prothrombin mutation (autosomal dominant inheritance, increased plasma prothrombin concentration)
- Antiphospholipid syndrome (acquired, associated with venous and arterial thrombosis)
- Blood transfusion
- Long travel
- Nonthrombotic PE etiologies
  - Fat embolus
  - Tumor embolus
  - Bone marrow embolus
  - Air embolism
  - Amniotic fluid embolus (when fetal membranes leak or tear at the placental margin)
  - Cement and bony fragment embolism (after total hip or knee replacement)
  - Hair, talc, or cotton embolism (from injection drug users who inject themselves with substances)
- If upper extremity DVT, consider other potential causes
  - Cancer
  - Central venous catheter
  - Pacemaker
  - Implantable cardioverter-defibrillator

DIAGNOSTIC TESTS

LABS

- CBC
  - Evaluate for polycythemia, anemia, thrombocytosis, and leukocytosis
- CMP
  - Evaluate the patient's kidney function, electrolytes, and hepatic function
- Age-adjusted D-dimer
  - Calculate the patient's simplified Wells' criteria score (see Diagnostic Scoring Systems and Diagnostic Algorithm sections) to know when ordering a D-dimer is indicated
  - Sensitivity
    - > 80% for DVT
    - > 95% for PE
  - Not a specific test; can be elevated in
    - MI
    - Pneumonia
    - Sepsis
    - Cancer
    - Postoperative states
    - Second or third trimester of pregnancy
  - Used mostly to help rule out DVT or PE in the ED
  - Rarely has a useful role in hospitalized patients because levels are frequently elevated due to systemic illness
- Troponin
  - Elevated with submassive and massive PEs from RV microinfarction (see Pathophysiology section)
- BNP
  - Elevated with submassive and massive PEs from RV stretching
- PT, PTT, and INR
  - To measure if bleeding diathesis is present
- Hypercoagulable panel
  - Rarely ordered; not suggested except in very specific circumstances
- ABG depending on level of respiratory distress

IMAGING

- ECG
  - The most common finding of PE on ECG is sinus tachycardia

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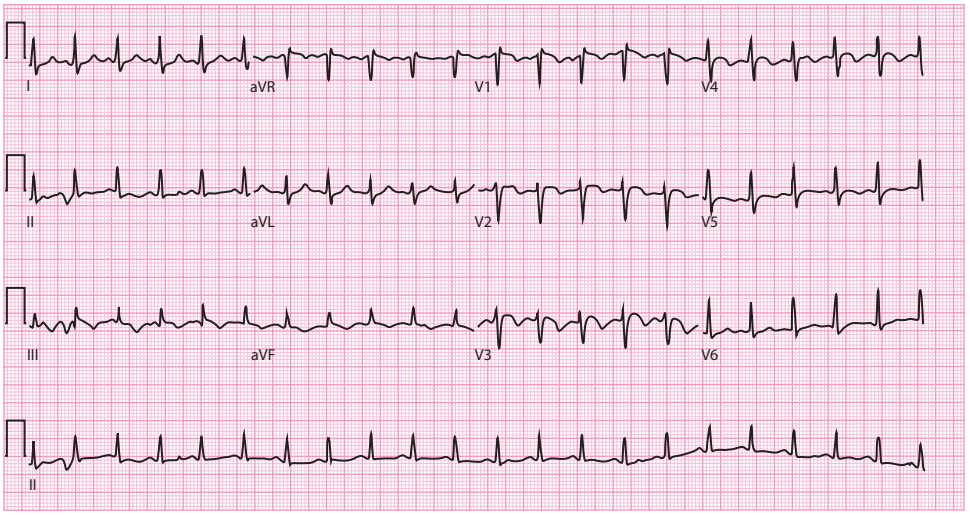

FIGURE 18-1 ECG with both the $S_1Q_3T_3$ sign and T-wave inversions in leads V_1–V_4—typical of an anatomically large pulmonary embolism. (Reproduced with permission from Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - $S_1Q_3T_3$ (Fig. 18-1), RV strain (ST depression in II and T wave inversion in anterior precordial leads [V_1-$_4$]), acute right bundle branch block, and right axis deviation can occur
    - Also, look for signs of ischemia, ventricular hypertrophy, and pericarditis to rule out other conditions
- CXR
    - Most commonly the CXR is normal in PE
    - In a patient who has a normal CXR in the presence of hypoxemia, consider PE
    - Westermark's sign (focal oligemia)
    - Hampton's hump (peripheral wedge-shaped density usually at the pleural base)
    - Palla's sign (enlarged right descending pulmonary artery)
    - Also evaluates for other conditions causing dyspnea, such as infections, HF, pleural effusions, etc.
- Venous Doppler ultrasonography
    - Initial test for DVT
    - If positive for a DVT (loss of vein compressibility or direct visualization of the thrombus), begin anticoagulation immediately
    - You can mostly assume someone has a PE if they have dyspnea, tachypnea, and tachycardia with a positive venous Doppler for DVT
- CT angiography (CTA) of the chest
    - Imaging test of choice to diagnose PE if no contraindications such as AKI, late-stage CKD, or contrast allergy
    - May show RV enlargement and dysfunction (if present, higher likelihood of death within 30 days)
    - Perform if high likelihood of PE based on simplified Wells' criteria or an elevated age-adjusted D-dimer
    - If no PE is present, this may reveal an alternative diagnosis
- Lung ventilation/perfusion scan
    - Second-line diagnostic test for PE; performed if there is severe AKI, CKD, or contrast allergy
    - A high-probability scan for PE is one that shows ≥ 2 segmental perfusion defects in the presence of normal ventilation
    - If negative, it is safe to assume no PE if low clinical suspicion as well
    - Unfortunately, most patients have a nondiagnostic (intermediate read for PE probability) scan, and as many as 40% of patients with high clinical suspicion for PE but a low-probability ventilation/perfusion scan do in fact have a PE
- Transthoracic echocardiogram (TTE) and/or transesophageal echocardiogram (TEE)
    - TTE is not reliable for acute PE because most patients with PE have a normal TTE
    - Is a good test to exclude other mimics of PE, such as acute MI, and tamponade
    - May show McConnell's sign (hypokinesis of RV free wall with normal or hyperkinetic motion of the RV apex)

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- TEE is an alternative for unstable patients when CT angiography cannot be performed
- TEE can visualize saddle, right main, or left main thrombosis causing a massive PE

- MRI
  - If ultrasound for DVT is equivocal, MRI venography with gadolinium is a good choice to diagnose a DVT
  - MR pulmonary angiography may detect large proximal PEs but is not reliable for smaller segmental and subsegmental PEs
- Pulmonary angiography
  - Definitive study, but virtually replaced by CTA for diagnostic purposes
  - Perform if CTA was technically unsatisfactory and if catheter-directed thrombolysis or embolectomy is planned

DIAGNOSTIC SCORING SYSTEMS

- Scoring systems are used in the evaluation of VTE to reduce unnecessary testing

SIMPLIFIED WELLS' CRITERIA FOR DVT

- The following are all worth 1 point—but an alternative diagnosis at least as likely is –2 points:
  - Active cancer (treatment ongoing or within 6 months)
  - Paralysis, paresis, or recent immobilization of lower extremities
  - Recently bedridden for ≥ 3 days or major surgery within past 12 weeks
  - Localized tenderness along distribution of deep venous system
  - Entire leg swelling
  - Calf ≥ 3 cm larger than the other calf (measured 10 cm below the tibial tuberosity)
  - Pitting edema confined to symptomatic leg
  - Collateral superficial veins (nonvaricose)
  - Previous DVT
  - Alternative diagnosis at least as likely as DVT (–2 points)
- Score ≤ 0 → low prevalence (5%) → perform age-adjusted D-dimer testing
- Score 1 or 2 → moderate prevalence (17%) → perform age-adjusted D-dimer testing
- Score ≥ 3 → high prevalence (53%) → perform Doppler ultrasonography testing

SIMPLIFIED WELLS' CRITERIA FOR PE

- Alternative diagnosis less likely than PE (3 points)
- Clinical signs of DVT (leg swelling, pain with palpation) (3 points)
- Immobilization (bed rest ≥ 3 days) or surgery within 4 weeks (1.5 points)
- Heart rate > 100 beats/min (1.5 points)
- Prior PE or DVT (1.5 points)
- Active cancer (1 point)
- Hemoptysis (1 point)
- Score interpretation
  - < 2 → 1.3% prevalence of PE, low-risk → use Pulmonary Embolus Rule-out Criteria score (below) to determine if age-adjusted D-dimer testing should measured
  - 2–6 → 16.2% prevalence of PE, moderate-risk → perform age-adjusted D-dimer testing
  - > 6 → 37.5% prevalence of PE, high-risk → perform CT angiography

PULMONARY EMBOLUS RULE-OUT CRITERIA (PERC)

- Eight criteria—if the patient fulfills all eight and has a low probability of a PE (from Wells' score), then no further testing should be performed. Patients not fulfilling all eight criteria should have an age-adjusted D-dimer ordered.
  - Age < 50 years
  - Heart rate < 100 beats/min
  - SpO_2 ≥ 95%
  - No hemoptysis
  - No estrogen use
  - No prior DVT or PE
  - No unilateral leg swelling
  - No surgery/trauma requiring hospitalization within prior 4 weeks

DIAGNOSTIC ALGORITHMS OF PE AND DVT

- Figures 18-2 and 18-3 describe the diagnostic approach and basic management strategies for suspected DVT and PE

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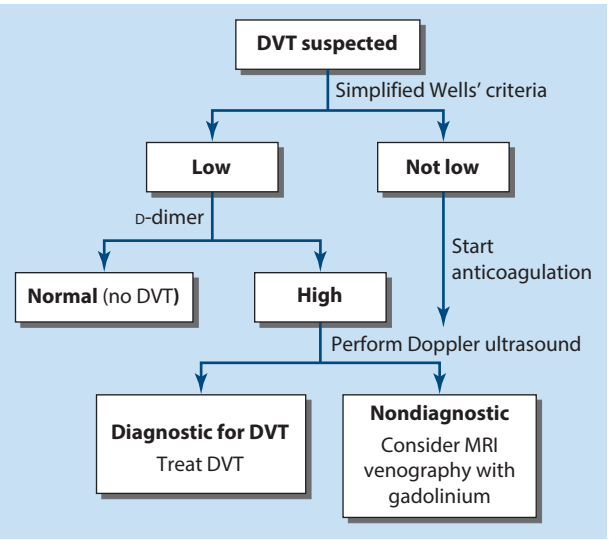

FIGURE 18-2 Diagnostic approach and evaluation of DVT. (Reproduced with permission from Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

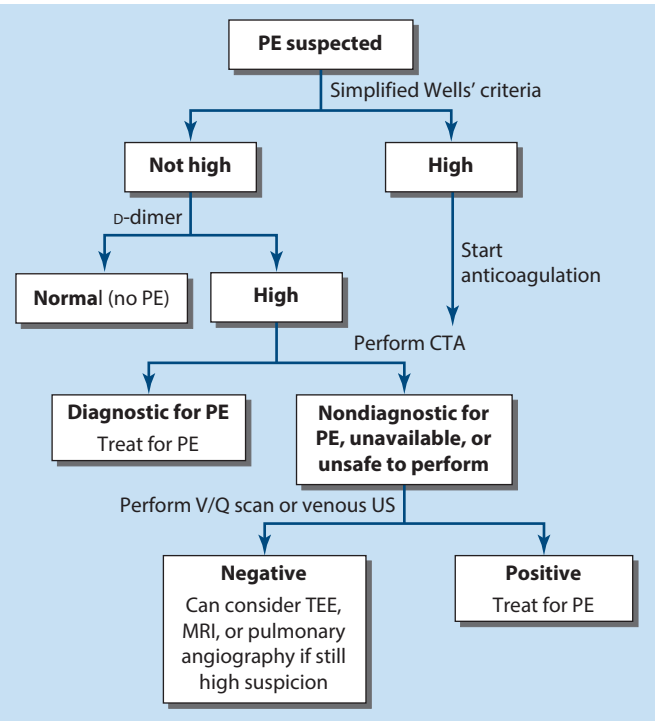

FIGURE 18-3 Diagnostic approach and evaluation of PE. CTA, CT angiography; TEE, transesophageal echocardiogram; US, ultrasound; V/Q, ventilation-perfusion. (Reproduced with permission from Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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MANAGEMENT

MANAGEMENT OF PE

Most patients will be admitted to the hospital for management and observation if they are diagnosed with a PE in the ED. However, a subset of patients can be discharged home from the ED with anticoagulation (usually DOAC therapy). The simplified Pulmonary Embolism Severity Index (PESI) score is used in the ED to decide if a patient should be admitted or discharged with a new PE.

RISK STRATIFICATION

- Simplified Pulmonary Embolism Severity Index (PESI) score
  - Each of the following receives 1 point if present
    - Age > 80 years
    - History of cancer
    - Chronic cardiopulmonary disease (combined variable history of HF and history of chronic lung disease)
    - Pulse ≥ 110 beats/min
    - Systolic BP < 100 mm Hg
  - Patients with a score ≥ 1
    - Have a higher risk of complications
    - Should be admitted to the hospital for management and observation
  - Patients with a score of 0
    - Can usually be discharged from the ED with a DOAC to home (also dependent on stable living and socioeconomic situation)
- Figure 18-4 describes the initial risk stratification and management of diagnosed PEs
- For patients needing hospitalization, the first step is to determine if the PE is hemodynamically stable versus unstable (submassive and massive)
  - Unstable
    - Hypotension with systolic BP < 90 mm Hg
    - A drop of the systolic BP > 40 mm Hg from their baseline for > 15 min, or
    - Requiring vasopressor or inotropic support
  - Stable: does not meet the criteria for unstable
- Risk-stratify the severity for the initial management plan
  - Low-risk → anticoagulation (or rarely, insertion of an inferior vena cava filter)
  - Submassive → anticoagulation with interventional radiology (IR) consult for possible IR-guided thrombolysis (individualize therapy)
  - Massive → anticoagulation with IR consult for fibrinolysis, embolectomy, surgery, or systemic recombinant tissue plasminogen activator (alteplase)

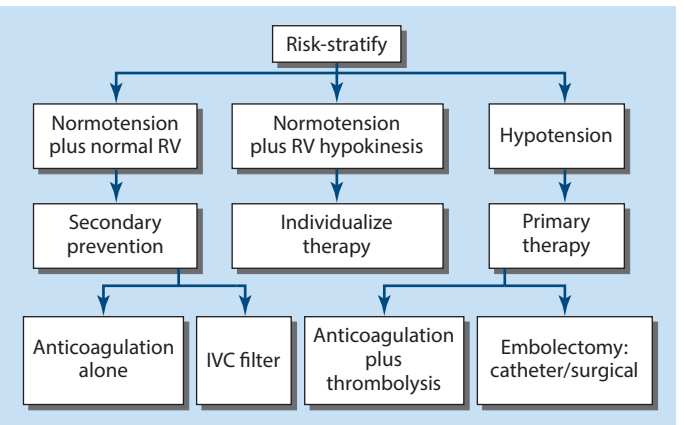

FIGURE 18-4 Acute management of pulmonary thromboembolism. IVC, inferior vena cava. (Reproduced with permission from Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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UNSTABLE (SUBMASSIVE AND MASSIVE) PE

- Supplemental oxygen to maintain SpO_2 > 92%
- In hemodynamically unstable PE, there is evidence of RV strain on portable imaging (transthoracic echocardiogram, for example, showing McConnell's sign) with systemic arterial hypotension and possibly obstructive shock
- Start an unfractionated heparin infusion
- Stabilize the patient with fluid boluses, inotropes/vasopressors (either norepinephrine or dobutamine is a first-line agent), and intubation if needed
  - Excessive fluids can exacerbate RV wall stress causing ischemia → worsening of LV compliance and filling → worsened interventricular septal shifting toward the LV
  - There is a low threshold to start inotropes/vasopressors (norepinephrine or dobutamine)
- Consider extracorporeal membrane oxygenation (ECMO) if norepinephrine or dobutamine does not improve the patient's shock
- If fibrinolysis is *not* contraindicated
  - Discontinue anticoagulation, administer a thrombolytic agent, and then resume anticoagulation
  - Recombinant tissue plasminogen activator (tPA) (alteplase) 100-mg IV infusion over 2 h (the sooner it is administered, the more effective it is)
    - Rapidly reverses right HF, resulting in a lower mortality rate by
      - Dissolving the pulmonary artery–obstructing clot
      - Preventing release of serotonin and other vasoconstrictors that cause pulmonary hypertension
      - Lysing the source of the thrombus in the pelvis/deep veins to reduce the likelihood of recurrent PE
    - Alteplase has an overall major bleeding rate of 10%, with a 2–3% risk of intracranial hemorrhage
  - The only approved indication for tPA in PE is a massive PE; it remains controversial in submassive PE
    - For patients with submassive PE, low-dose tPA plus anticoagulation reduced the incidence of pulmonary hypertension and of the composite outcome of pulmonary hypertension or recurrent PE compared with anticoagulation alone
  - Contraindications to fibrinolysis
    - Intracranial disease
    - Recent surgery
    - Trauma
- If fibrinolysis *is* contraindicated, perform catheter-directed therapy
  - Three modalities (a multidisciplinary team decides the optimal strategy)
    - Pharmacologic: low-dose continuous infusion of tPA
    - Mechanical: percutaneous thrombectomy
    - Pharmacomechanical: low-energy ultrasound-facilitated low-dose thrombolysis
- Surgical pulmonary embolectomy
  - Interest in surgical embolectomy has resurfaced due to the substantial risk of major hemorrhage with systemic fibrinolysis
  - More rapid referral to surgery before the onset of irreversible multisystem organ failure, improved surgical technique, and utilization of ECMO have increased the survival rate of surgical pulmonary embolectomy and have markedly improved RV function
- After completing the above steps and stabilizing the patient, proceed to stable PE management as described below

STABLE (LOW-RISK AND SUBMASSIVE) PE

- *The mainstay of treatment is anticoagulation*
- There are three major strategies of anticoagulation
  - Oral anticoagulation monotherapy with DOACs
  - Unfractionated heparin (UFH), low-molecular-weight-heparin (LMWH, e.g., enoxaparin), or fondaparinux either as monotherapy or more often "bridged" to warfarin
  - Parenteral anticoagulation, switched after 5 days to dabigatran or edoxaban
- *DOACs are now the preferred treatment strategy*
  - Apixaban and rivaroxaban are oral agents that
    - Do not require bridging
    - Do not require lab monitoring
    - Act within hours of ingestion
    - Have a few drug–drug interactions
    - Do not require limitation of green leafy vegetables
  - DOACs are contraindicated in pregnant or breastfeeding patients
  - DOACs can be prescribed at the beginning of a hospitalization for PE without needing UFH or LMWH first (especially if a stable low-risk PE)

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- Apixaban 10 mg PO bid for 1 week, then 5 mg bid
  - In patients with ≥ 2 of the following, decrease the maintenance dose from 5 mg bid to 2.5 mg bid
    - Age > 80 years
    - Body weight < 60 kg
    - Serum creatinine > 1.5 mg/dL
- Rivaroxaban 15 mg PO bid for 3 weeks, then 20 mg daily with dinner
  - For creatinine clearance (CrCl) 15–50 mL/min, reduce the maintenance dose from 15 mg daily to 10 mg daily
- Dabigatran or edoxaban
  - Bridge with UFH, LMWH, or fondaparinux for 5 days, then stop and switch to either dabigatran or edoxaban
  - Dabigatran dosage depends on CrCl
    - For CrCl > 30 mL/min, 150 mg PO bid
    - For CrCl 15–30 mL/min, reduced to 75 mg PO bid
  - Edoxaban
    - Dose: 60 mg daily
    - If CrCl 15–50 mL/min, reduce dose to 30 mg PO daily
- Several studies have shown that DOACs, such as apixaban, dabigatran, and rivaroxaban, are noninferior in terms of VTE recurrence risk and VTE mortality rate and have lower/similar bleeding risks compared with warfarin [1,2]
- DOACs are now mostly recommended for cancer-associated VTE (prior recommendation was to use LMWH)

- UFH, LMWH, or fondaparinux as monotherapy or a bridge to warfarin
  - UFH infusion is sometimes used for hospitalized patients with stable PE if they have markers of elevated-risk PE (such as elevated cardiac biomarkers and tachycardia) without evidence of RV dysfunction
    - Typically dosed to achieve a target activated partial thromboplastin time of 60–80 s (many hospitals have a heparin protocol)
    - Can be turned off quickly if patient worsens clinically, allowing drug levels to exit the system rapidly in case a patient needs fibrinolysis or a catheter-directed intervention
  - LMWH (e.g., enoxaparin)
    - Dosage: 1 mg/kg bid subcutaneous (adjust or do not use in impaired renal function)
    - No lab monitoring required
  - Fondaparinux
    - Dosage is weight-based, subcutaneous, given daily, and adjusted for impaired renal function
    - No lab monitoring required
  - Warfarin
    - Indicated in patients who are pregnant or have antiphospholipid syndrome
    - Must be overlapped (bridged) with UFH, LMWH, or fondaparinux to avoid paradoxical clotting
    - Once an INR target of 2.5 has been achieved, the other agent can be discontinued (usually at 5–7 days)
    - Dosing depends on what will achieve and maintain a therapeutic INR (consult pharmacy)
    - Major bleeding has been associated with warfarin, even at therapeutic INR levels
- Inferior vena cava (IVC) filter
  - The two principal indications for IVC filter placement include
    - Active bleeding present, which precludes the use of anticoagulation
    - Recurrent VTE despite adequate anticoagulation
  - A soft indication for IVC filters includes prevention of recurrent PE in patients who are not candidates for anticoagulation
  - There is an increased rate of DVTs after IVC filter placement
  - Retrievable filters can be placed and removed for specific indications
    - Patients with an anticipated temporary bleeding disorder
    - Patients at temporary high risk of PE, such as those undergoing surgery with previous perioperative PE
- Pulmonary thromboendarterectomy
  - Chronic thromboembolic pulmonary hypertension (CTEPH) develops in ~2% of acute PE patients
  - Patients with PE who initially have pulmonary hypertension should be followed up at 6 weeks and possibly 6 months with repeat transthoracic echocardiography to determine the status of the pulmonary hypertension
  - Patients impaired by dyspnea from CTEPH should be considered for pulmonary thromboendarterectomy

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MANAGEMENT OF LOWER EXTREMITY DVT

- Primary therapy includes anticoagulation with agents listed under Stable (Low-Risk) PE and/or inferior vena cava (IVC) filter placement
  - Anticoagulation regimens are as listed under PE
  - IVC filter same as for PE
    - The addition of IVC filter placement to routine anticoagulation for patients with proximal DVT leads to a 4% absolute reduction of PE risk. The modest benefit of IVC filter placement was offset by doubling the rate of recurrent DVT at 2 years.
- Secondary therapy consists of clot dissolution or clot extraction with catheter-directed therapy if advanced therapy beyond anticoagulation is warranted
  - This is reserved for patients with extensive iliofemoral DVT to help prevent postthrombotic syndrome
    - After 2-year follow-up, there was a trend toward less postthrombotic syndrome among patients with iliofemoral DVT (compared with only femoral DVT) who received catheter-directed thrombolysis compared with anticoagulation alone
- Prescribe below-the-knee graduated compression stockings (30–40 mm Hg or 20–30 mm Hg to lessen patient discomfort) replaced every 3–6 months if swelling was present on diagnosis

MANAGEMENT OF UPPER EXTREMITY DVT

- As the rate of peripherally inserted central catheters has increased, so has the rate of upper extremity DVTs
- If truly a deep VTE, anticoagulation is warranted
- If superficial, treat with supportive care

VTE IN MALIGNANCY

- Originally, the CLOT trial recommended that patients with cancer should be treated with LMWH (e.g., dalteparin, enoxaparin) compared to warfarin
  - In patients with cancer, dalteparin reduced VTE recurrence without increasing bleeding risk or deaths compared to warfarin [3]
  - Patients with GI cancer are generally treated with LMWH or apixaban rather than other DOACs due to lower bleeding risk
- However, recent trials are now suggesting that DOACs, such as apixaban, rivaroxaban, and edoxaban, are noninferior to LMWH
  - Oral rivaroxaban compared to dalteparin for the treatment of cancer-associated VTE showed a reduction in the 6-month VTE recurrence rate, with similar major bleeding rates [4]
  - Oral edoxaban was noninferior to dalteparin with respect to the composite outcome of recurrent VTE or major bleeding; the rate of recurrent VTE was lower, but the rate of major bleeding was higher with edoxaban than with dalteparin [5]
- Overall, which agent to use for cancer-associated VTE depends on the patient and the patient's bleeding risks
- Treatment duration is usually indefinite or until cancer is cured

DURATION OF ANTICOAGULATION

- There are changing recommendations over the treatment duration for VTEs
- Currently, extended oral anticoagulation without an end date should be considered for patients with a first episode of VTE and
  - No identifiable risk factor
  - A persistent risk factor (e.g., inflammatory bowel disease, autoimmune disease)
  - A minor transient or reversible risk factor (intermediate risks listed below)
- Risk of recurrent VTE after discontinuing anticoagulation based on patient factors
  - Low risk (< 3% per year)
    - Major surgery, or
    - Trauma-associated VTE
  - Intermediate risk (3–8% per year)
    - Minor surgery
    - Hospitalized with acute medical illness
    - Pregnancy or estrogen use
    - Long-distance flight
    - Inflammatory bowel disease
    - Autoimmune disease, or
    - No identifiable risk factor associated with VTE
  - High risk (> 8% per year, i.e., major risk factors)
    - Active cancer, or
    - Antiphospholipid syndrome-associated VTE

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- If extended therapy is not warranted (i.e., a first VTE without a high risk or major persistent risk factor identified), treatment duration is 3–6 months
- Discussion with the patient's primary care clinician near the prespecified end duration of anticoagulation should occur to see if longer therapy should continue
    - Factors include the risk of bleeding versus risk of recurrence
    - However, the risk of recurrence is expected to be similar if anticoagulants are stopped after 3 months compared with longer treatment periods (e.g., 12–24 months)

COMPLICATIONS

- PE
    - Cardiac arrest/death
    - Shock
    - Dysrhythmias
    - Pulmonary infarction
    - Pleural effusion
    - Post-PE syndrome
    - Chronic thromboembolic pulmonary hypertension
- DVT
    - PE
    - Cerebrovascular accident from paradoxical embolus
    - Postthrombotic syndrome
        - Also known as chronic venous insufficiency
        - Damage to the venous valves of the leg worsens quality of life by causing ankle or calf pain especially after prolonged standing (Fig. 18-5)



FIGURE 18-5 Skin ulceration in the medial malleolus from postthrombotic syndrome of the leg. (Used with permission from Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- Recurrent DVT
- Phlegmasia alba dolens
  - Patient with a swollen and white leg because of early compromise of arterial flow secondary to extensive DVT
- Phlegmasia cerulen dolens
  - A precursor of frank venous gangrene
  - Characterized by severe swelling and cyanosis and blue discoloration of the extremity

- Heparin-induced thrombocytopenia (HIT)
  - Usually occurs 4–5 days after heparin use
  - Replace heparin with argatroban or bivalirudin as soon as suspected and send a HIT panel and serotonin release assay
  - For a full discussion, see **Chap. 33**
- Bleeding associated with anticoagulation use
  - The most serious adverse effect of anticoagulation is hemorrhage
    - Administer protamine sulfate if bleeding is associated with heparin or LMWH
    - Administer idarucizumab if associated with dabigatran
    - Administer prothrombin complex concentrate if bleeding is associated with a severe bleed from warfarin
      - Minor bleeding can be managed with either fresh frozen plasma and/or IV/PO vitamin K
      - Alternatively, can stop the warfarin and observe depending on the bleed and clinical context

PROGNOSIS

- PE-related mortality in the United States decreased from 6 per 100,000 in 2000 and plateaued at ~4.5 per 100,000 in 2017
  - In contrast, Europe's age-standardized annual PE-related mortality rate has continued to decrease linearly since 2000
- In the United States, PE-related mortality is increasing among young and middle-aged adults
- The median age at death from PE decreased from 73 years in 2000 to 68 years in 2018
- During this period, the annual PE mortality was up to 50% higher in Black persons compared with White persons
- The 30-day mortality rate is higher among patients hospitalized with PE from disadvantaged socioeconomic areas

PATHOPHYSIOLOGY

- Inflammation is now recognized as a trigger of acute VTE (see Risk Factors section for medical illnesses linked to precipitate VTE)
- Virchow's triad (venous stasis, hypercoagulability, and endothelial injury), usually with an inflammatory trigger, leads to recruitment of activated platelets
  - Proinflammatory mediators are released → platelet aggregation and activation occur → microparticles are released that contain proinflammatory mediators that bind neutrophils releasing their nuclear material to form web-like extracellular networks called *neutrophil extracellular traps* that contain histones and stimulate platelet-dependent thrombin generation
  - Venous thrombi form in this environment of stasis, low oxygen tension, and upregulation of proinflammatory genes
- Embolization from DVT → to the vena cava → right atrium → right ventricle → lodges in the pulmonary artery, causing acute PE
  - A patent foramen ovale may allow an embolization from the leg into the arterial circulation (such as the brain), causing a paradoxical emboli and ischemic stroke
- PE (**Fig. 18-6**)
  - Arterial hypoxemia and an increased A–a gradient occur
  - Increased anatomic and physiologic dead space occurs, causing ventilation of the affected area without perfusion
  - Increased pulmonary vasculature resistance occurs from vascular obstruction and/or platelet secretion of vasoconstricting neurohumoral agents such as serotonin
  - Vasoactive mediators are released, leading to ventilation-perfusion mismatch at sites remote from the embolus, accounting for the discordance between a small PE and a large A–a gradient
  - Alveolar hyperventilation occurs from stimulation of irritant receptors
  - Increased airway resistance occurs from constriction of airways distal to the bronchi
  - Pulmonary compliance decreases due to lung edema, lung hemorrhage, or loss of surfactant

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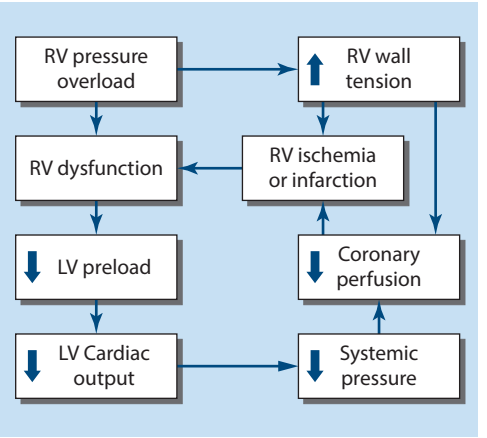

FIGURE 18-6 Pathophysiology of PE. (Reproduced with permission from Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Pulmonary hypertension (from obstruction and neurohumoral mediator release) → RV wall tension increases → RV microinfarction, dilation, and dysfunction → increased BNP from RV stretching
- The interventricular septum bulges into and compresses an intrinsically normal LV (McConnell's sign)
- Compression of the right coronary artery → ischemia → RV microinfarction → RV MI → increased cardiac biomarkers
- Diastolic LV dysfunction impairs LV filling → potential for a reduction in LV cardiac output → hypotension → circulatory collapse and death

RISK FACTORS

- Virchow's triad
  - Venous stasis: bed rest, HF, air travel, AF
  - Endothelial injury: trauma, surgery, prior DVT, inflammation
  - Hypercoagulability: malignancy, factor V Leiden mutation, prothrombin gene mutation, antiphospholipid syndrome
- Inflammation risk factors and medical illnesses that are linked to precipitate VTE
  - Ulcerative colitis and Crohn's disease
  - Rheumatoid arthritis
  - Psoriasis
  - Type 2 diabetes mellitus
  - Obesity/metabolic syndrome and sedentary lifestyle (a Japanese study found that each 2-h per day increment of watching television is associated with a 40% increased likelihood of fatal PE)
  - Hypercholesterolemia, especially elevated LDL
  - Lipoprotein(a)
  - Pneumonia
  - Acute coronary syndrome
  - Acute stroke
  - Cigarette smoking
  - Sepsis and septic shock
  - Erythropoiesis-stimulating agents
  - Blood transfusions
  - Malignancy
    - Malignancies that are higher risk for VTE: gastrointestinal, pancreatic, stomach, colorectal, diffuse large B cell lymphoma
    - Risk factors for patients with malignancy that increase their chance of VTE: presence of central venous catheters, blood transfusions, erythropoietic-stimulating agent use, chemotherapy, surgery
- Prior history of VTE
- Age > 60
- Long-distance air or motorcar travel

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- Pregnancy and postpartum state
- Hypertension
- COPD or chronic lung disease
- Chronic HF
- Estrogen use (birth control, postmenopausal hormone replacement therapy)
- Nephrotic syndrome (loss of antithrombin III in urine), CKD
- Trauma and surgery

ADMITTING ORDERS

- Admit to floor, ICU if shock/severe cardiopulmonary disease
- Diagnosis: DVT or PE
- Condition: guarded, critical
- Vital signs: q4h, call clinician for heart rate > 100 beats/min or systolic BP < 100 mm Hg
- Nursing: oxygen by nasal canula to maintain SpO_2 > 92%
- Diagnostic tests
  - CBC
  - CMP
  - Troponin
  - BNP
  - PT/INR
  - Age-adjusted D-dimer
  - ECG
  - CXR
  - CT angiography of the chest, lower extremity Doppler ultrasound, and transthoracic echocardiogram, if appropriate
- Medications
  - Apixaban 10 mg PO bid or rivaroxaban 15 mg PO bid
  - Enoxaparin 1 mg/kg subcutaneously bid, or
  - Heparin infusion

DISCHARGE INFORMATION

- Educate about anticoagulation adherence and its risks
- If discharged on warfarin, schedule nutrition consult before discharge for vitamin K diet education, as well as scheduled INR checks and warfarin clinic management
- Prescribe 30–mm Hg compression stockings for DVT associated with lower extremity swelling
- Follow up with primary care clinician
- In patients with PE and initial pulmonary hypertension, recheck echocardiogram at 6 weeks, and possibly at 6 months, to evaluate pulmonary hypertension status

CASE ANSWERS

1. This patient presented with clinical signs and symptoms of a DVT that was confirmed with Doppler imaging. Given that the patient's simplified Wells' criteria score for DVT and PE were high-risk (5 and 8.5, respectively), a D-dimer was not necessary prior to imaging studies. While waiting for the CT angiography (CTA), a CBC, CMP, BNP, and troponin should be ordered to assess for other causes of dyspnea (e.g., pneumonia with a leukocytosis or anemia), as well as to risk-stratify how severe a PE is if diagnosed (via cardiac biomarker elevations).
2. This patient with a normal BP from his baseline and elevated cardiac biomarkers without RV strain on imaging has a submassive PE. In order to determine if the patient should be admitted, the simplified Pulmonary Embolism Severity Index (PESI) score should be calculated. This patient has two qualifying factors (active cancer and pulse ≥ 100 beats/min), making his risk of complications high. Therefore, admission to the hospital for observation and management is recommended.
3. After the patient's Doppler ultrasound reveals a DVT, anticoagulation therapy should be started, even before the CTA results. Oxygen should be administered if his SpO_2 drops to < 92%. The choice of anticoagulant in DVT with submassive PE is starting a DOAC, administering enoxaparin, or initiating a continuous infusion of unfractionated heparin. As these patients can decompensate, many clinicians will initially begin an infusion of unfractionated heparin in case the patient needs an urgent intervention (e.g., systemic fibrinolysis or catheter-directed alteplase). In patients with malignancy related VTE who remain stable, transitioning to a DOAC is the preferred therapy. In low-risk PEs, starting with a DOAC is the preferred choice unless there are contraindications.

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LANDMARK TRIALS

[1] Piazza G et al. Apixaban for extended treatment of provoked venous thromboembolism. N Engl J Med 393:1166, 2025. [PMID: 40888734]
- *Summary:* In patients with VTE who have completed 6–12 months of anticoagulation, long-term apixaban treatment reduces recurrent VTE or all-cause mortality without increasing rates of major bleeding.

[2] EINSTEIN-PE investigators et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 366:1287, 2012. [PMID: 22449293]
- *Summary:* Among patients with acute PE, rivaroxaban is noninferior to warfarin in preventing recurrent VTE and is associated with similar bleeding rates.

[3] Lee AYY et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349:146, 2003. [PMID: 12853587]
- *Summary:* In patients with cancer, dalteparin reduced VTE recurrence without increasing bleeding risk or deaths compared with warfarin. (Emerging evidence shows that DOACs are just as effective.)

[4] Young AM et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). J Clin Oncol 36:2017, 2018. [PMID: 29746227]
- *Summary:* Oral rivaroxaban compared with dalteparin for the treatment of cancer-associated VTE showed a reduction in the 6-month VTE recurrence rate, with similar major bleeding rates.

[5] Raskob GE et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378:615, 2018. [PMID: 29231094]
- *Summary:* Oral edoxaban was noninferior to dalteparin with respect to the composite outcome of recurrent VTE or major bleeding. The rate of recurrent VTE was lower, but the rate of major bleeding was higher with edoxaban than with dalteparin.

FURTHER READING

- Bauer KA et al. Treatment of venous thromboembolism in patients with malignancy. UpToDate. https://www.uptodate.com/contents/anticoagulation-therapy-for-venous-thromboembolism-lower-extremity-venous-thrombosis-and-pulmonary-embolism-in-adult-patients-with-malignancy. Accessed January 16, 2026.
- Goldhaber SZ. Deep-venous thrombosis and pulmonary thromboembolism, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- McGee S. DVT, in *Evidence-Based Physical Diagnosis*, 6th ed. Amsterdam, Elsevier, 2026.
- McGee S. Pulmonary embolism, in *Evidence-Based Physical Diagnosis*, 6th ed. Amsterdam, Elsevier, 2026.

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19 Acute Coronary Syndrome

KEY POINTS

1. Acute coronary syndrome (ACS) encompasses both acute MI with ST-segment elevation (STEMI) and those with non–ST-segment elevation acute coronary syndrome (NSTE-ACS). These conditions result in an acute change in myocardial oxygen demand or supply. Cardiac ischemia and necrosis develop over time, causing damage to the cardiac muscle and electrical system.
2. Chest pain that is dull or crushing is the most common symptom of ACS. The pain may radiate to the arms or jaw, and it may be associated with dyspnea and diaphoresis. Exam findings are often nonspecific in ACS but may include tachycardia, hypotension, and an S_3 gallop.
3. An ECG is vital in making a prompt diagnosis of ACS. The ECG should be performed as soon as the patient has first medical contact. A high-sensitivity troponin, CBC, BNP, D-dimer, PT/PTT/INR, and CXR should be performed as quickly as possible, but the results of those tests should not delay management in patients with STEMI.
4. Both NSTE-ACS and STEMI patients should receive aspirin, 325 mg, as well as anti-ischemic therapy with nitroglycerin, β-blockers, and potentially morphine. In the case of NSTE-ACS, anticoagulation with heparin and a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel) should be added, and a decision should be made to pursue either an early invasive strategy (with percutaneous intervention [PCI]) or medical therapy alone. In STEMI patients, anticoagulation and emergent reperfusion therapy via primary PCI (preferred) or fibrinolysis is necessary.
5. Acute HF with cardiogenic shock and life-threatening dysrhythmias may develop in patients with ACS. Mechanical complications, such as free wall and papillary muscle rupture, may occur. The mortality rate after NSTE-ACS and STEMI is 5–15% in the first year.

EPIDEMIOLOGY & DEFINITIONS

Ischemic heart disease (IHD) causes more death and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the United States, where 20.5 million persons have IHD. Approximately 3–4% of the population has sustained an MI. Primary prevention has delayed the disease to later in life across socioeconomic groups. Data have shown a decline in the rate of deaths from IHD, about half of which is attributable to treatments and half to prevention by risk factor modification. IHD is a major contributor to the number of disability-adjusted life-years (DALYs) experienced globally.

Acute coronary syndrome (ACS) encompasses a group of conditions representing myocardial ischemia precipitated by an acute change in myocardial oxygen demand or supply. Patients are categorized into two groups initially to facilitate evaluation and management:

1. Patients with STEMI
2. Patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS)

Patients with *unstable angina* are included in the NSTE-ACS group.

Figure 19-1 describes the spectrum of ACS. The incidence of NSTE-ACS is rising due to the increasing burden of obesity, diabetes, and CKD in an aging population, whereas the incidence of STEMI is declining because of the greater use of aspirin and statins and less smoking. Stable angina differs because predictable exertion brings it on; it is not precipitated by an acute event, and brief rest relieves the pain in the setting of a stable plaque. Myocardial injury occurs when there is evidence of elevated cardiac troponin levels with at least one value above the 99th percentile; it is termed *acute myocardial injury* if there is a rise and/or fall of troponin levels. This can occur in many settings, not always in the face of ischemia or infarction.

CLINICAL VIGNETTE

A 70-year-old man presents to the ED after awakening from sleep with crushing substernal chest pain for the past hour. He started sweating in the car on his way to the ED. The pain radiates to both arms and his lower jaw. On examination, he is afebrile, heart rate is 110 beats/min, respiratory rate is 20 breaths/min, BP is 152/84 mm Hg, and oxygen saturation is 88% on room air. His hand is clutched in a fist in front of his chest. You note bilateral diagonal earlobe creases. The

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triage nurse hands you his ECG, which shows ST elevations of 0.4 mm in leads V_1–V_4. He has no other known health conditions. You administer aspirin, 325 mg, and sublingual nitroglycerin, three times spaced out 5 min apart, but he does not experience pain relief. The closest percutaneous intervention–capable hospital is 150 min away.

GUIDING QUESTIONS

1. What is this patient's diagnosis?
2. What medications would you administer to this patient immediately?
3. What reperfusion strategy would you choose for this patient?

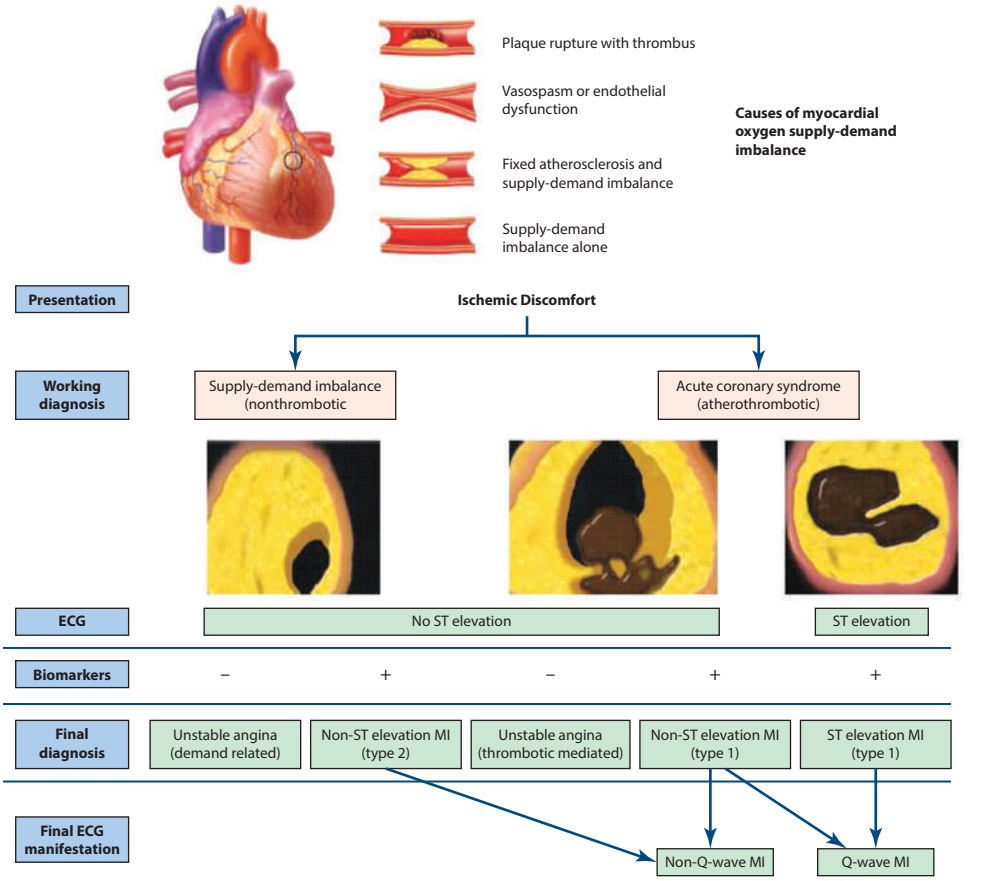

FIGURE 19-1 Acute coronary syndromes. Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (*right*) or subtotally occlusive thrombus (*middle*). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority ultimately develop a Q wave on the electrocardiogram (ECG; Q-wave MI), while a minority do not develop Q waves and, in the past, were said to have sustained a non–Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non–ST-segment elevation MI (NSTEMI), a distinction that is ultimately made based on the presence or absence of a biomarker of myocardial injury such as cardiac troponin detected in the blood. (Reproduced with permission from Hamm Scirica BM, Libby P, Morrow DA: ST-elevation myocardial infarction: Pathophysiology and clinical evolution, in *Braunwald's Heart Disease*, 12th ed, Libby P et al (eds). New York, Elsevier, 2022, Figure 37-1, pp 636-661.)

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HISTORY

When someone presents with chest pain, it is important to rule out life-threatening conditions (e.g., MI, aortic dissection, PE, pneumothorax, pericarditis with or without tamponade, esophageal rupture). The description of the pain helps differentiate between cardiac and noncardiac pain. It is also important to look for risk factors of ischemic heart disease such as the following:

- Age
- Sex
- Diabetes
- Hypertension
- Hyperlipidemia
- Smoking
- Family history
- Obesity

Note that certain populations (diabetics, women) are prone to more atypical presentations (e.g., nausea, abdominal pain), and the clinician must have a high clinical suspicion in order to treat the condition in a timely manner.

NSTE-ACS symptoms present as chest discomfort that is severe and has at least one of the following three features:

1. Occurrence at rest (or with minimal exertion), lasting > 10 min
2. Of relatively recent onset (i.e., within the prior 2 weeks), and/or
3. A crescendo pattern, i.e., distinctly more severe, prolonged, or frequent than previous episodes

Half of STEMI patients present with a precipitating factor, such as vigorous exercise, emotional stress, or a medical or surgical illness. Additionally, an ECG should be performed before or as the history is gathered. The physical exam similarly should be performed simultaneously with the history. If the patient is having a STEMI, you may have to perform an abbreviated history.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Typical patient is an older smoker with metabolic syndrome with chest pain that is
    - Worse with exertion
    - Possibly better with rest and nitrates
    - Left-sided/substernal
    - Nonpositional
    - Nonpleuritic
    - Characterized by radiation to the left jaw or either bilateral arms or a single arm
    - Nontender to palpation
- Chest pain description
  - Cardiac pain is usually a pressure or tightness in a retrosternal location
  - Musculoskeletal pain is usually dull or sharp and reproducible with movement or palpation
  - Pleuritic pain is usually not angina
- Location
  - Can be middle of the chest (retrosternal), upper abdomen, middle back
- Radiation
  - Typically, to left jaw and left arm; can also be to both arms or right arm
  - Radiation to the trapezius ridge is *not* seen in STEMI (helps with diagnosis of pericarditis)
  - May radiate up as high as the occipital lobe but not below the umbilicus
- Duration/severity
  - NSTE-ACS pain usually does not last as long and is not as severe as a STEMI
  - A sense of impending doom can be a sign of STEMI
- Pain at rest or with exertion?
  - Any ACS can occur at rest or with exertion
  - Stable angina more likely if pain occurs only with exertion
- Trauma to the area?
  - Usually, the pain will be musculoskeletal in nature, or if severe trauma may cause myocardial contusion or injury to the aorta
- Tenderness to palpation? Positional pain?
  - Indicative of a musculoskeletal or pleuritic condition
- Nausea and vomiting?
  - Can be an atypical presentation of ACS

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- Dyspnea?
  - With acute ischemia, LV systolic dysfunction can lead to pulmonary vascular congestion
- Sweating?
  - Severe diaphoresis is a sign of STEMI
- Syncope?
  - Can be a symptom of acute myocardial ischemia
- History of previous chest pain?
  - What has been done for it in the past?
  - How is this similar?
  - How is this different?
- Relief with nitroglycerin?
  - Can help determine if pain is more likely to be ACS
  - Nitroglycerin can also relieve the pain of diffuse esophageal spasm
- How far can you walk without stopping? What stops you?
  - An assessment of their baseline activity level and how this has changed is useful, especially in unstable angina
- Diamond-Forrester classification
  - Only use if you are considering angina as the main etiology
  - Helps determine correct terminology for chest pain, whether it is typical, atypical, or nonanginal chest pain
  - The three characteristics of typical chest pain are
    - Substernal chest pain that is
    - Worsened by exertion or stress and
    - Relieved by nitroglycerin or rest
  - Typical chest pain: 3/3 of the above
  - Atypical chest pain: 2/3 of the above
  - Nonanginal chest pain: 1 or none of the above

PAST MEDICAL HISTORY

- History of angina?
  - And how may this be similar to or different from usual, and what has been done for it in the past?
- History of CAD?
  - How was it diagnosed, and how severe is it?
- History of hypertension?
  - How controlled is it?
- History of diabetes?
  - Can present with atypical symptoms for ACS and is a risk factor for CAD
- History of hyperlipidemia?
  - More likely to have plaques in coronary arteries
- History of HF?
  - When was their last echocardiogram?
  - What is the cause of their HF (e.g., is it ischemic)?
- Menopause history?
  - Women after menopause have a higher risk of mortality from heart disease than men
- Recent medical or surgical illness?
  - Risk of STEMI is higher in patients with recent medical illness

SURGICAL HISTORY

- Coronary angiography history?
- CABG history?

SOCIAL HISTORY

- Use of alcohol and recreational drugs (especially cocaine and/or amphetamines), smoking
- Occupation
- Living situation
- Sexual history

FAMILY HISTORY

- Male family members with an MI at ≤ 55 years of age?
- Female family members with an MI at ≤ 65 years of age?

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MEDICATIONS

- Aspirin use?
  - Important in the Thrombolysis in Myocardial Infarction (TIMI) risk score
- Sildenafil or α_2-blocker use?
  - Important because nitrates cannot be administered if the patient has taken sildenafil or an α_2-blocker recently

PHYSICAL EXAM

A quick, thorough exam should be performed while obtaining the history to rule out life-threatening conditions. If the patient is stable, then signs of cardiac disease should be examined.

Likelihood ratios for individual positive or negative findings on physical exam can be clinically useful in determining whether MI or CAD exists. When a finding can be either positive or negative, then the likelihood ratios are called the *positive likelihood ratio* (PLR) or the *negative likelihood ratio* (NLR). A finding that has a PLR > 1 indicates that the positive finding is associated with the presence of MI or CAD; a finding that has an NLR of < 1 indicates that the finding is associated with the absence of MI or CAD. The further either ratio is from 1, the more likely MI or CAD is either present or absent. For example, a PLR of 3 = 20% probability patient has condition, a PLR of 4 = 25% probability patient has condition, a PLR of 5 = 30% probability patient has condition, and a PLR of 10 = 45% probability patient has condition.

- Vitals
  - Tachycardia is commonly seen in ACS
  - BP may be hypo- or hypertensive
    - Systolic BP < 100 mm Hg (PLR 3.6 for MI)
    - If aortic dissection suspected, measure BP in both arms; a difference > 20 mm Hg between the two arms may suggest dissection
    - Ankle-to-arm pressure index < 0.9 (PLR 4.0 for CAD)
- General exam
  - Levine's sign: hand clutched into a fist in front of the chest; not a specific sign
  - Patients with MI may appear anxious and restless
- Cardiac
  - S_3 gallop (PLR 3.2 for MI) or S_4, new murmur, and paradoxical splitting of S_2 may be present
  - New or worsening mitral regurgitation may indicate inferior wall MI
  - New aortic regurgitation may indicate ascending aortic dissection
  - A pericardial friction rub may be heard in patients with transmural STEMI at some time in the course of illness or in pericarditis
  - Carotid exam for evaluation of bruits
  - Evaluate the JVP for signs of distention
  - Kussmaul's sign (a rise in JVP with inspiration) may be present if there is an RV infarct
  - Tenderness on palpation of the chest wall highly predicts costochondritis
- Respiratory
  - Crackles may be present with MI causing acute HF
  - Tracheal deviation may indicate a tension pneumothorax
- Skin
  - Diaphoresis can be a sign of STEMI (diaphoresis and substernal chest pain > 30 min strongly suggest STEMI)
  - Cyanosis can be present in ACS or hypoxia
  - Xanthoma: sign of dyslipidemia and indicates the patient has a risk factor for cardiac disease
  - Diagonal earlobe crease (Frank's sign) is a sign of possible CAD
  - Peripheral edema may be present in MI with acute HF
- Abdominal exam
  - GI symptoms are the most common reason for a person to present with chest pain
  - Hepatomegaly may be a sign of chronic right-sided HF
- Vascular exam
  - Decreased pulses can indicate vascular disease and a higher risk of CAD
- HEENT
  - Arcus senilis (a white or grayish opaque ring about the circumference of the cornea) (PLR 3.0 for CAD)

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS OF ACS

- Vascular and cardiac causes
  - Stable angina/NSTE-ACS/STEMI/Prinzmetal's angina

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    - Aortic dissection
        - Sudden onset of severe tearing or ripping chest pain
        - Could be anterior chest pain or radiate to the back depending on where the dissection is located
        - Uneven BPs in the arms and decreased pulses in the legs
    - Pericarditis
        - Pleuritic chest that improves with leaning forward and radiates to the trapezius ridge
        - Friction rub murmur and diffuse ST-segment elevation and PR-segment depression (switched in lead aVr)
    - Aortic stenosis
        - Exertional chest pain with a crescendo-decrescendo systolic murmur radiating to the carotids
    - PE
        - Pleuritic chest pain, dyspnea, cough, hemoptysis, hypoxemia
        - May have accompanying findings of a DVT
        - ECG most commonly reveals sinus tachycardia, but may show $S_1Q_3T_3$
    - Cardiomyopathy
        - Cardiac disease history, enlarged heart on CXR
        - May have ECG changes of LV hypertrophy or ischemia
    - Myocarditis
        - Younger person with chest pain, murmur, and a recent viral illness
    - Hypertrophic cardiomyopathy
        - Younger person who has exertional chest pain
        - May have syncope with exercise and a family history of hypertrophic cardiomyopathy
    - Takotsubo cardiomyopathy
        - Usually in women, chest pain that is cardiac in nature
        - Can be after an emotional event
        - Hypokinesis of the mid- and apical LV on ventriculography
    - Thoracic aneurysm
        - Pain in the jaw, neck, upper back; coughing, hoarseness, dyspnea
- Pneumonia
    - Acute fever and chills, dyspnea, productive cough, pleuritic chest pain, and a consolidation on CXR
- Pleuritis
    - Pleuritic chest pain in a patient with lung disease history and prolonged smoking history
- Pneumothorax
    - Pleuritic chest pain, asymmetric breath sounds, tracheal deviation, CXR findings of pneumothorax
- Bronchitis
    - Pleuritic chest pain, dyspnea, hemoptysis, fever, cough
- GI causes
    - Esophageal rupture
    - Mallory-Weiss tear
        - Chest pain
        - Severe vomiting followed by hematemesis
        - Persons with alcohol use disorder or bulimia nervosa
    - Diffuse esophageal spasm (may be relieved with nitroglycerin just like ACS)
        - Chest pain that may radiate to the jaw, arms, or back
        - Dysphagia is common
    - Peptic ulcer disease
        - Aching or gnawing epigastric pain
        - Can be accompanied by nausea and vomiting, early satiety, weight loss, maybe NSAID use, alcohol use disorder, or *Helicobacter pylori* history
    - GERD
        - History of reflux pain (retrosternal pain/burning shortly after eating)
- Cocaine use
    - Acts to constrict vessels; can cause acute ischemia with vasoconstriction of the coronary vessels
- Costochondritis/Tietze syndrome
    - Usually trauma- or exercise-associated
    - Palpation and position changes reproduce the pain
- Anxiety/panic attack
    - Dyspnea
    - Some sort of precipitating event
    - Possible psychiatric history

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DIFFERENTIAL DIAGNOSIS OF ELEVATED TROPONIN LEVELS

While an elevated troponin is concerning for an MI, the differential diagnosis of an elevated troponin from a non-MI etiology (e.g., acute myocardial injury secondary to PE) should be considered (Table 19-1). It is also important to note the patient's clinical picture (e.g., is the picture consistent with ischemia or not), and if the troponin is rising/falling or stable with serial checks in defining whether the elevation is from MI, acute myocardial injury, or chronic myocardial injury (Fig. 19-2).

ETIOLOGY OF ACS

- Ischemic heart disease
- Atherosclerosis
- Hypertension
- Embolus (rare)
- An acute precipitating event, such as vigorous exercise or an acute medical or surgical illness
- Genetics

DIAGNOSTIC TESTS

LABS

- CBC
  - Anemia can cause chest pain due to myocardial tissue hypoxia
  - Leukocytosis
    - May indicate infectious process
    - Also occurs with STEMI, appearing within a few hours after the onset of pain, and persists for 3–7 days; the WBC count often reaches 12,000–15,000 cells/μL
- CMP
  - Evaluate for
    - Electrolyte abnormalities (especially potassium and magnesium)
    - Kidney and liver function
    - Hyperglycemia
- Cardiac biomarkers (preferably high-sensitivity troponin)
  - Measured serially to see if a change (delta troponin) occurs, and to measure the plateau in many cases
  - High-sensitivity troponin assays can be performed more frequently (q2h) than conventional troponin assays
  - Cardiac biomarker proteins
    - Released from necrotic heart muscle after STEMI and myocardial injury
    - Rate of liberation of specific proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow
    - *Cardiac-specific troponins* have amino acid sequences that differ from those of the skeletal muscle forms of these proteins, allowing the development of highly specific troponin assays, making them the preferred biomarkers for MI
    - In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI, as contemporary urgent reperfusion strategies require making a decision from clinical and ECG findings of STEMI, rather than waiting for troponin values
    - Figure 19-3 describes the enzyme kinetics of cardiac biomarkers based on the time of infarction to lab measurement
- BNP
  - Helps determine if HF may also be present
- D-dimer
  - Measure if concerned about a PE using simplified Wells' criteria
- Lipid panel
  - Hyperlipidemia and hypercholesterolemia are risk factors for CAD
- PT/PTT/INR
  - Helps determine if a bleeding diathesis is present, which can complicate management strategies

IMAGING

- ECG
  - ST-segment depressions
    - Seen in one-third of patients with NSTE-ACS
    - Can be transient or persist for as long as several days

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TABLE 19-1 Causes of Troponin Elevation Other Than Acute Coronary Syndromes

Acute Disease

Cardiac and vascular

- Acute HF
- Acute aortic dissection
- Apical ballooning syndrome
- Endocarditis
- Myocarditis
- Pericarditis
- Cerebrovascular accident
  - Ischemic stroke
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- Kawasaki disease
- Critical illness
  - Hypotension
  - GI bleeding
  - Thrombotic thrombocytopenic purpura

Respiratory

- Acute PE
- ARDS

Muscular damage

- Rhabdomyolysis

Infectious

- Sepsis
- Viral illness

Other acute causes of troponin elevation

- Toxic exposure
  - Carbon monoxide
  - Hydrogen sulfide
  - Colchicine

Chronic Disease

- Chronic HF
- Cardiac infiltrative disorders
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
  - Scleroderma
- Hypertension
- Diabetes
- Hypothyroidism
- ESRD

Myocardial Injury

- Cancer chemotherapy
- Envenomation
- Endurance athletics

Reproduced with permission from Bates ER, Moliterno DJ, Patel R. Evaluation and Management of Non-ST-Segment Elevation Acute Coronary Syndromes. In Fuster V, Narula J, Vaishnava P, Leon MB, Callans DJ, Rumsfeld JS, Poppas A. eds. *Fuster and Hurst's The Heart, 15e*. McGraw Hill Education; 2022.

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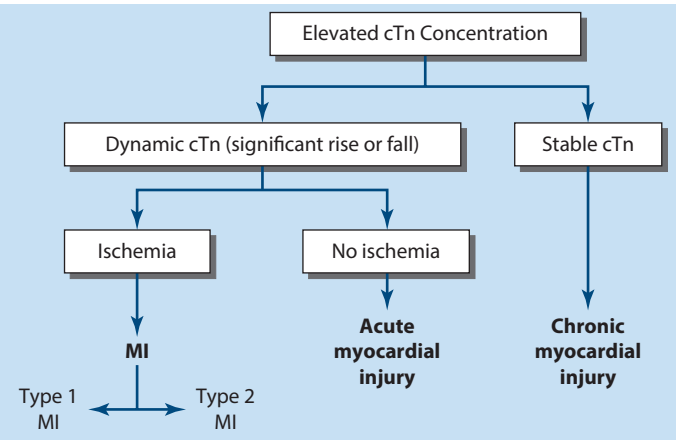

FIGURE 19-2 Clinical classification of patients with elevated cardiac troponin (cTn). (Reproduced with permission from Morrow DA. Chest discomfort, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- T-wave changes
  - Occur in NSTE-ACS
  - Less specific sign of ischemia unless they are new and deep T-wave inversions (≥ 0.3 mV)
- ST-segment elevation is seen in STEMI (see **Chap. 53** for acute and evolving ECG changes of STEMI)
  - Diagnostic criteria for STEMI
    - New ST-elevation at the J-point in 2 contiguous leads with the cut-point

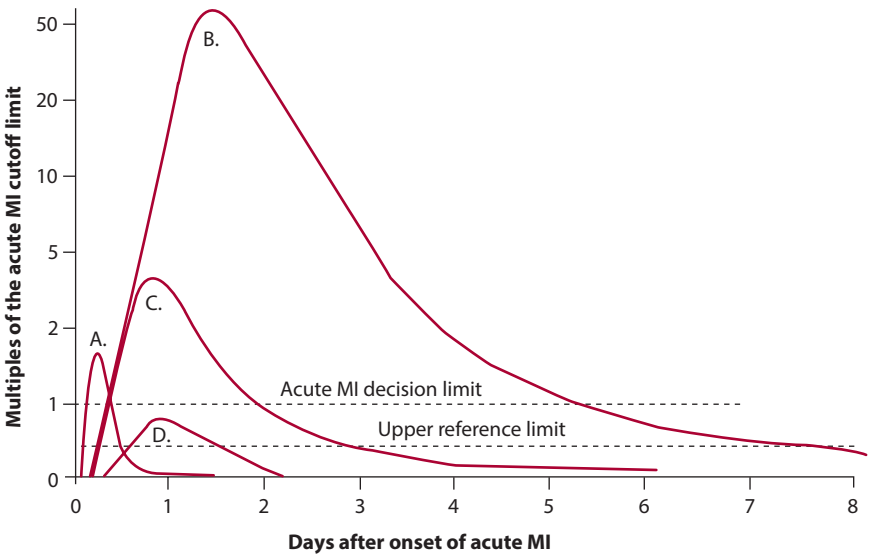

FIGURE 19-3 The change in cardiac biomarkers in the blood following the start of symptoms of acute MI. The peak of curve A shows the early release of myoglobin CK-MB isoform. The peak of curve B shows the significant elevation of cardiac troponin. The peak of curve C shows the elevation of CK-MB after an MI. The peak of curve D shows the increase in cardiac troponin after NSTE-ACS. The dotted line at 1 is set as a relative scale to point out the cutoff concentration for acute MI. (From Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem. 1999;45:1104, by permission of Oxford University Press.)

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- In all leads other than leads V_2–V_3: ≥ 0.1 mV (1 mm on standard scale)
- In leads V_2–V_3
  - ≥ 0.2 mV (2 mm) in men ≥ 40 years old
  - ≥ 0.25 mV (2.5 mm) in men < 40 years old
  - ≥ 0.15 mV (1.5 mm) in women regardless of age

- Evaluate for new left bundle branch block (LBBB), Q waves, LV hypertrophy, T-wave inversions, tachycardia, and heart blocks
  - In the setting of new LBBB, use Sgarbossa's criteria
  - There is 90% specificity for a STEMI if at least 3 points of Sgarbossa's criteria are met
    - Concordant ST elevation ≥ 1 mm in leads with a positive QRS complex (5 points)
    - Concordant ST depression ≥ 1mm in leads V_1–V_3 (3 points)
    - ST elevation ≥ 5 mm in a lead with a negative QRS complex (2 points)

- CXR
  - Aortic dissection is suggested by widened mediastinum (nondiagnostic)
  - Evaluates for other causes of chest pain, such as
    - Pneumonia
    - Pneumothorax
    - Esophageal rupture
    - Signs of HF
- Echocardiogram (especially for patients in whom NSTE-ACS or STEMI is diagnosed prior to discharge)
  - Evaluates for pericardial effusion, cardiomegaly, thoracic dissections/aneurysms, and regional wall motion abnormalities to suggest coronary artery occlusion
  - The echocardiogram will evaluate the LV ejection fraction post-MI, which is important for management strategies
- CT angiography of chest if warranted
  - Order if suspect aortic dissection, aneurysm, or PE when signs of STEMI are not clearly present
- Cardiac CT angiography (CT coronary)
  - Assesses for the presence of epicardial coronary artery obstruction
  - A test that rates the likelihood of CAD and, in the right clinical setting, risk-stratifies patients for ACS

MANAGEMENT

INITIAL TRIAGE

The decision to admit a patient with chest pain from the ED to the hospital depends on their initial ECG, clinical history, risk factors, and troponin values. Most EDs, in conjunction with hospital medicine and the cardiology department, have developed a chest pain algorithm that helps early decision-making for initial triaging and disposition recommendations. Figure 19-4 describes a typical strategy. Patients with STEMI undergo emergent reperfusion strategies. Patients with NSTE-ACS begin early medical therapy and are admitted with either an early invasive strategy or medical therapy alone. In patients without clear STEMI or NSTE-ACS, the HEART score (Table 19-2) is a risk stratification tool to help predict the risk of 6-week major adverse cardiac events (MACE) in patients presenting to the ED. Many patients will be admitted for "ACS rule-out" for observation, serial troponin and ECG checks, and rapid evaluation of the patients' risk of ischemic heart disease.

RISK STRATIFICATION OF NSTE-ACS

Patients with a low likelihood of ischemia can usually be managed in the ED, admitted to observation in the hospital, or admitted to a dedicated "chest pain" unit if available. Evaluation of such patients includes clinical monitoring for recurrent chest discomfort and continuous monitoring of ECGs and serial troponins. In patients for whom there is diagnostic uncertainty or in intermediate-risk patients, stress testing to detect and grade ischemia or cardiac CT angiography to assess epicardial coronary artery obstruction may be considered.

For patients who are "ruled in" for NSTE-ACS, management with anti-ischemic and antithrombotic therapy should begin immediately. A decision also needs to be made about whether the patient needs an early invasive strategy for evaluation and potential management of plaque rupture (see Invasive versus Conservative Strategy section).

OVERALL GOALS OF TREATMENT FOR ACS

- Control discomfort
  - Nitroglycerin, morphine
- Reduce myocardial oxygen demand
  - β-Blockers, nitroglycerin, calcium channel blockers, morphine
- Improve coronary blood flow (when indicated)
  - PCI, fibrinolysis, or CABG

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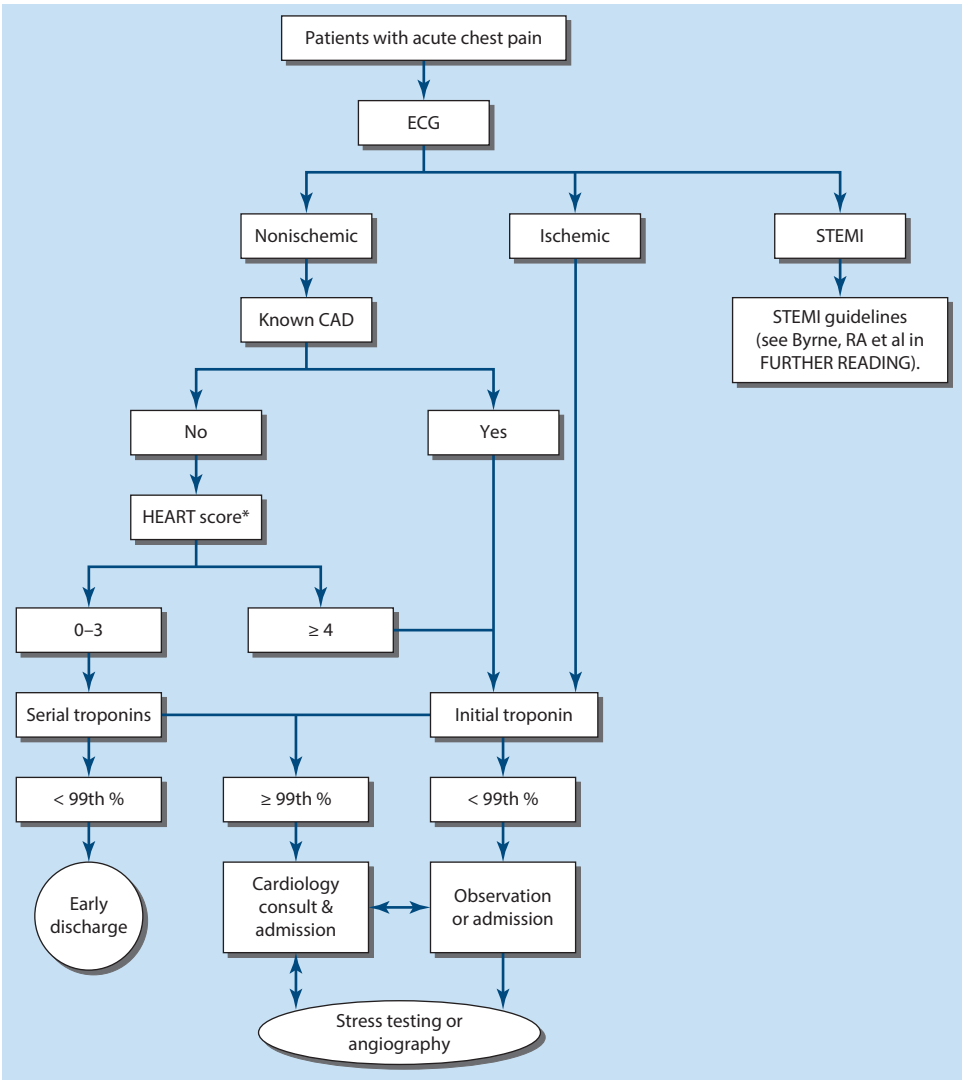

FIGURE 19-4 The HEART pathway for evaluation of acute chest pain. *The Heart Score assigns 0, 1, or 2 points depending on the extent of abnormality for each of the History, ECG, Age, Risk factors, and Troponin. (Reproduced with permission from JL Januzzi et al: Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC scientific expert panel. *J Am Coll Cardiol*. 2019, 73:1059-1077.)

- Prevent intracoronary thrombosis
  - Aspirin, clopidogrel, enoxaparin or heparin, high-dose statins
- Correct hypoxemia
  - Oxygen administration, if needed

MANAGEMENT OF NSTE-ACS

- Quick reference of treatments
  - Oxygen administration if oxygen saturation < 90%
  - IV access
  - Continuous telemetry monitoring
  - Aspirin chewed 325 mg, then 81 mg PO daily

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TABLE 19-2 HEART Score Categories, Point Values, and Score Interpretation

*H*istory	–0 points for slightly suspicious for ACS –1 point for moderately suspicious for ACS –2 points for highly suspicious for ACS
*E*CG	–0 points for a normal ECG –1 point for nonspecific repolarization disturbance No ST deviation but LBBB, LVH, repolarization changes (e.g., digoxin) –2 points for significant ST depression ST deviation not due to LBBB, LVH, or digoxin
*A*ge	–0 points for < 45 –1 point for 45–65 –2 points for > 65
*R*isk factors Hypertension, hypercholesterolemia, diabetes, obesity (BMI > 30), smoking (current, or smoking cessation within the last 3 months), positive family history for CAD (parent or sibling with IHD before age 65); atherosclerotic disease: prior MI, PCI/CABG, CVA/TIA, or peripheral arterial disease	–0 points for no known risk factors –1 point for 1–2 risk factors –2 points for ≥ 3 risk factors or history of CAD
Initial *T*roponin Use local troponin assays and corresponding cutoffs	–0 points for normal value –1 point for 1–2 times the normal limit –2 points for > 2 times the normal limit

Score interpretation:

- Score 0–3 → 0.9–1.7% risk of adverse cardiac event at 6 weeks (usually discharged from ED)
- Score 4–6 → 12–16.6% risk of adverse cardiac event 6 weeks (usually admitted for further investigation)
- Score ≥ 7 → 50–65% risk of adverse cardiac event 6 weeks (usually candidates for early invasive strategies; see TIMI risk score)

CVA, cerebrovascular accident; IHD, ischemic heart disease; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; TIMI, Thrombolysis in Myocardial Infarction.
[*Source:* Original.]

    - Sublingual nitroglycerin, IV nitroglycerin infusion, β-blocker, and possibly IV morphine for anti-ischemic pain
    - High-dose statins
    - Clopidogrel, ticagrelor, or prasugrel
    - Unfractionated heparin infusion or low-molecular-weight heparin (enoxaparin)
    - Invasive or conservative treatment strategies (i.e., revascularization via PCI or medical therapy alone)
- General initial order of administration: oxygen → aspirin (325 mg) → nitroglycerin → heparin or enoxaparin → β-blocker → statin
- Consult cardiology while starting the preceding therapies (and discuss which should be administered)

ANTI-ISCHEMIC THERAPY FOR NSTE-ACS (TABLE 19-3)

- Sublingual nitroglycerin
    - Dose: 0.4 mg × 3 in 5-min intervals
    - A mainstay of anti-ischemic treatment; acts to decrease preload and afterload
    - If the patient is still having ischemic chest discomfort after three doses, infuse IV nitroglycerin at 5–10 μg/min; it can be increased 10 μg/min q3–5min until symptoms are relieved, systolic BP falls to < 90 mm Hg, or the dose reaches 200 μg/min
    - Contraindicated in the presence of RV infarction or hypotension, or if the patient has taken sildenafil or vardenafil (within 24 h) or tadalafil (within 48 h)
- β-Blockers
    - Dose: metoprolol tartate IV 5 mg q2min × 3 doses, then 25 mg by mouth q6–12h
    - The other mainstay of anti-ischemic therapy by reducing myocardial oxygen needs
    - Target to a heart rate of 50–60 beats/min
    - Avoid in the presence of acute or severe HF, low cardiac output, hypotension, high-degree AV block, or active bronchospasm

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TABLE 19-3 Recommendations for Anti-Ischemic Drugs in the Acute Phase of NSTE-ACS

THERAPY	RECOMMENDATION	WHEN TO AVOID
Nitrates	• Use sublingual or intravenous nitrates to relieve angina • Use intravenous nitrates if recurrent angina, uncontrolled hypertension, or signs of heart failure • Consider in patients with vasospastic angina	• Recent use of a PDE-5 inhibitor[a] • Hypotension • Right ventricular infarct • Severe aortic stenosis
β-blockers	• Initiate early for ischemic symptoms • Continue long-term therapy	• PR interval > 0.24 s • Second- or third-degree atrioventricular block • Heart rate < 50 beats/min • Systolic BP < 90 mm Hg • Shock or Killip class III or IV heart failure • Severe reactive airways disease
Calcium channel blockers	• Consider in patients with vasospastic angina • Consider in patients with contraindications to β-blockers	• Systolic BP < 90 mm Hg • Pulmonary edema • Left ventricular dysfunction[b] • Avoid short-acting nifedipine
Morphine or other narcotic analgesics[c]	• Continued severe angina despite three sublingual nitroglycerin tablets • Recurrent ischemia despite adequate anti-ischemic therapy	• Hypotension • Respiratory depression • Confusion or obtundation

[a]Sildenafil or vardenafil < 24 h or tadalafil < 48 h. [b]Diltiazem or verapamil. [c]Concomitant administration may delay the absorption and blunt the antiplatelet effect of oral $P2Y_{12}$ inhibitors. PDE-5, phosphodiesterase type 5. (Reproduced with permission from Giugliano RP et al. Non-ST-segment elevation acute coronary syndrome (non-ST-segment elevation myocardial infarction and unstable angina), in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Calcium channel blockers: verapamil or diltiazem
  - Recommended if patients have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and β-blockers, or contraindications to either nitrates or β-blockers
- Morphine
  - Dose: 1–5 mg IV q5–30min
  - Administer if continued ischemic chest pain despite the maximal anti-ischemic agents above and without contraindications to morphine
- High-dose statins: atorvastatin
  - Dose: 40 or 80 mg qhs
  - Early administration of high-dose statins prior to PCI and continued thereafter has been shown to reduce both early and late recurrent ischemic events [1]
  - In patients without an adequate response to maximally tolerated statins (i.e., < 50% decrease in LDL), addition of ezetimibe 10 mg daily and/or a PCKS9 inhibitor (alirocumab, evolocumab) early after ACS has been shown to further reduce LDL and prevent future cardiovascular events
- ACE-Is or ARBs can also be considered, especially in patients with type 2 diabetes mellitus

ANTITHROMBOTIC THERAPY FOR NSTE-ACS (TABLE 19-4)

- Antiplatelet and anticoagulant drugs represent the second major cornerstone of treatment
- Antiplatelet therapy
  - Aspirin
    - Dose: 150–325 mg (non–enteric coated) should be given to everyone immediately
    - Followed by maintenance therapy of 75–100 mg daily
  - Clopidogrel, ticagrelor, or prasugrel (platelet $P2Y_{12}$ receptor blockers)
    - Should be given to everyone (in the absence of a high risk for bleeding), irrespective of whether an invasive or conservative strategy is selected
    - Clopidogrel
      - Dose: 300–600 mg loading dose (300 mg if no PCI, 600 mg if PCI planned), then 75 mg daily

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TABLE 19-4 Clinical Use of Antithrombotic Therapy	
Oral Antiplatelet Therapy	
Aspirin	Loading dose of 150–325 mg PO of nonenteric formulation followed by 75–100 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 600 mg (if PCI planned) or 300 mg (if no PCI planned), followed by 75 mg/d
Prasugrel	Pre-PCI: Loading dose of 60 mg followed by 10 mg/d In patient with body weight < 60 kg or > 75 years old, maintenance dose of 5 mg/d
Ticagrelor	Loading dose of 180 mg followed by 90 mg bid
Intravenous Antiplatelet Therapy at the Time of PCI	
Cangrelor	30-μg/kg bolus followed by 4-μg/kg/min infusion for 2 h or duration of procedure
Eptifibatide	180-μg/kg bolus followed in 10 min by second bolus of 180 μg/kg with infusion of 2.0 μg/kg/min for up to 18 h
Tirofiban	25 μg/kg/min over 3 min, followed by infusion of 0.15 μg/kg/min for up to 18 h
Parenteral Anticoagulantsa	
Unfractionated heparin	Bolus 70–100 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg/h titrated to ACT 250–300 s
Enoxaparin	0.5-mg/kg IV bolus at the time of PCI *or* 1 mg/kg subcutaneous q12h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg daily if creatine clearance < 30 mL/min
Bivalirudin	Initial IV bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h
Fondaparinux	2.5 mg subcutaneously daily (only prior to PCI)
Oral Anticoagulant Drugs (concomitant treatment after PCI)	
VKA	Dosing based on INR value and the respective clinical indication
Apixaban	Maintenance dose 5 mg (dose reduced to 2.5 mg) bid
Dabigatran	Maintenance dose 150 mg (dose reduced to 75 mg) bid in the United States; outside the United States, either 110 or 150 mg bid may be used
Edoxaban	Maintenance dose 60 mg (dose reduced to 30 mg) daily
Rivaroxaban	Maintenance dose 20 mg (dose reduced to 15 mg) daily In patients without AF or venous thromboembolism 2.5 mg bid may be used

All dose reductions for patients meeting criteria. ACT, activated clotting time; VKA, vitamin K antagonists (e.g., warfarin). (Reproduced with permission from Giugliano RP et al. Non-ST-segment elevation acute coronary syndrome (non-ST-segment elevation myocardial infarction and unstable angina), in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Irreversible blocker of the $P2Y_{12}$ receptor, and when combined with aspirin, it confers a 20% relative reduction in CV deaths, MI, or stroke, compared to aspirin alone, but is associated with a 1% increase in major bleeding
- Some patients have an inadequate response to clopidogrel due to a genetic variant of the cytochrome P450 system involving the *2C19* gene that leads to reduced conversion of clopidogrel into its active metabolite

- Ticagrelor
  - Dose: 180-mg loading dose, then 75 mg bid
  - Potent reversible platelet $P2Y_{12}$ inhibitor that reduces the risk of CV death, mortality, and MI compared with clopidogrel across a broad spectrum of patients with ACS, but increases the risk of bleeding [2]
  - Dyspnea may develop in some patients soon after administration, although the symptoms are often transient and infrequently serious
  - Unlike prasugrel, it demonstrated benefit whether patients were managed conservatively or with an early invasive strategy
- Prasugrel
  - Dose: 60-mg loading dose, then 10 mg daily
  - Achieves a more rapid onset and higher level of irreversible platelet inhibition than clopidogrel

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        - Compared with clopidogrel, prasugrel reduces the combined risk of CV death, MI, stroke, and stent thrombosis but has increased bleeding in patients for whom PCI is planned
        - Contraindicated in patients with prior stroke or TIA or at high risk for bleeding, and should be administered once the coronary anatomy is known (i.e., post–coronary angiography)
    - Glycoprotein IIb/IIIa inhibitors
        - Reserved for patients undergoing PCI with a high coronary thrombus burden on angiography or thrombotic complications of PCI (ordered by cardiology in the cath lab)
    - Duration of dual antiplatelet therapy (DAPT, aspirin plus a $P2Y_{12}$ inhibitor)
        - Long-term DAPT should continue preferably for 12 months in NSTE-ACS without an indication for long-term full anticoagulation (e.g., AF)
        - Ticagrelor or prasugrel are favored over clopidogrel
        - The duration of DAPT depends on the risk of bleeding versus thrombosis
        - A shorter duration of DAPT (i.e., 3–6 months) may be considered for patients at high risk for bleeding who are not at high ischemic risk
            - These patients should stop aspirin and continue on a $P2Y_{12}$ inhibitor alone
        - Longer-duration DAPT (> 12 months) is favored in patients with high atherothrombotic risk (e.g., due to stenting of the left main coronary artery or proximal left anterior descending or proximal bifurcating coronary arteries, recurrent MI, or stent thrombosis)
        - After DAPT is no longer needed, antiplatelet monotherapy with a single antiplatelet should be continued thereafter
        - If a patient is taking a DOAC for AF, the duration of DAPT should be shortened (e.g., stop aspirin after hospital discharge or at most at 1 month after PCI, except for patients at very high risk for ischemic events)
            - A $P2Y_{12}$ inhibitor plus DOAC should be continued for 1 year
            - After 1 year, most patients should be transitioned to oral anticoagulation monotherapy without concomitant antiplatelet treatment
- Anticoagulants
    - Four options are available: (1) unfractionated heparin (UFH), (2) low-molecular-weight heparin (LMWH) (enoxaparin), (3) bivalirudin, and (4) fondaparinux
        - UFH and LMWH are the most commonly used agents
    - UFH
        - Administered as a continuous infusion with a targeted aPTT (per hospital heparin protocol)
        - This has long been the mainstay of therapy given that it acts quickly and the infusion can be discontinued quickly before a procedure
    - Enoxaparin
        - Dose: 1 mg/kg subcutaneously bid
        - This has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy (however, it is accompanied by a modest increase in bleeding)
        - Enoxaparin stays in the system longer and may add technical complexity to during PCI
    - Bivalirudin
        - Dose: 0.75 mg/kg IV × 1, then 1.75 mg/kg/h for procedure duration
        - Similar efficacy to either UFH or LMWH and is used just prior to and/or during PCI
        - Rarely used in conservatively managed patients
    - Fondaparinux
        - Dose: 2.5 mg IV × 1 then 2.5 mg subcutaneously daily
        - Equivalent efficacy to LMWH but has a lower risk of major bleeding
        - Requires supplemental UFH to prevent procedure-related thrombosis
    - In patients in whom NSTE-ACS develops while receiving treatment with a DOAC, the DOAC should be discontinued when one of the four parenteral anticoagulants is initiated

INVASIVE VERSUS CONSERVATIVE STRATEGIES

- Patients "ruled in" for NSTE-ACS should receive the above anti-ischemic and antithrombotic therapies, and additionally, a decision needs to be made whether the patient needs an early invasive strategy for evaluation and potential management of plaque rupture
- The TIMI (Table 19-5) or GRACE score is used to evaluate cardiac risk, selecting which patients require early invasive intervention (Fig. 19-5)
- Among intermediate- to high-risk patients with NSTE-ACS, an early invasive strategy is associated with fewer recurrent MIs and improved long-term survival compared with a noninvasive strategy [3]
    - TIMI risk score of 5–7 is determined to be high risk for NSTE-ACS

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TABLE 19-5 Thrombolysis in Myocardial Infarction (TIMI) Risk Score for NSTE-ACS

Risk Markers	
• Age ≥ 65 years • Known CAD (≥ 50% stenosis) • ST deviation > 0.5 mm on presenting ECG	• ↑ Cardiac markers • ≥ 2 original episodes in prior 24 h • Prior angina • ≥ 3 CAD risk factors
NO. OF RISK MARKERS	**INCIDENCE OF ADVERSE CARDIAC EVENTS[a] (%)**
0/1	5
2	8
3	13
4	20
5	26
6/7	41

[a]Risk at 14 days of death, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization. Reproduced with permission from Giugliano RP et al. Non-ST-segment elevation acute coronary syndrome (non-ST-segment elevation myocardial infarction and unstable angina), in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- In an invasive strategy, coronary angiography is recommended within 2 h of presentation for patients who are unstable or within 24 h in high-risk stable patients, followed by coronary revascularization (PCI or CABG) depending on coronary anatomy
- Two studies comparing an immediate invasive strategy (1.4–4.7 h after presentation) reduced the rate of death or MI compared with delayed invasive strategy (61–62 h)
- In patients at low risk, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy
  - In low-risk patients, order a coronary CT or stress testing
  - A conservative strategy consists of anti-ischemic and antithrombotic therapy followed by a "selective invasive approach" in which the patient is observed closely and coronary angiography is conducted if coronary CT shows the presence of epicardial coronary stenosis, rest pain or ST-segment changes recur, a biomarker of necrosis becomes positive, or there is evidence of severe ischemia on a stress test

FURTHER HOSPITAL MANAGEMENT OF NSTE-ACS

- All patients should receive an echocardiogram before discharge to evaluate LV function
- All patients should be educated on risk factor modification of hyperlipidemia (goal LDL < 55), BP control, control of hyperglycemia, and smoking cessation
- If the patient has diabetes, also prescribe an ACE-I or ARB and an SGLT-2 inhibitor

INITIAL MANAGEMENT OF STEMI

- Quick reference of treatments
  - Oxygen administration if oxygen saturation < 90%
  - IV access
  - Continuous telemetry monitoring
  - Aspirin chewed 325 mg, then 81 mg by mouth daily
  - Sublingual nitroglycerin, IV nitroglycerin infusion, IV β-blockers, and/or possibly IV morphine for anti-ischemic pain
  - Emergent reperfusion therapy via either PCI or fibrinolytics with cardiology consultation
  - Clopidogrel, ticagrelor, or prasugrel
  - Unfractionated heparin or low-molecular-weight heparin
  - ACE-I or ARB, and oral β-blockers
  - High-dose statins
  - Spironolactone (in select patients)
- Goals in the ED include
  - Control of cardiac discomfort
  - Rapid identification of patients who are candidates for emergent reperfusion therapy
  - Avoidance of inappropriate discharge of patients with STEMI

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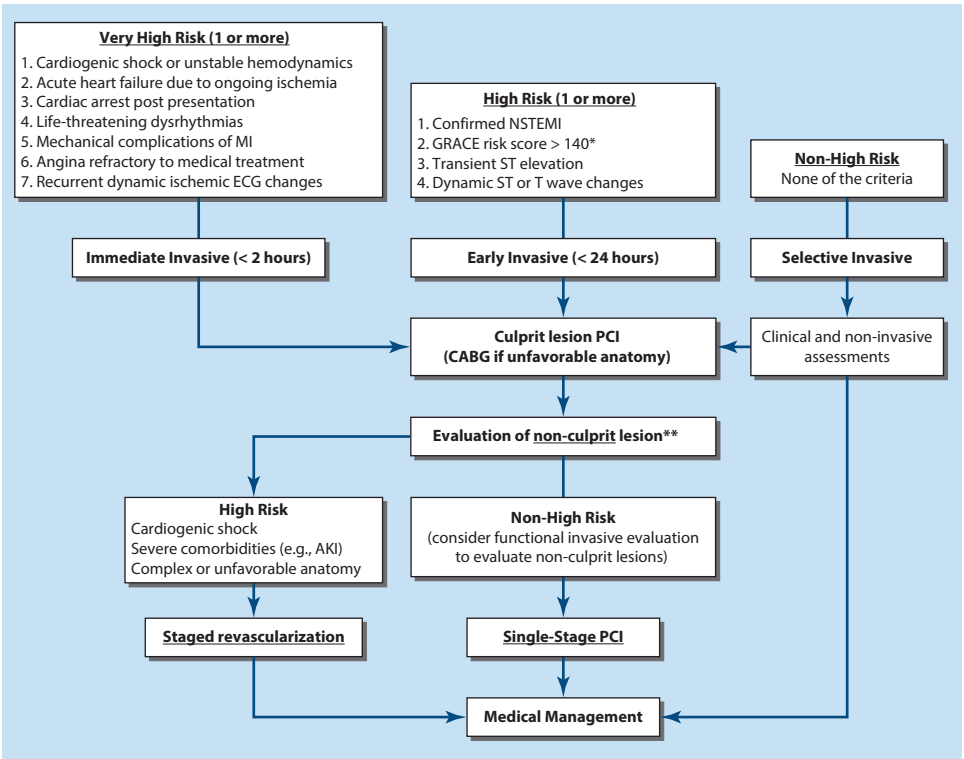

FIGURE 19-5 Selection, timing, and staging of invasive strategy in patients with non–ST-elevation ACS. Patients with non–ST-elevation ACS who have one or more very high-risk features should undergo immediate invasive strategy with coronary angiography as soon as possible (within 2 h), unless absolute contraindications exist. An early invasive strategy should be considered within 24 h in stable patients with one or more high-risk features. Stable patients with no very high- or high-risk features should be managed with a selective invasive approach in which clinical noninvasive assessments and patient preferences are used to guide management. *Fox KA, BMJ Open 2014;4:e004425. https://doi.org/10.1136/bmjopen-2013-004425. **In patients with multivessel disease, single-stage PCI during the index procedure to achieve complete coronary revascularization should be considered in the absence of cardiogenic shock, severe comorbidities such as AKI, or coronary anatomy that is unfavorable or high risk requiring evaluation for the Heart Team for CABG vs complex coronary intervention. GRACE, Global Registry of Acute Coronary Syndrome Events. (Reproduced with permission from Giugliano RP et al. Non-ST-segment elevation acute coronary syndrome (non-ST-segment elevation myocardial infarction and unstable angina), in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Minimize the time from first contact to initiation of reperfusion therapy with a "time-to-door of first device" of ≤ 90 min, or a "door-to-needle time" of ≤ 30 min
        - This may involve transfer from a non-PCI hospital to one that is PCI-capable (door-in-door-out time of ≤ 30 min) if the PCI-capable hospital is ≤ 120 min away
- Many treatments are initiated in the ED and continued during the in-hospital phase
- Consult cardiology as soon as a STEMI is recognized on ECG
- Treatment strategies are similar to NSTE-ACS therapies with some differences (mainly reperfusion strategies)

CONTROL OF DISCOMFORT

- Sublingual nitroglycerin
    - Dose: 0.4 mg up to three doses at 5-min intervals for persistent pain
    - Decreases preload and dilates infarct-related coronary vessels or collaterals, decreasing myocardial oxygen demand and increasing supply, respectively
    - IV nitroglycerin infusion can be considered for recurrent or persistent chest pain after three sublingual doses, especially if with ongoing ischemia on ECG

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- See NSTE-ACS section for contraindications to nitroglycerin use
- An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can be reversed promptly with rapid administration of atropine 0.5 mg IV

- Morphine
  - Dose: 1–5 mg IV q5–30min
  - Very effective for STEMI pain; administer if continued ischemic chest pain despite maximal nitrates and without contraindications to morphine
  - May reduce sympathetically mediated arteriolar and venous constriction, resulting in venous pooling and reduced cardiac output and arterial pressure (responds well to elevating the legs and/or giving fluids)
  - The patient may experience nausea and diaphoresis that eventually passes
  - Has a vagotonic effect that may cause bradycardia or heart block, particularly in patients with inferior infarction
    - These respond well to atropine 0.5 mg IV
- β-Blockers
  - Metoprolol 5 mg IV q2–5min for a total of three doses for goal heart rate 60–70 beats/min
  - Reduces myocardial oxygen demand and hence ischemia
  - Reduces the risk of reinfarction and ventricular fibrillation
  - Avoid if heart rate < 60 beats/min, systolic BP < 100 mm Hg, PR interval > 0.24 s, or signs of acute HF
- Anticoagulation
  - Anticoagulation with UFH should begin in the ED
  - Cardiology will decide whether to continue during the PCI itself

LIMITATION OF INFARCT SIZE WITH REPERFUSION THERAPY

- The central zone of necrotic tissue is irretrievably lost at the time of STEMI presentation, but the surrounding ischemic myocardium (ischemic penumbra) may be improved by timely restoration of coronary perfusion
- Reperfusion, via either primary PCI or fibrinolysis, accelerates the opening of infarct-related arteries that may have naturally occurred and also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished
- Primary PCI (PCI without preceding fibrinolysis)
  - Effective in restoring perfusion when carried out emergently in the first few hours of MI
  - More effective than fibrinolysis in opening occluded coronary arteries and, when performed by experienced teams, is associated with better short-term and long-term outcomes
  - Preferred over fibrinolysis unless time-to-delivery of first device is anticipated to be > 120 min
  - Also preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is high, or symptoms have been present > 2–3 h
  - Contemporary studies show that in STEMI patients without shock, performing PCI on nonculprit coronary vessels, either during the index procedure or within 45 days, results in a lower rate of cardiovascular events and a lower need for subsequent ischemia-driven revascularization [4]
  - In contrast, in patients with cardiogenic shock, routine PCI of nonculprit arteries during the initial primary PCI is contraindicated due to an increase in the rate of death or severe kidney failure compared with culprit-only PCI
- Fibrinolysis
  - If timely PCI is not available and no contraindications are present, fibrinolytic therapy should ideally be given within 30 min of presentation (door-to-needle time ≤ 30 min)
  - Recombinant tissue plasminogen activator (tPA) (alteplase), streptokinase, tenecteplase (TNK), and reteplase (rPA) are FDA-approved fibrinolytic agents
    - tPA (15-mg bolus then 50 mg IV over 30 min), TNK, and rPA are more effective than streptokinase at restoring full perfusion and have a small edge in improving survival as well
  - Antiplatelets and antithrombotics are also required (see below)
  - Once a patient receives fibrinolysis, they should be transferred to a PCI-capable hospital, as they may need rescue PCI in addition to fibrinolysis (fibrinolysis reperfusion failure is high)
  - *Contraindications to fibrinolysis*
    - Cerebrovascular hemorrhage at any time in life
    - A nonhemorrhagic stroke or other cerebrovascular event within the past year
    - Marked hypertension (systolic BP > 180 and/or diastolic > 110 mm Hg) at any time during the acute presentation
    - Suspicion of aortic dissection
    - Active internal bleeding (excluding menses)
  - Relative contraindications to fibrinolysis (requires a risk-benefit assessment)
    - Current use of anticoagulants (INR ≥ 2.0)

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        - A recent (< 2 weeks) invasive or surgical procedure or prolonged (> 10 min) cardiopulmonary resuscitation
        - Known bleeding diathesis
        - Pregnancy
        - A hemorrhagic ophthalmic condition (hemorrhagic diabetic retinopathy)
        - Active peptic ulcer disease
        - History of severe hypertension that is currently adequately controlled
    - *Hemorrhage* is the most frequent and the most serious complication of fibrinolytics
        - Hemorrhagic strokes occur in ~0.5–0.9% of patients (rates increase with advanced age > 70 years)
    - Minimize unnecessary venous or arterial interventions if receiving fibrinolytics

HOSPITAL MANAGEMENT OF STEMI

- After reperfusion therapy, patients should be admitted to the cardiac ICU
- Continuous telemetry monitoring
- Bedrest for the first 6–12 h (reduces work of the heart), then sit in a chair with feet dangling within the first 24 h (reduces pulmonary capillary wedge pressure)
- Nothing by mouth or only clear liquids for the first 4–12 h (risk of emesis and aspiration soon after STEMI), then provide a cardiac diet

ANTITHROMBOTIC AGENTS

- Antiplatelets (see NSTE-ACS section for details of drugs)
    - Continue aspirin, 81 mg daily
    - Add a $P2Y_{12}$ inhibitor, such as clopidogrel, ticagrelor, or prasugrel
    - Treatment duration and strategies are similar to those in the NSTE-ACS section
- Anticoagulation (see NSTE-ACS section for details of drugs)
    - Unfractionated heparin (UFH) infusion (should start near pre-PCI) initial bolus of 60 U/kg (max 4000 U) followed by an initial infusion of 12 U/kg/h (max 1000 U/h)
        - The aPTT target is 1.5–2 times the control value
    - After PCI or fibrinolysis, can switch to low-molecular-weight heparin (LMWH), 1 mg/kg bid
        - Enoxaparin is superior to UFH but has increased bleeding rates (safety outcomes and efficacy still favor LMWH)
        - If PCI is performed and the patient has no other indications for anticoagulation, anticoagulation can usually discontinue shortly after PCI
    - Bivalirudin or fondaparinux are other options but have complexities in data interpretation and administration
    - If an anticoagulant is needed for AF, strategies are similar to the NSTE-ACS section

β-BLOCKERS

- Indicated for most patients, especially those with a reduced ejection fraction post-MI
- Contraindications
    - Acute HF or severely compromised LV function
    - Heart block
    - Orthostatic hypotension
    - History of asthma (relative contraindication)
- Some patients with an excellent long-term prognosis (an expected mortality rate of < 1% per year, patients < 55 years, no previous MI, with normal ventricular function, no complex ventricular ectopy, and no angina) have markedly diminished potential benefit of β-blocker therapy

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) INHIBITORS

- ACE-Is reduce the mortality rate after STEMI [5], and the mortality benefits are additive to those achieved with aspirin and β-blockers
    - Maximum benefit is seen in high-risk patients (anterior infarction, a prior infarction, and/or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE-Is are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic BP > 100 mm Hg) from ventricular remodeling and subsequent reduction in the risk of HF
    - Prescribe indefinitely after STEMI in patients with
        - Clinical HF
        - An imaging study showing a reduction in global LV function or a large regional wall motion abnormality, or
        - Hypertension

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- ARBs should be administered to STEMI patients who are intolerant of ACE-Is and have either clinical or radiologic signs of HF
- Spironolactone or eplerenone should be prescribed for patients who
  - Are already receiving therapeutic doses of ACE-I/ARBs
  - Have an ejection fraction (EF) ≤ 40%
  - Have either symptomatic HF or diabetes, and
  - Do not have significant kidney dysfunction (creatinine ≥ 2.5 g/dL in men or ≥ 2.0 g/dL in women) or hyperkalemia (≥ 5.0 mEq/L)
- Angiotensin receptor–neprilysin inhibitors
  - Are more effective than ACE-I/ARB therapy in patients with symptomatic HF and reduced EF
  - However, they are not more effective than ACE-I/ARB therapy in preventing the development of incident HF in patients early post-MI

ADJUNCT THERAPIES

- High-dose statins (atorvastatin 40 or 80 mg qhs)
  - If LDL not at goal over time, consider ezetimibe or PCSK9 inhibitors (see NSTE-ACS section)
- Colchicine at a low dose can be considered to reduce major adverse cardiac events after MI, but low-quality evidence reflects its use
- Control blood glucose while in the hospital (reduces mortality rate)
- Measure serum magnesium and potassium and correct deficits to minimize the risk of dysrhythmias
- All patients should receive an echocardiogram to assess LV function
- Cardiac rehabilitation, if available, should be utilized while hospitalized and continued after discharge
- Some patients, after primary reperfusion has occurred, may ultimately need CABG surgery [6,7]
  - Patients who need to be referred for multidisciplinary CABG evaluation have
    - Three-vessel disease
    - Two-vessel disease with significant proximal left anterior descending artery (LAD) stenosis and either ejection fraction (EF) < 50% or demonstrable ischemia on noninvasive testing
    - Multivessel disease with diabetes
    - Significant left main coronary artery stenosis
    - Left main coronary artery equivalent disease ≥ 70% stenosis of proximal left LAD and proximal left circumflex artery
- Certain patients may benefit from primary prevention of sudden cardiac death (SCD) with the placement of an implantable cardioverter defibrillator (ICD)
  - ICD placement depends on the patient's EF, NYHA class, and whether NSVT or inducible NSVT is present
  - Cardiology should help guide which patients are referred for ICD placement

RV INFARCTION

- Conventional ECG shows ST elevation in II, III, and aVf for inferior wall MI (can also include RV) and ST depression in V_1 and V_2 for posterior MI
- Confirm RV infarction with a right-sided ECG (V_4R)
- Patients may have exam findings of JVD, peripheral edema, bradycardia, and clear lung fields
- Do not administer β-blockers, nitroglycerin, or morphine
  - These patients are preload dependent, and these agents will reduce preload
- Administer IV fluid boluses to improve preload
- Have atropine available, as symptomatic bradycardia may occur (the right coronary artery supplies the AV node)
- Otherwise, manage as NSTE-ACS and STEMI

COMPLICATIONS

- RV and/or LV failure (see Chap. 20)
- Hypovolemia
- Cardiogenic shock
- Dysrhythmias (most common cause of sudden death after MI)
  - Accelerated idioventricular rhythm (benign finding if within 24 h)
  - Heart block
  - Sinus node dysfunction
  - Supraventricular rhythms (sinus tachycardia, atrial flutter, AF, accelerated junctional rhythms)
  - Ventricular premature beats

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TABLE 19-6 Mechanical Complications of STEMI

CHARACTERISTIC	VENTRICULAR SEPTAL RUPTURE	RUPTURE OF THE VENTRICULAR FREE WALL	PAPILLARY MUSCLE RUPTURE
Incidence	0.2–3% without reperfusion therapy, 0.2–0.34% with fibrinolytic therapy, 3.9% in patients with cardiogenic shock	Approximately 0.3–1%; fibrinolytic therapy does not reduce risk; primary PCI seems to reduce risk	Approximately 0.1–1% (posteromedial more frequent than anterolateral papillary muscle rupture)
Time course	Bimodal peak; within 24 h and 3–5 days; range, 1–14 days	Bimodal peak; within 24 h and 3–5 days; range, 1–14 days	Bimodal peak; within 24 h and 3–5 days; range, 1–14 days
Clinical manifestations	Chest pain, shortness of breath, hypotension	Anginal, pleuritic, or pericardial chest pain; syncope; hypotension; restlessness; sudden death	Abrupt onset of shortness of breath and pulmonary edema; hypotension
Physical findings	Harsh holosystolic murmur, thrill, S_3, accentuated S_2, pulmonary edema, RV and LV failure, cardiogenic shock	JVD (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic shock	A soft murmur in some cases, no thrill, variable signs of RV overload, severe pulmonary edema, cardiogenic shock
Echocardiographic findings	Ventricular septal rupture, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload	> 5-mm pericardial effusion not visualized in all cases; layered, high-acoustic echoes within the pericardium (blood clot); direct visualization of tear; signs of tamponade	Hypercontractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe mitral regurgitation on color flow Doppler echocardiography
Right-heart catheterization	Increase in oxygen saturation from the RA to RV, large *v* waves	Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures in the cardiac chambers)	No increase in oxygen saturation from the RA to RV, large *v* waves, very high PCWP

PCWP, pulmonary capillary wedge pressure; RA, right atrium. Reproduced with permission from Bohula EA, Morrow DA: ST-elevation myocardial infarction: Management, in *Braunwald's Heart Disease*, 12th ed, Libby P et al (eds). New York, Elsevier, 2022, pp 662-713.

    - Ventricular tachycardia
    - Ventricular fibrillation
- Mechanical complications (Table 19-6 provides further details of select complications)
    - Free wall rupture
    - Ventricular septal defect
    - Papillary muscle rupture → mitral regurgitation
    - LV thrombus → requires full anticoagulation for 3 months; can use a DOAC
    - Ventricular aneurysm and pseudoaneurysm
        - Persistent ST-segment elevation
- Pericarditis
- Thromboembolism
- Dressler's syndrome
    - Autoimmune disease with fever and increased ESR that occurs weeks after the MI

PROGNOSIS

- Patients with documented NSTE-ACS exhibit a wide spectrum of early (30 days) risk of death, ranging from 1% to 10%, and a recurrent ACS rate of 5–15% during the first year
- The 1-year mortality rate after STEMI is ~15% and is fourfold higher in patients > 75 years
- The long-term prognosis is poor in patients with a STEMI, but the mortality rate has improved with early reperfusion therapies and medical therapy

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PATHOPHYSIOLOGY

NSTE-ACS

- Imbalance of oxygen demand/supply, most commonly from one of three processes that lead to coronary arterial thrombosis
  - Plaque fissure with inflammation (increased activity of effector T cells from immunity dysregulation)
  - Plaque fissure without inflammation
  - Plaque erosion, which is present in at least one-third of ACS and is recognized with increased frequency
- A fourth process, without thrombosis, may be caused by epicardial or microvascular spasm or increased myocardial oxygen demand, typically in the presence of fixed epicardial coronary obstruction
- Partially occluding lipid-laden thrombus forming on a disrupted atherothrombotic plaque with subsequent intravascular thrombus leading to flow-limiting but nonocclusive subendocardial ischemia leads to ST depressions (**Fig. 19-6**)
- Coronary spasm, progressive coronary atherosclerosis, increased oxygen demand from fever, tachycardia, hypotension, or thyrotoxicosis worsens ischemia

STEMI

- Coronary blood flow decreases abruptly after thrombotic occlusion of a coronary artery previously affected by atherosclerosis at a site of vascular injury
  - This injury is produced or facilitated by factors such as
    - Cigarette smoking
    - Hypertension
    - Lipid accumulation
    - Inflammation
- In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted either through erosion or rupture, and conditions (local or systemic) favor thrombogenesis
- Plaques prone to rupture have a rich lipid core and a thin fibrous cap, but other characteristics include expansive remodeling, neovascularization (angiogenesis), plaque hemorrhage, adventitia inflammation, and a "spotty" pattern of calcification
- A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded (Fig. 19-6)
- After an initial platelet monolayer forms at the site of the disrupted plaque, various agents (collagen, adenosine diphosphate, epinephrine, serotonin) promote platelet activation
- Platelet activation → thromboxane A_2 and fibrin are released, and potential resistance to fibrinolysis develops
- The glycoprotein IIb/IIIa receptor changes its conformation into its functional state and develops a high affinity for soluble adhesive proteins such as fibrinogen, resulting in further platelet binding and platelet cross-linking and aggregation

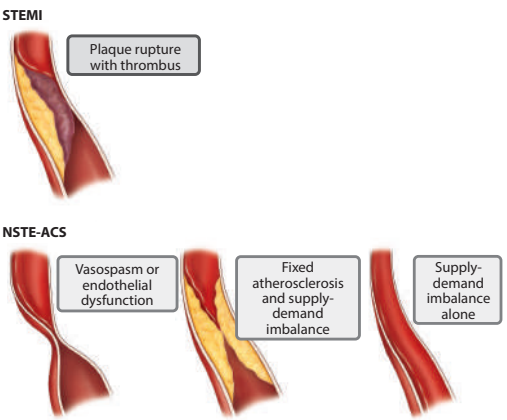

FIGURE 19-6 Pathophysiology of MI and NSTE-ACS. (Reproduced with permission from Huppert LA, Dyster TG. Diseases and pathophysiology in cardiology, in *Huppert's Notes: Pathophysiology and Clinical Pearls for Internal Medicine*, LA Huppert, TG Dyster (eds). New York, McGraw Hill, 2021.)

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- The coagulation cascade is activated, activating factors VII and X, leading to conversion of prothrombin into thrombin, and fibrinogen into fibrin
- Rarely, STEMI may be due to coronary emboli, congenital coronary abnormalities, coronary vasospasm, or spontaneous coronary artery dissection
- Transluminal fully occlusive ischemia leads to ST elevations

RISK FACTORS

- Modifiable risk factors
  - Diabetes mellitus: goal hemoglobin A_{1c} < 7.0
  - Smoking
  - Hypertension: goal BP < 140/< 90 mm Hg
  - Hyperlipidemia
    - Goal LDL < 100 mg/dL; better if < 55 mg/dL
    - Goal HDL > 40 mg/dL; better if > 60 mg/dL
- Nonmodifiable risk factors
  - Sex (men; then women have a higher risk of mortality from heart disease after menopause)
  - Family history of CAD

ADMITTING ORDERS

- Admit to the medicine floor or cardiac ICU
- Diagnosis: NSTE-ACS/STEMI
- Condition: guarded
- Vital signs: unit routine, continuous telemetry
- Activity: bedrest
- Nursing
  - Oxygen supplementation to maintain oxygen saturation > 90%
  - IV access
  - Check glucose before each meal and bedtime
  - Call clinician for recurrent chest pain or systolic BP < 100 mm Hg or > 180 mm Hg or heart rate < 50 beats/min or > 100 beats/min
- Diet: nothing by mouth or clear liquids for first 4–12 h, then cardiac diet
- Fluids: depends on fluid status and whether there are signs of HF
- Diagnostic tests
  - ECG
  - CXR
  - Troponins
  - CBC
  - CMP
  - PT/PTT/INR
  - Lipids
  - Magnesium and phosphate
  - BNP
  - D-dimer if indicated
  - Echocardiogram
- Medications
  - Aspirin chewed 325 mg, then 81 mg PO daily
  - Sublingual nitroglycerin
    - Dose: 0.4 mg × 3 in 5-min intervals
    - Contraindicated by signs of right-sided HF (JVD, edema), hypotension, or heart rate < 50 beats/min
    - Also contraindicated if patient has recently taken sildenafil or α_2-blockers
  - β-Blockers
    - IV metoprolol tartrate, 5 mg q2min × 3 doses, then 25 mg PO q6–12h
    - Contraindicated if
      - Heart rate < 50 beat/min
      - Hypotension
      - Bronchospasm (relative contraindication) or
      - Signs of right-sided HF (JVD, edema)

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- Morphine IV 2–5 mg q5–30min if pain not controlled
- Unfractionated heparin infusion or enoxaparin 1 mg/kg subcutaneously
- Atorvastatin, 40–80 mg qhs
- A $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel)
- ACE-I within 24 h
- Coronary angiography according to TIMI risk score, within 90 min on arrival if STEMI
- Fibrinolysis within 30 min of presentation if no timely PCI available
  - Recombinant tissue plasminogen activator (tpA) (alteplase), 15-mg bolus then 50 mg IV over 30 min
    - Contraindications: cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (systolic BP > 180 and/or diastolic > 110 mm Hg) at any time during the acute presentation, suspicion of aortic dissection, active internal bleeding (excluding menses)

DISCHARGE INFORMATION

- Provide education on all new medications, their importance, and duration they are to be used
- Educate on management of risk factor modification, including BP goal, smoking cessation, diabetes management, appropriate BMI goal, and the importance of exercise
- Refer to cardiac rehabilitation before discharge
- Schedule follow-up with primary care provider and cardiology

CASE ANSWERS

1. This patient's chest pain description and appearance on exam are concerning for ACS. With the ECG showing ST elevations in the anterior leads, this is a STEMI until proven otherwise.
2. For all patients with a STEMI, aspirin 325 mg, sublingual nitroglycerin, IV β-blockers, and potentially IV morphine (if the pain is resistant to nitroglycerin) should be administered for antiplatelet and anti-ischemic therapy in the ED. Anticoagulation with heparin and the addition of a $P2Y_{12}$ inhibitor should be initiated with the guidance of cardiology.
3. Reperfusion strategies include either primary PCI or fibrinolysis. PCI is the preferred strategy if a capable PCI center is within 120 min. Therefore, this patient (150 min away from a PCI center) should receive fibrinolysis assuming they have no contraindications. A "door-to-needle time" of ≤ 30 min is the goal of fibrinolysis. Afterward, the patient should be transferred for angiography at a PCI-capable hospital.

LANDMARK TRIALS

[1] Schwartz GG et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A randomized controlled trial. JAMA 285:1711, 2001. [PMID: 11277825]
- *Summary:* The MIRACL trial showed that early initiation of atorvastatin post–NSTE-ACS reduced the combined endpoint of death, nonfatal MI, cardiac arrest, and ACS requiring hospitalization at 16 weeks compared with placebo.

[2] Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045, 2009. [PMID: 19717846]
- *Summary:* The PLATO trial showed that compared with clopidogrel, ticagrelor significantly reduced the rate of CV death, MI, or stroke, but with an increased bleeding rate.

[3] Invasive compared with noninvasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and fast revascularisation during InStability in Coronary artery disease Investigators. Lancet 354:708, 1999. [PMID: 10475181]
- *Summary:* The FRISC II trial showed that among intermediate- to high-risk patients with NSTE-ACS, an early invasive strategy is associated with fewer recurrent MIs and improved long-term survival compared with a noninvasive strategy.

[4] Wiviott SD et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 380:347, 2019. [PMID: 30415602]
- *Summary:* The COMPLETE trial showed that among patients with STEMI and multivessel CAD, complete revascularization was superior to culprit lesion–only PCI in reducing the risk of CV death or MI, as well as the risk of CV death, MI, or ischemia-driven revascularization.

[5] GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet 343:1115, 1994. [PMID: 7910229]

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- *Summary:* The GISSI-3 trial showed that lisinopril reduces the odds of 6-week mortality by 11% when administered within 24 h of acute MI.

[6] Serruys PW et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 360:961, 2009. [PMID: 19228612]
- *Summary:* The SYNTAX trial showed that CABG resulted in fewer major CV events at 1 year compared with PCI among patients with three-vessel and/or left main disease.

[7] Stone GW et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 375:2223, 2016. [PMID 27797291]
- *Summary:* The EXCEL trial showed that in patients with left main CAD and low-intermediate anatomic complexity, PCI with second-generation drug-eluting stents is noninferior to CABG with respect to a primary outcome of death, stroke, or MI at 3 years, though with a nonsignificant trend toward increased mortality.

FURTHER READING

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20 Heart Failure

KEY POINTS

1. Heart failure (HF) results from the inability of the heart to pump sufficient blood to meet the metabolic demands of the body. It is a major cause of morbidity and mortality worldwide, and a high economic and resource burden on the health care system.
2. HF is often initially asymptomatic. Then, as the disease progresses, patients becomes gradually symptomatic with dyspnea, fatigue, and weight gain from excess fluid buildup. These symptoms manifest as orthopnea, paroxysmal nocturnal dyspnea, and bendopnea. Exam findings that are helpful in diagnosing HF and acute HF include presence of JVD and a positive hepatojugular reflex, laterally displaced apical impulse, and an S_3 gallop.
3. HF is a clinical diagnosis and is defined as having symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality and at least one of the following: (1) elevated BNP or (2) objective evidence of cardiogenic pulmonary or systemic congestion. An echocardiogram is essential to assess the structure and function of the myocardium and categorizes patients into HF with reduced, mildly reduced, or preserved ejection fraction (HFrEF, HFmrEF, and HFpEF, respectively), which is important for chronic management strategies. In acute HF, a troponin, BNP, CBC, CMP, iron studies, UA, ECG, and CXR are indicated to assess the severity and potential precipitating factors of the HF exacerbation.
4. For patients with acute HF, diuretics to reduce elevated left-sided filling pressure are the mainstay of management. In HFrEF, medication classes that improve clinical outcomes include ARNIs/ACE-Is/ARBs, β-blockers, mineralocorticoid receptor antagonists, and SGLT-2Is. HFmrEF is treated similarly to HFrEF. For HFpEF, SGLT-2Is have the best evidence, while ARNIs/MRAs can be considered in select patients. For all classes, diuretics control fluid congestion and improve symptoms and rates of HF hospitalizations, but not mortality. Control of chronic comorbidities and risk factor modification are recommended for all HF classes.
5. Patients with acute HF commonly have AKI termed *cardiorenal syndrome*. Worsening valvular disease, AF, cor pulmonale, and recurrent hospitalizations are other common complications of HF. The overall 5-year survival following the diagnosis of HF is ~50%. Following HF admission, mortality rates are 8–14% at 30 days, 26–37% at 1 year, and up to 75% at 5 years, with a short-term mortality of 5% while hospitalized.

EPIDEMIOLOGY & DEFINITIONS

HF is a major cause of morbidity and mortality worldwide. An estimated 6.7 million American adults are being treated for HF, with > 600,000 new cases diagnosed each year. Globally, it is estimated that 56.2 million people are living with HF with prevalence varying greatly by country. The prevalence increases significantly with age (Fig. 20-1). The lifetime risk of HF has increased to 24%, and data suggest the prevalence of HF will rise to 8.5 million Americans by 2030. Rates of HF hospitalizations in the United States declined from 2010 to 2014, followed by an increase from 2014 to 2017. The overall cost of HF care is high (~$22.3 billion in the United States in 2018) and rising, with costs for HF hospitalization expected to reach $70 billion in 2030.

HF: the inability of the heart to pump sufficient blood to meet the metabolic demands of the body, defined as having symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality and at least one of the following: (1) elevated BNP levels or (2) objective evidence of cardiogenic pulmonary or systemic congestion.

Chronic HF: the long-standing symptoms and/or signs of HF treated with medical and device therapy in patients who are at risk for worsening HF.

Acute HF (also termed *acute decompensated HF*): the rapid onset of worsening symptoms of HF.

Acute pulmonary edema: a clinical scenario in which a patient presents with rapidly worsening signs and symptoms of pulmonary congestion typically due to severely elevated left heart filling pressures.

HF with reduced ejection fraction (HFrEF): HF associated with an EF of < 40%; formerly known as *systolic HF*, it occurs primarily from ischemic and nonischemic cardiomyopathy.

HF with preserved ejection fraction (HFpEF): HF associated with an EF of ≥ 50%; formerly known as *diastolic HF*, it occurs primarily from hypertensive, infiltrative, and hypertrophic heart diseases.

HF with mildly reduced ejection fraction (HFmrEF): HF associated with an EF of 40–49%.

New York Heart Association (NYHA) Functional Classification (Table 20-1): categorizes patients based on the amount of effort required to provoke breathlessness. The NYHA does not correlate well with other objective

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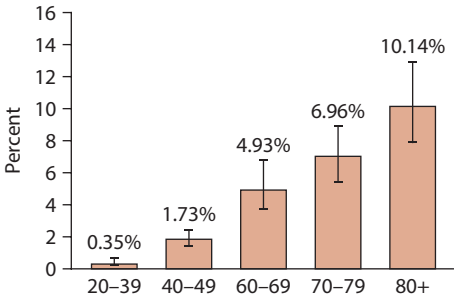

FIGURE 20-1 HF prevalence by age categories. Prevalence of heart failure among U.S. adults ≥ 20 years of age by age, from the National Health and Nutrition Examination Survey (NHANES), 2017–2020. (Reproduced with permission from Bozkurt B et al: *J Card Fail*. 2023; 29:1412.)

measures of cardiac structure (i.e., LV size or EF) or function (e.g., peak oxygen consumption). Patients can move between classes based on their current symptoms.

American College of Cardiology/American Heart Association (ACC/AHA) HF Classification: categorizes patients into both structural and functional categories. As opposed to the NYHA, once patients move from one category to a more advanced category, they cannot be recategorized to a lower category.

- Stage A: at risk for HF but without structural heart disease or symptoms of HF
- Stage B: structural heart disease but without signs or symptoms of HF
- Stage C: structural heart disease with prior or current symptoms of HF
- Stage D: refractory HF requiring specialized interventions

CLINICAL VIGNETTE

A 70-year-old man presents to the ED with progressively worsening shortness of breath over the last week. At baseline, he can walk three times around his neighborhood block before he becomes dyspneic, but 6 days ago the dyspnea began much earlier, and over the past 2 days it has occurred with minimal activity inside of the house (such as cooking or dressing himself). Normally, he sleeps with two pillows to prop his head up to avoid dyspnea at night but made a transition to his living room recliner due to nighttime awakenings with gasping for air.

On review of systems, he has bilateral lower extremity edema, and his weight has increased by 9 kg over the last month. He has a history of HF, which was diagnosed 5 years ago, and his last transthoracic echocardiogram was 6 months ago, showing an EF of 35%. He states he recently moved across the country to live closer to his son and has not yet established care with a primary care physician or cardiologist. He ran out of all his medications 1 month ago. On exam, he is afebrile, heart rate is 110 beats/min, respiratory rate is 20 breaths/min, BP is 172/86 mm Hg, and oxygen saturation is 86% on room air. The JVP is 12 cm, and the hepatojugular reflux test is positive. The heart rate is regular on palpation, and there is an S_3 gallop on auscultation. There are diffuse crackles on pulmonary exam with dullness to percussion in the bilateral lower lung fields. His lower extremities have 2+ dependent pitting edema up to the knees bilaterally.

TABLE 20-1 New York Heart Association Functional Classification

FUNCTIONAL CLASS	LIMITATION	CLINICAL ASSESSMENT
I	None	Ordinary physical activity does not cause undue fatigue, dyspnea, palpitations, or angina.
II	Mild	Comfortable at rest. Ordinary physical activity (e.g., carrying heavy packages) may result in fatigue, dyspnea, palpitations, or angina.
III	Moderate	Comfortable at rest. Less than ordinary physical activity (e.g., getting dressed) leads to symptoms.
IV	Severe	Symptoms of heart failure or angina are present at rest and worsen with any activity.

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GUIDING QUESTIONS

1. What diagnostic tests would you order?
2. What medications would you administer in the ED?
3. What medications are indicated for the treatment of this patient's chronic HF to maximize clinical outcomes?

HISTORY

The onset of HF is usually gradual, but it can be precipitated by certain events (e.g., MI). The most common complaints stem from volume overload with elevation in pulmonary and/or venous pressures. Dyspnea is a cardinal manifestation of left HF and may arise with increasing severity as exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Other symptoms to evaluate for in acute HF are fatigue, edema, confusion, and abdominal pain. It is important to inquire in the history about

1. Current versus baseline functional status
2. Weight gain
3. Medications
4. Recent changes in medications
5. Last performed echocardiogram

As HF is usually long-standing in early stages, patients may become symptomatic before a diagnosis is made. In this situation, many precipitating factors may change a patient's asymptomatic chronic HF into acute HF at the time of diagnosis in a hospitalization. Table 20-2 describes precipitating factors in HF. These precipitants should be investigated in a patient with known chronic HF who comes to the ED with an acute HF episode.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - An older person with dyspnea, worsening orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and decreased exercise tolerance
- Dyspnea?
  - Most common symptom of left HF
  - Fast-shallow breathing is indicative of dyspnea from HF
  - Bendopnea: dyspnea when leaning forward; associated with increased cardiac filling pressures in a low cardiac output state

TABLE 20-2 Precipitating Factors in HF

Patient-Related
Excess exertion or emotional stress
Excess fluid and/or sodium intake
Nonadherence with medications
Heavy alcohol use
Provider-Related
Use of medications that cause salt and water retention (e.g., NSAIDs)
Prescribed use of medications with negative inotropic properties (e.g., calcium channel blocker)
Unrecognized congestion and inadequate use of diuretics
HF-Related
Uncontrolled hypertension
Myocardial ischemia or MI
Atrial or ventricular dysrhythmias
PE
Other Disease States
Systemic infection
Worsening renal or liver failure
Hyperthyroidism
Untreated sleep apnea
Anemia or iron deficiency syndrome

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- Dyspnea on exertion worse than baseline?
  - Indicates they may have an acute exacerbation of their HF, but could also be a COPD exacerbation or other conditions
- Fatigue? Weakness?
  - Common symptoms of left HF with a low cardiac output state
- Orthopnea?
  - Worsening? How many pillows do you sleep with, and is this more than normal?
  - Patients may sleep in a recliner chair when worsening
  - Usually occurs later in the acute HF disease course than dyspnea on exertion
- Nocturnal cough?
  - Symptom of left HF that is often overlooked
- Paroxysmal nocturnal dyspnea?
  - Dyspnea that awakens a patient suddenly from sleep with feelings of anxiety and suffocation, requiring them to sit upright for relief
  - Symptom of left HF and may be associated with coughing and wheezing
- Sputum production?
  - Pink and frothy in quality
  - Can be a sign of pulmonary vascular congestion and edema surrounding the bronchi
- Wheezing?
  - HF can cause wheezing from edema around the bronchi called cardiac asthma
- Confusion?
  - Sign of inadequate brain perfusion, late sign of HF with a low-cardiac-output state
- Nocturia?
  - Symptom of right HF; lying supine improves cardiac output and renal perfusion, causing diuresis at night
- Chest pain?
  - Can be a sign of acute ischemia causing LV failure, which needs to be addressed immediately
- Edema?
  - Dependent pitting edema that is worsened with prolonged standing and better with leg elevation
- Early satiety? Anorexia?
  - Can be a sign of right HF if there is hepatomegaly/ascites
- Nausea?
  - Can be a symptom of acute ischemia or right HF from ascites, hepatomegaly, and bowel edema
- Abdominal pain/bloating?
  - This is usually overlooked, but if the patient is having abdominal pain, this can be from hepatomegaly causing stretching of the liver capsule, ascites, or gut edema from right HF

PAST MEDICAL HISTORY

- History of HF?
  - How was it diagnosed?
  - How is it being treated?
  - History of exacerbations?
  - Last echocardiogram?
- History of CAD?
  - How was it diagnosed?
  - How is it being treated?
- History of diabetes mellitus?
  - How is it being treated?
  - Last HbA_{1c}?
  - Compliance with diet and medications?
- History of hypertension?
  - How is it being treated?
  - Adherence with diet and medications?
- History of hyperlipidemia?
  - How is it being treated?

SOCIAL HISTORY

- Alcohol use: binges can cause acute HF episodes
- Smoking
- Use of recreational drugs (specifically methamphetamine use)
- Occupation

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- Living situation
- Sexual history

FAMILY HISTORY

- History of cardiomyopathy in the family?

MEDICATIONS

- If they have a history of HF, check for medication adherence
- Ask about medications that can worsen or cause HF
  - NSAID use?
  - Calcium channel blocker use?
  - Thiazolidinedione (TZD) use?
  - Doxorubicin or trastuzumab use?

PHYSICAL EXAM

The physical exam will check fluid status, mental status, pulse pressure, fever, and signs of shock. This will help you determine whether the patient is wet or dry, and warm or cold. This will help guide your treatment plan during acute HF episodes.

Likelihood ratios for individual positive or negative findings on physical exam can be clinically useful in determining whether HF exists. When a finding can be either positive or negative, then the likelihood ratios are called the *positive likelihood ratio* (PLR) or the *negative likelihood ratio* (NLR). A finding that has a PLR > 1 indicates that the positive finding is associated with the presence of HF; a finding that has an NLR of < 1 indicates that the finding is associated with the absence of HF. The further either ratio is from 1, the more likely HF is either present or absent. For example, a PLR of 3 = 20% probability patient has condition, a PLR of 4 = 25% probability patient has condition, a PLR of 5 = 30% probability patient has condition, and a PLR of 10 = 45% probability patient has condition.

- General appearance
  - In severe acute HF, the patient may not be able to lie flat, will sit upright, and may not be able to finish a sentence due to severe dyspnea
  - May have pallor from anemia or duskiness because of a low cardiac output
  - Cachexia
    - With severe chronic HF may have weight loss and bitemporal or upper extremity wasting with cachexia
    - Poor prognostic factor if cachexia is present
- Vital signs
  - Hypertension may initially be present
  - Hypotension and decreased pulse pressure can be signs of cardiogenic shock
  - Hypoxemia and tachypnea may be present; may have Cheyne-Stokes respirations in advanced HF
  - Tachycardia is often present (PLR 5.5) to compensate for a low stroke volume
  - Abnormal Valsalva response (PLR 7.6)
- Cardiac
  - Lateral point of maximal impulse displaced downward and to the left (PLR 5.8)
  - S_3 gallop (PLR 3.9 for reduced EF)
  - S_4 (sign of preserved EF)
  - Holosystolic murmurs of mitral and tricuspid regurgitation are present in advanced HF
  - May have an irregularly irregular rhythm if also has AF
  - Thready pulse is present in cardiogenic shock
  - Pulsus alternans: reduced LV contraction in every other cardiac cycle due to incomplete recovery causing reduction in the LV stroke volume with each alternate beat
  - JVP exam
    - Normal JVP is ≤ 8 cm
    - If elevated, can be a sign of right HF (PLR 3.9)
    - JVD with hepatojugular reflex (PLR 8.0): putting pressure on the liver increases pressure from the inferior vena cava → superior vena cava, causing JVD
    - Kussmaul's sign (elevation of JVP during inspiration) may be present in severe biventricular HF; poor prognostic sign if present
  - Bendopnea test (PLR 3.2)
    - The patient sits in a chair and bends forward at the waist as if putting on their shoes
    - The time to dyspnea (if it develops) is measured
    - If dyspnea develops within 30 s, the test is positive, indicating that there are elevated left heart filling pressures

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- Respiratory
  - Crackles (from transudation of fluid from the intravascular space into the alveoli) may be heard in all lung fields in acute HF or pulmonary edema
    - Crackles may be absent in long-standing chronic HF due to the increased ability of lymphatic drainage from chronically elevated pulmonary capillary wedge pressures
  - Wheezing and rhonchi (from congestion of the bronchial mucosa)
  - Dullness to percussion with pleural effusions (either bilateral or right-sided)
- Abdomen
  - Hepatomegaly
    - Sign of right HF, usually tender if present
    - The liver may pulsate during systole if tricuspid regurgitation is present
  - Splenomegaly and ascites are present in long-standing hepatic congestion
- Extremities
  - Lower extremity edema
    - Dependent, symmetric, and pitting
    - May become reddened and indurated with weeping over time
  - Anasarca: massive, generalized edema involving the legs, sacrum, and abdominal wall in advanced volume-overloaded states
  - Cool extremities? Peripheral cyanosis?
    - This is a feature of cardiogenic shock

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS OF HF BY SIGN OR SYMPTOM

- Dyspnea
  - COPD: causes dyspnea, dyspnea on exertion, increased cough, wheezing, and prolonged expiratory phase from chronic lung disease similar to left HF symptoms
  - Pneumonia: causes dyspnea and dyspnea on exertion, but has an acute onset of fever/chills and productive cough
  - PE: dyspnea, tachycardia, hypoxemia, with an unrevealing CXR; if large, can cause symptoms of right HF with JVD and edema
  - Pulmonary arterial hypertension: dyspnea on exertion, clear lung fields, loud P_2, can have edema
  - Anemia and iron-deficiency anemia: reduced oxygen-carrying capacity of blood, causing dyspnea
  - Neuromuscular causes of dyspnea (scoliosis, amyotrophic lateral sclerosis, myasthenia gravis): symptoms dependent on their specific etiology
- Edema
  - Venous insufficiency: bilateral edema with chronic reddening of the skin with ulcers and weeping, absence of JVD, hepatomegaly, and dyspnea
  - Nephrotic syndrome: no JVD; UA with significant proteinuria
  - DVT: unilateral leg edema with erythema and cramp-like pain
  - Lymphedema: unilateral and nonpitting edema of the involved extremity
  - Myxedema: nonpitting pretibial edema; has other features of hypothyroidism (e.g., fatigue, obesity, hair thinning, bradycardia, cold intolerance, constipation, delayed relaxation of deep tendon reflexes)
  - Cirrhosis: pitting edema, absence of JVD, presence of spider angiomata, caput medusae, jaundice, platypnea, and palmar erythema
- Ascites
  - Hepatic cirrhosis: causes edema, hepatomegaly at first, hypotension, but has other physical exam findings that are more specific to cirrhosis and the absence of JVD
  - Portal vein thrombosis: no JVD or dyspnea
  - Malignant carcinomatosis: cancer history, no JVD, tenderness to palpation of abdomen
- Pleural effusions
  - Chronic infection of the pleural space: night sweats, weight loss, no JVD
  - Lung cancer: weight loss, night sweats, extensive smoking history, no JVD, imaging findings of lung cancer
  - Collagen vascular or rheumatologic disease: historic clues of diseases are present, no JVD
- JVD
  - Constrictive pericarditis: pain typical of pericarditis, ascites, pulsus paradoxus (drop in BP > 10 mm Hg with inspiration) without Kussmaul's sign
  - Cardiac tamponade: presence of Beck's triad (hypotension, JVD, muffled heart sounds), pulsus paradoxus, and electrical alternans on ECG

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TABLE 20-3 Selected Causes of HF

HF with Reduced Ejection Fraction	
CAD	Nonischemic cardiomyopathy
MI	Infiltrative disorders
Myocardial ischemia	Familial disorders
	Tachycardia-induced
Valvular heart disease	Toxic cardiomyopathy
Aortic stenosis or regurgitation	Chemotherapy, immunotherapy
Mitral or tricuspid regurgitation	Drugs such as hydroxychloroquine
	Alcohol, cocaine
Congenital heart disease	Chronic lung/pulmonary vascular disease
Intracardiac shunts	Cor pulmonale
Repaired defects	Pulmonary arterial hypertension
Systemic RV failure	
Infectious	Autoimmune disease
Chagas	Giant cell myocarditis
HIV	Lupus myocarditis
HF with Preserved Ejection Fraction	
Hypertension	CAD
Valvular heart disease	Restrictive cardiomyopathy
Aortic stenosis	Amyloidosis
Mitral stenosis	Sarcoidosis
	Hemochromatosis
	Glycogen storage disease
Hypertrophic cardiomyopathy	Radiation therapy
Constrictive pericarditis	Aging
Myocarditis	Endomyocardial fibroelastosis
Obesity	End-stage renal disease
High-Output HF	
Thyrotoxicosis	Arteriovenous shunt
Obesity	Cirrhosis
Anemia	Vitamin B deficiency (beriberi)
Chronic lung disease	Myeloproliferative disorder

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- Superior vena cava syndrome: upper body swelling with bluish discoloration, cough, hoarseness, and positive Pemberton's sign (facial plethora, redness, and cyanosis appear after a patient elevates both arms above their head)

ETIOLOGY

The etiology of HF can be categorized on a patient's ejection fraction (EF) or high-output HF (Table 20-3). The most common cause of HF currently is CAD, accounting for 60–75% of cases, with hypertension contributing in ~75% of cases.

DIAGNOSTIC TESTS

LABS

- CBC
  - Evaluate for anemia, which can exacerbate underlying ischemic heart disease or quality of life; rarely, severe anemia can cause high-output HF
  - Leukocytosis may indicate a possible infectious source of dyspnea rather than HF
- CMP
  - Hyponatremia occurs in acute HF and is a poor prognostic finding in advanced HF
  - BUN/SCr usually rises in a prerenal state with acute HF (cardiorenal syndrome)
  - Check albumin levels (may be low in HF, cirrhosis, or nephrosis)

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- Long-standing right HF may lead to modest elevations in liver function tests
  - Marked elevations of AST/ALT with lactic acidosis from HF suggest cardiogenic shock with a low cardiac output state
- Manage hyperglycemia and electrolyte abnormalities

- Troponin
  - Rule out ischemia and MI as a cause of acute HF exacerbation
- BNP
  - An elevated BNP from baseline is suggestive of an acute HF episode
  - A useful test to differentiate dyspnea from HF from other etiologies of dyspnea
  - The BNP is higher in patients with HFrEF compared to patients with HFpEF
  - Can be used to establish disease severity and prognosis in chronic HF
  - Increases with the patient age and may be high in renal impairment
  - The BNP is falsely low in obese patients
- TSH
  - Evaluate for hypothyroidism causing myxedema as a differential of lower extremity edema
  - Evaluate for hyperthyroidism causing high-output HF
- UA
  - Order if have nocturia and/or polyuria
  - Also evaluate for proteinuria if edema is present to rule out nephrotic syndrome
- Lipid panel
  - Evaluates for dyslipidemia as a risk factor for ischemic cardiomyopathy
- Galectin-3 and soluble ST2: newer biomarkers approved for assessing prognosis in HF; not widely used currently
- Iron studies
  - Hospitalized patients with an acute HFrEF exacerbation benefit from intravenous iron supplementation depending on abnormalities in iron metabolism
- ABG if severe respiratory distress
  - Acute flash pulmonary edema may occur and lead to severe respiratory distress
- Other tests are reserved for targeted testing from history and exam to diagnose an etiology of HF
  - ANA
  - Rheumatoid factor
  - Serum free light chains
  - Serum protein electrophoresis
  - Ferritin
  - Ceruloplasmin
  - Hepatitis C
  - HIV

IMAGING

- ECG
  - Evaluate for
    - Dysrhythmias
    - LV hypertrophy (LVH)
    - Ischemia (new and/or old)
    - QRS width
    - Presence of a left bundle branch block
  - Reduced QRS voltage may be seen with restrictive or infiltrative cardiomyopathies
  - Acute ischemia causing acute HF exacerbation may be seen
  - A normal ECG virtually excludes LV systolic dysfunction
- CXR
  - HF typically reveals
    - An enlarged cardiac silhouette
    - Cephalization of interstitial markings
    - Kerley B lines (short, horizontal white lines seen on CXR indicating thickened lobular septa due to fluid or other infiltrates)
    - Pulmonary vascular congestion
  - Pleural effusions
    - May occur from elevation of pleural capillary pressure and the resulting transudation of fluid into the pleural cavities
    - Usually occurs bilaterally, but can occur unilaterally on the right

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- The absence of these findings in chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid
- Helps rule out COPD, pneumonia, and pneumothorax as other etiologies of dyspnea

- Transthoracic echocardiogram
  - Useful test as it assesses
    - LV size
    - Valvular anatomy and function
    - Regional wall motion abnormalities
    - Intracavity thrombi
    - Pericardial effusions
    - Overall function of the heart
  - Assesses EF (important for management purposes)
    - HFrEF shows depressed LVEF < 40%
    - HFpEF shows normal EF (≥ 50%), LVH, and abnormal diastolic filling on Doppler
- MRI
  - Gold standard test for LV mass, volumes, and function in determining specific causes of HF (e.g., ischemic cardiomyopathy, myocarditis, amyloidosis, hemochromatosis)

PROCEDURES

- Coronary angiogram when volume status is euvolemic
  - Most patients with HF should have a coronary angiogram to assess for an ischemic versus nonischemic etiology of HF
  - If MI is causing an acute HF episode, PCI can manage the myocardial ischemia
- Right heart catheterization and pulmonary artery catheter placement and monitoring
  - Confirms elevated pulmonary pressures
  - Not routinely performed in acute exacerbations; can be useful in the ICU to determine responses to intravenous vasoactive and diuretic therapy
- RV endomyocardial biopsy
  - Controversial procedure, but can
    - Detect myocarditis (lymphocytic, eosinophilic, sarcoid, or giant cell)
    - Diagnose cardiac amyloidosis
    - Diagnose chemotherapy- or immunotherapy-related LV failure
    - Screen for cardiac allograft rejection following heart transplant

DIAGNOSTIC APPROACH

- Figure 20-2 describes the diagnostic approach to the initial assessment of patients presenting with HF

MANAGEMENT

MANAGEMENT OF ACUTE DECOMPENSATED HF (ADHF)

It is important to classify the type of acute HF exacerbation because the type will change your management (Fig. 20-3). There are four different categories:

1. Typical
2. Pulmonary edema
3. Low output
4. Cardiogenic shock

ADHF is a heterogeneous clinical syndrome most often needing hospitalization due to the confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance.

GENERAL PRINCIPLES OF ADHF MANAGEMENT

- Manage the underlying cause of exacerbation (e.g., medication nonadherence, dietary salt indiscretion, medications [NSAIDs, thiazolidinediones, cold and flu preparations, etc.], coronary ischemia, dysrhythmias, worsening valvular disease, infection, VTE)
- The goal is to optimize hemodynamics, relieve congestion, reduce afterload, and maximize organ perfusion
- Supplemental oxygen if needed to maintain SpO_2 > 92%
- Sodium-restricted diet
- Fluid restriction only if hyponatremic
- Continuous telemetry monitoring

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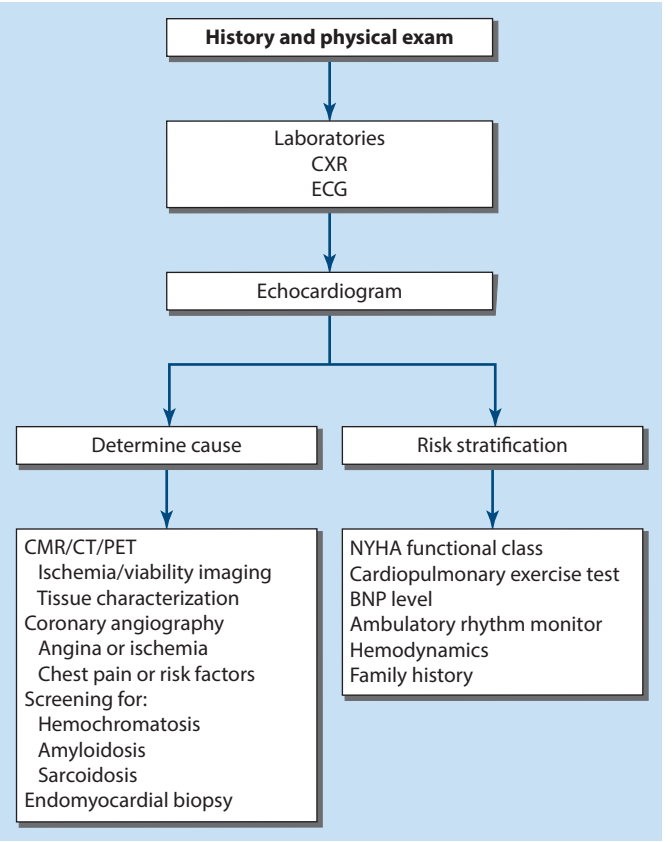

FIGURE 20-2 Initial assessment of patients presenting with HF. The initial evaluation starts with a thorough history and physical exam, focusing on detection of comorbidities including hypertension, diabetes, and hyperlipidemia. In addition, identification of valvular heart disease, vascular disease, history of mediastinal radiation, or exposure to cardiotoxins (e.g., chemotherapy, alcohol, illicit drugs) may help determine underlying cause. A family history of sudden death, HF, dysrhythmias, or cardiomyopathy is also useful. Routine laboratory evaluation (see text) should also be performed. CXR is useful to detect cardiomegaly and fluid overload and to rule out pulmonary disease. A 12-lead ECG should be performed to detect abnormalities of cardiac rhythm and conduction, LV hypertrophy, and evidence of myocardial ischemia or MI. Two-dimensional echocardiography with Doppler imaging is indicated to assess cardiovascular structure and function and detect abnormalities of the myocardium, heart valves, or pericardium. Further imaging and lab tests aimed at identifying a specific cause of cardiomyopathy depend on information obtained from the history and physical exam. In all patients, risk stratification should be performed to assess severity of illness, guide therapy, and provide prognosis to patient and family. CMR, cardiac magnetic resonance imaging; NYHA, New York Heart Association. (Reproduced with permission from Givertz MM, Mehra MR. Heart failure: Pathophysiology and diagnosis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Strict ins and outs (I/O) monitoring
- Daily standing weight measurement
- Frequent volume status exams to assess response to therapies (e.g., diuretics)
- Frequent electrolyte testing
  - With early aggressive intravenous diuresis, electrolyte abnormalities (hypokalemia, hypomagnesemia) can occur, and repletion to keep the K^+ and Mg^{2+} at least above 4.0 mEq/dL and 2.0 mg/dL, respectively, optimizes cardiac function
- Guideline-directed medical therapy (GDMT)
  - All patients should be continued and/or initiated on GDMT while hospitalized (see Management of Chronic HFrEF, HFmrEF, and HFpEF sections)

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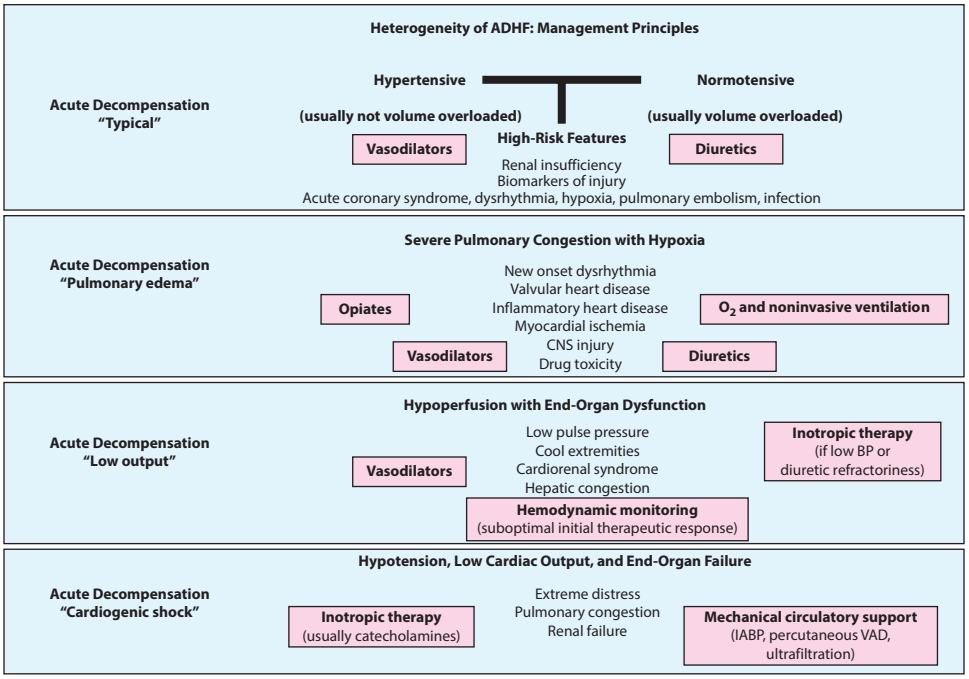

FIGURE 20-3 The distinctive phenotypes of acute decompensated HF (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not covered in this figure or text.) IABP, intra-aortic balloon pump; VAD, ventricular assist device. (Reproduced with permission from Desai A, Mehra MR. Heart failure: Management, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Continue β-blocker on admission unless the patient has cardiogenic shock, has severe volume overload, or was not consistently taking the medication prior to admission
  - Continuing β-blocker therapy was correlated with a propensity-adjusted lower risk of postdischarge death [HR], 0.60; 95% [CI], 0.37–0.99). However, withdrawing therapy correlated with higher propensity-adjusted mortality and a higher risk for mortality (HR, 2.3; 95% CI, 1.2–4.6).
- Continue SGLT-2I during admission
- Hold ACE-I/ARB/ARNI/MRA if in cardiogenic shock, SCr > 3 mg/dL, and/or potassium is > 5.5 mEq/dL on admit; otherwise, continue the medications
- Patients who were started on GDMT while hospitalized had higher rates of adherence to pharmacologic therapy and may be associated with improved outcomes in the early discharge interval

- Table 20-4 describes the doses and frequencies of diuretics, vasodilators, and inotropic therapies

VOLUME MANAGEMENT

- Intravenous loop diuretics (e.g., furosemide or bumetanide, with possible addition of metolazone or acetazolamide)
  - Dosing is based on their home PO dose (40 mg PO furosemide is equivalent to 20 mg IV furosemide)
    - Administer 2–2.5 times their home dose in intravenous formulation and then titrate from there based on I/Os and daily standing weights
  - The sooner diuretics are administered, the better the outcomes
    - Diuretics administered within 60 min lowered in-hospital mortality more than later treatment (2.3 vs 6%)
  - Among patients with ADHF, high-dose loop diuretics are associated with better symptom improvements than low-dose loop diuretics at the cost of some renal impairment, while continuous diuretic infusions are no better than intermittent diuretic boluses
    - If high doses of diuretics are required or when the effect is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels
  - The dose and frequency of diuretic therapy are an art (not a science), and adjustments are regularly needed

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TABLE 20-4 Vasoactive Therapy in Acute Decompensated HF

GENERIC DRUG	USUAL DOSING	SPECIAL CAUTION	COMMENTS
Diuretics			**First line of therapy in volume overload with congestion; initial IV high dose (2.5 × home dose) recommended knowing there is a higher risk of renal impairment compared to low dose (1 × home dose)**
Furosemide	20–240 mg/d	Monitor for electrolyte loss	In severe congestion, use intravenously and consider continuous infusion if requiring high doses
Torsemide	10–100 mg/d	Monitor for electrolyte loss	High bioavailability, can be given orally; anecdotally more effective in advanced HF states if furosemide less bioavailable (due to gut congestion)
Bumetanide	0.5–5 mg/d	Monitor for electrolyte loss	Can be used orally; intermediate bioavailability
Adjuvant diuretics for augmentation	N/A	Metolazone, chlorthalidone, spironolactone, acetazolamide	Acetazolamide is useful in presence of alkalosis (bicarbonate level > 27 mEq/L); metolazone given in 2.5- to 10-mg doses; concomitant use of loop diuretics and thiazides associated with risk for severe hypokalemia, careful laboratory monitoring advised; spironolactone is useful in presence of severe hypokalemia and normal kidney function
Vasodilators			**Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved BP**
Nitroglycerin	10–20 µg/min, increase up to 200 µg/min	Headache, flushing, tolerance	Most common vasodilator but often underdosed; effective in higher doses
Nesiritide	Bolus 2 µg/kg and infusion at 0.01 µg/kg/min	Hypotension	Decrease in BP may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
Nitroprusside	0.3 µg/kg/min titrated to 5 µg/kg/min	Thiocyanate toxicity in AKI and/or CKD (> 72 h)	Requires arterial line placement for titration for precise BP management and prevention of hypotension
Inotropic Therapy			**Use in hypotension, end-organ hypoperfusion, or shock states**
Dobutamine	2–20 µg/kg/min	Increased myocardial oxygen demand, dysrhythmia	Short acting, an advantage; variable efficacy in presence of β-blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
Milrinone	0.375–0.75 µg/kg/min	Hypotension, dysrhythmia	Decrease dose in AKI and/or CKD; avoid initial bolus; effectiveness retained in presence of β-blockers
Levosimendan	0.1 µg/kg/min; range, 0.05–0.2 µg/kg/min	Hypotension, dysrhythmia	Long acting; should not be used in presence of low BP; similar effectiveness as dobutamine but effectiveness retained in presence of β-blockers

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- For those refractory to loop diuretics, addition of a thiazide, such as chlorthalidone or IV metolazone, to provide sequential nephron blockade, may enhance natriuresis and facilitate decongestion (at the risk of hypokalemia)
- Can consider the addition of acetazolamide to facilitate greater decongestion
    - Addition of acetazolamide to loop diuretic therapy was demonstrated to facilitate greater decongestion but was not associated with a reduction in HF readmissions or mortality
- Regular physical exam of volume status, JVP, and lung exam are important clinical markers of diuretic success
- Frequent electrolyte and kidney function monitoring
- Have the patient sit at the edge of the bed or chair with legs dangling (reduces preload)
- Continue "active" IV diuresis until euvolemia is achieved, then transition to a PO diuretic
- Measurement of a discharge BNP may be helpful in assessing the adequacy of therapy and severity of HF
- Diuretics have not been shown to decrease mortality, but they do decrease hospitalizations
- Chronic oral loop diuretic therapy is appropriate for most patients at discharge to maintain decongestion (decision of which diuretic to use, its dose, and frequency is an art)
    - When patient achieves euvolemia, try to maintain the volume status without making them lose water weight or regain water weight (the optimal dose/frequency is unique to each patient)
- Ultrafiltration (UF)
    - In an initial study evaluating UF versus conventional therapy, fluid removal was improved, and subsequent HF hospitalizations and urgent clinic visits were reduced with UF
    - However, no improvement in renal function or subjective differences in dyspnea scores or mortality were observed
        - The UF group had more adverse events related to kidney failure, bleeding complications, and intravenous catheter-related complications
    - Therefore, UF is rarely used clinically
- Cardiorenal syndrome
    - Increasingly recognized as a complication of acute decompensated HF
    - ~ 30% of patients hospitalized for ADHF exhibit abnormal renal function from baseline, and this is associated with longer hospitalizations and mortality
    - Treatment is mostly diuretic therapy as above, and some patients need inotropic therapy to improve renal perfusion

VASOACTIVE THERAPY

- Intravenous nitroglycerin, nitroprusside, and nesiritide
    - Vasodilators are used to lower intracardiac filling pressures and reduce systemic vascular tone
    - Rapidly reduce preload and afterload
    - Indicated in patients with pulmonary edema and in restoring end-organ perfusion for those with low cardiac output and high systemic vascular resistance (e.g., hypertension)
    - Nitroglycerin impacts venous tone and ventricular preload
        - Commonly used in conjunction with diuretics for pulmonary edema
    - Nitroprusside is a potent arterial and venous vasodilator
        - Reserved for those with adequate arterial pressure or invasive hemodynamic monitoring due to risk of hypotension (also risk of thiocyanate toxicity)
    - Nesiritide acts as an intermediate between nitroglycerin and nitroprusside, with some suggestions of more rapid reduction of pulmonary capillary wedge pressure and pulmonary vascular resistance compared with nitroglycerin
        - Routine use of nesiritide is not recommended, as trials have found worsening renal insufficiency and hypotension
- Serelaxin and urodilatin have been explored but currently are not recommended for use

INOTROPIC THERAPY

- Dobutamine
    - Usually the first-line agent in cardiogenic shock given its short-acting nature
    - Has variable effects in the presence of β-blockers
- Dopamine
    - Has dose-dependent effects on α_1, β_1, β_2, and dopaminergic receptors
    - Low-dose dopamine has been explored as an adjunct to diuretics to preserve renal function and augment diuresis but does not provide an advantage over routine diuretic use
- Milrinone stimulates myocardial contractility promoting peripheral and pulmonary vasodilation and its effectivesness is retained in the presence of β-blockers

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ADJUNCT THERAPIES

- Morphine
  - Dose: 2–8 mg IV, may be repeated after 2–4 h
  - Decreases preload by increasing venous capacitance and can decrease symptoms of dyspnea in patients with pulmonary edema
  - May lead to CO_2 retention by reducing ventilatory drive
- Treatment of iron-deficiency anemia
  - In patients with iron deficiency, with LVEF of < 50%, and who were stabilized after an episode of acute HF, treatment with ferric carboxymaltose was safe and reduced the risk of HF hospitalizations with no apparent effect on the risk of cardiovascular death

MANAGEMENT OF CHRONIC HFrEF & HFmrEF

The goal of therapy is to reduce and prevent LV remodeling by controlling excess body water, afterload reduction, and augmentation of contractility (see Pathophysiology section). ACE inhibitors/ARBs and β-blockers were the first agents to show an improvement in mortality. Mineralocorticoid receptor antagonists (MRAs) and arteriovenous dilators also improve mortality but can be used only in certain situations. ARNIs have been shown to have better outcomes than ACE-Is/ARBs if tolerated. SGLT-2Is are now recommended for all HF patients regardless of the ejection fraction (EF) due to improved mortality in all classes. These agents improve cardiac structure and function with consequent reduction in symptoms, improved quality of life, decreased burden of hospitalizations, and improved mortality from both pump failure and dysrhythmias.

- GDMT for HFrEF (attempt to have all patients on these four classes of medications; see **Table 20-5**)
  - RAAS inhibitors (ARNIs, ACE-Is, or ARBs)
    - ARNIs are the preferred class of the three
  - β-Blockers
  - Mineralocorticoid receptor antagonists (MRAs)
  - SGLT-2Is

NEUROHORMONAL ANTAGONISM

- ARNIs (e.g., sacubitril-valsartan)
  - Sacubitril inhibits neprilysin, which will increase natrial peptides and bradykinin
  - Among patients with HFrEF, treatment with an ARNI *reduces CV mortality or HF hospitalizations* compared with enalapril. It is also associated with a reduction in all-cause mortality. [1]
  - Starting an ARNI in the inpatient setting is well tolerated
    - Among patients with HFrEF who were hospitalized for ADHF, the initiation of sacubitril-valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy without worsening renal function, hyperkalemia, symptomatic hypotension, or angioedema
  - A switch from an ACE-I to ARNI requires a 36 h washout period due to risk of angioedema
- ACE-Is (e.g., lisinopril)
  - Higher doses as tolerated → decreased hospitalizations
  - Enalapril reduces 4-year mortality by 16% and reduces HF hospitalizations when added to conventional therapy in patients with HFrEF [2]
  - Cough and angioedema can cause ACE-Is to be contraindicated
- ARBs (e.g., losartan)
  - Use if cannot tolerate ARNIs or ACE-Is
  - When HFrEF therapy included ACE-I but not β-blockers, addition of valsartan to standard HFrEF therapy did not improve survival but reduced the incidence of the composite endpoint of morbidity and mortality, largely through a decrease in HF hospitalizations
- β-Blockers
  - There are three proven β-blockers that decrease mortality (and a further 35% reduction in mortality when added to ACE-Is/ARBs)
    - Carvedilol
    - Metoprolol succinate
    - Bisoprolol
  - β-Blockers can initially worsen symptoms at first; start with low doses then increase slowly (uptitrate every 2 weeks as tolerated; stop if symptomatic hypotension or heart rate < 60 beats/min)
  - Carvedilol reduces the risk of death or HF hospitalization by 31% compared with placebo in NYHA class III–IV HF with EF < 25%
  - In patients with symptomatic HFrEF with EF ≤ 40%, long-acting metoprolol led to a 34% reduction in all-cause mortality [3]
  - When added to standard therapy including diuretics and ACE-Is, bisoprolol results in a 34% reduction in all-cause mortality in patients with HFrEF (LVEF ≤ 35%) and NYHA III–IV symptoms

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TABLE 20-5 Guideline-Directed Pharmacologic Therapy and Target Doses in HF with Reduced Ejection Fraction

DRUG CLASS	GENERIC DRUG	INITIATION (mg)	TARGET DOSE (mg)
ACE-Is			
	Lisinopril	2.5–5 daily	20–35 daily
	Enalapril	2.5 bid	10–20 bid
	Captopril	6.25 tid	50 tid
	Trandolapril	0.5–1 daily	4 daily
ARBs			
	Losartan	50 daily	150 daily
	Valsartan	40 bid	160 bid
	Candesartan	4–8 daily	32 daily
Mineralocorticoid Receptor Antagonists			
	Eplerenone	25 daily	50 daily
	Spironolactone	12.5–25 daily	25–50 daily
β-Blockers			
	Metoprolol succinate CR/XL	12.5–25 daily	200 daily
	Carvedilol	3.125 bid	25–50 bid
	Bisoprolol	1.25 daily	10 daily
Arteriovenous Vasodilators			
	Hydralazine/isosorbide dinitrate	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/ isosorbide dinitrate	37.5/20 qid	75/40 qid
ARNI			
	Sacubitril-valsartan	24/26 bid	97/103 bid
SGLT-2 Inhibitor			
	Dapagliflozin	10 daily	10 daily
	Empagliflozin	10 daily	10 daily
	Sotagliflozin	200 daily	200 daily
Novel Therapies			
	Vericiguat (sGC stimulator)	2.5 daily	10 daily
	Omecamtiv mecarbil (myosin activator)	25 bid	Up to 50 bid (based on plasma concentrations)

sGC, soluble guanylyl cyclase. Reproduced with permission from Desai A, Mehra MR. Heart failure: Management, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- It does not matter which medication class is initiated first, as outcomes did not vary based on the sequence of initiation
- The combination of medications listed above is better than maxing out the dose of one class and not being able to start another because of hypotension
    - Still attempt to uptitrate doses to as high as tolerated over time

MINERALOCORTICOID RECEPTOR ANTAGONISTS

- Administer for NYHA class II–IV if EF < 40%
- Spironolactone
    - First line; use eplerenone if spironolactone cannot be tolerated
    - Can cause gynecomastia, erectile dysfunction, and diminished libido
    - Blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with severe HF [4]
- Eplerenone reduces risk of death and hospitalization in patients with moderate systolic dysfunction and NYHA class II symptoms

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SGLT-2Is

- Empagliflozin, dapagliflozin, or sotagliflozin
  - Administer regardless of the presence or absence of diabetes
  - Among patients receiving recommended therapy for HF, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for HF than those in the placebo group, regardless of the presence or absence of diabetes [5]

ARTERIOVENOUS DILATORS

- Hydralazine/isosorbide dinitrate: treatment adherence can be difficult with tid dosing
- Mortality benefit shown among Black Americans who were already on an ACE-I/ARB and a β-blocker, but to a lesser extent than ACE-Is
- Used if ACE-I/ARB/ARNI causes renal insufficiency or hyperkalemia
- Isosorbide dinitrate plus hydralazine improves survival and reduces hospitalization among Black patients with HFrEF

NOVEL AGENTS

- Vericiguat: novel soluble guanylyl cyclase that is well tolerated—may have use in advanced HF as an adjunct to guideline-directed medical therapy
- Omecamtiv mecarbil: a myosin activator that may have use in late-stage HF

ADJUNCT THERAPIES

- Oral diuretics (furosemide, bumetanide, torsemide; see Table 20-4))
  - Neurohormonal activation results in salt and water retention; diuretic therapy is typically required to remedy congestive symptoms
    - However, loop diuretics also increase neurohormonal activation; therefore, *dosing should be minimized as much as possible* to maximize the balance of risk and benefit
  - Loop diuretics are preferred to thiazide diuretics due to their potent effect on renal sodium excretion
  - Dose adjustments are frequently needed
  - No decrease in mortality; used to control symptoms and reduce hospitalizations
- Digoxin
  - Administer only for symptomatic relief despite optimal hormonal blockade and adequate volume control
  - Requires digoxin level monitoring, and low doses are sufficient to achieve beneficial outcomes without breaching the therapeutic safety index
  - Digoxin reduces hospitalization rates but does not impact mortality among patients with HFrEF
- Ivabradine
  - Reduces mortality and HF hospitalizations in select patients with NYHA II–IV and LVEF ≤ 35% with resting heart rate ≥ 70 beats/min in normal sinus despite treatment with an evidence-based β-blocker (or maximally tolerated β-blocker), ACE-I/ARB, and MRAs
  - Used as a possible adjunct to patients who cannot tolerate β-blocker therapy
- Fish oil
  - Treatment with long-chain omega-3 polyunsaturated fatty acids (ω-3 PUFAs) has been shown to be associated with modestly improved clinical outcomes in patients with HFrEF
- Exercise
  - Improves patients' sense of well-being and correlates with a trend toward mortality reduction
- Nocturnal positive airway pressure to treat OSA
- SGLT-2Is should be used, but avoid thiazolidinediones in patients with diabetes
- Catheter ablation for AF when NYHA II–IV and LVEF ≤ 35%
  - In patients with AF and symptomatic (NYHA II–IV) systolic HF (LVEF ≤ 35%), catheter ablation is associated with a 16.1% absolute reduction in death or hospitalization for HF compared with medical therapy (rate or rhythm control). This difference was driven by both a 11.6% absolute risk reduction in death and a 15.2% absolute reduction in hospitalization for HF. Catheter ablation was also associated with greater improvement in LVEF and long-term maintenance of sinus rhythm.
- Cardiac resynchronization therapy
  - Consider for patients with EF ≤ 35% and NYHA class II–IV with QRS ≥ 150 ms or left bundle branch block
  - Among patients with HF with LVEF ≤ 30% and QRS duration ≥ 130 ms, placement of an implantable cardioverter-defibrillator (ICD) with cardiac resynchronization therapy reduces the rate of mortality or HF events compared with ICD placement alone. This benefit was driven primarily by a reduction in HF events.
- Cardiac contractility modulation (CCM)
  - A device-based therapy that involves nonexcitatory electrical stimulation to the RV septal wall during the absolute myocardial refractory period to augment the strength of subsequent myocardial contraction

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- May improve HF symptoms, functional capacity, and quality of life, but has no effect on HF hospitalization or mortality
- Can be considered in patients with EF 25–50% and a narrow QRS complex (for whom cardiac resynchronization therapy is not an option) who desire improvement of symptoms and quality of life

- ICD
  - Used for primary prevention in EF ≤ 35% and NYHA class I–III in patients who have been on adequate GDMT
  - Secondary prevention for any patient who has had sudden cardiac arrest from dysrhythmias
  - Another indication is in patients with MI who have been on optimal GDMT with residual EF ≤ 30% even if asymptomatic
  - ICD placement in addition to standard medical therapy was associated with a trend toward decreased mortality among symptomatic patients with moderate nonischemic dilated cardiomyopathy, LVEF ≤ 35%, nonsustained ventricular tachycardia, and NYHA class II–III symptoms
- Low-sodium diet (< 2 g/day)
- Avoid calcium channel blockers and NSAIDs
- CABG + optimal medical therapy for patients with ischemic cardiomyopathy has shown decreased mortality from all causes over the long term (10 years)
  - Among patients with ischemic cardiomyopathy and LVEF ≤ 35%, the addition of CABG to optimal medical therapy does not significantly reduce all-cause mortality after 5 years but reduces cardiovascular-related deaths and hospitalizations; after 10 years, there is a significant reduction in all-cause mortality with CABG
- Mitral valve regurgitation surgery
  - Severe mitral valve regurgitation may benefit from MitraClip procedures in select patients, with a reduction in both HF hospitalizations and mortality at 2 years
  - Among patients with HF and moderate to severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of GDMT, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for HF and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications exceeded a prespecified safety threshold.
- Providing HF patients with all the various classes of medications that reduce mortality is important (**Fig. 20-4**)
  - Studies show, unfortunately, that a very low percentage of patients with HF receive all the different drug classes that are indicated
  - Other ineffective treatments and treatments that have worsened mortality are described in Figure 20-4

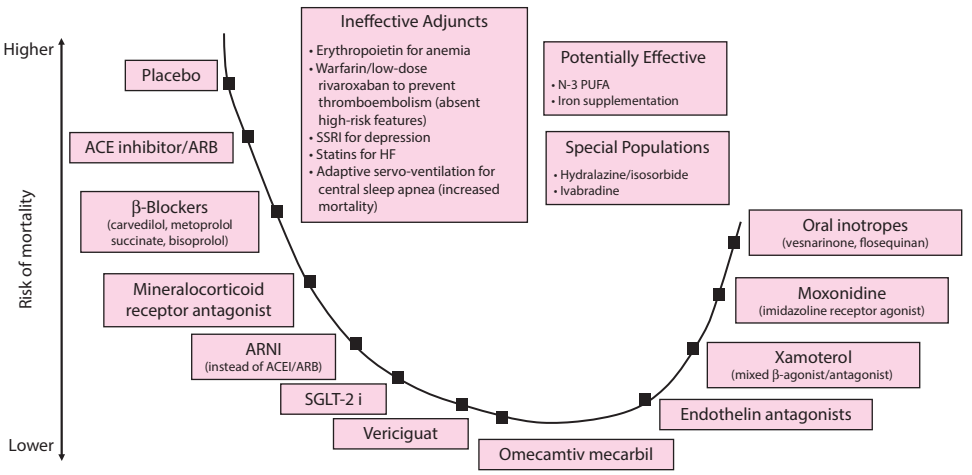

FIGURE 20-4 Progressive decline in mortality with ACE-Is or ARBs, ARNIs, β-blockers, mineralocorticoid receptor antagonists, SGLT-2 inhibitors, and balanced vasodilators. Addition of selected therapies (ivabradine, vericiguat) may further reduce HF hospitalization but does not substantially impact mortality. Further stack-on neurohormonal therapy is ineffective or results in worse outcomes. Management of comorbidity (e.g., iron deficiency, sleep apnea) is of unproven efficacy. PUFA, polyunsaturated fatty acid. (Reproduced with permission from Desai A, Mehra MR. Heart failure: Management, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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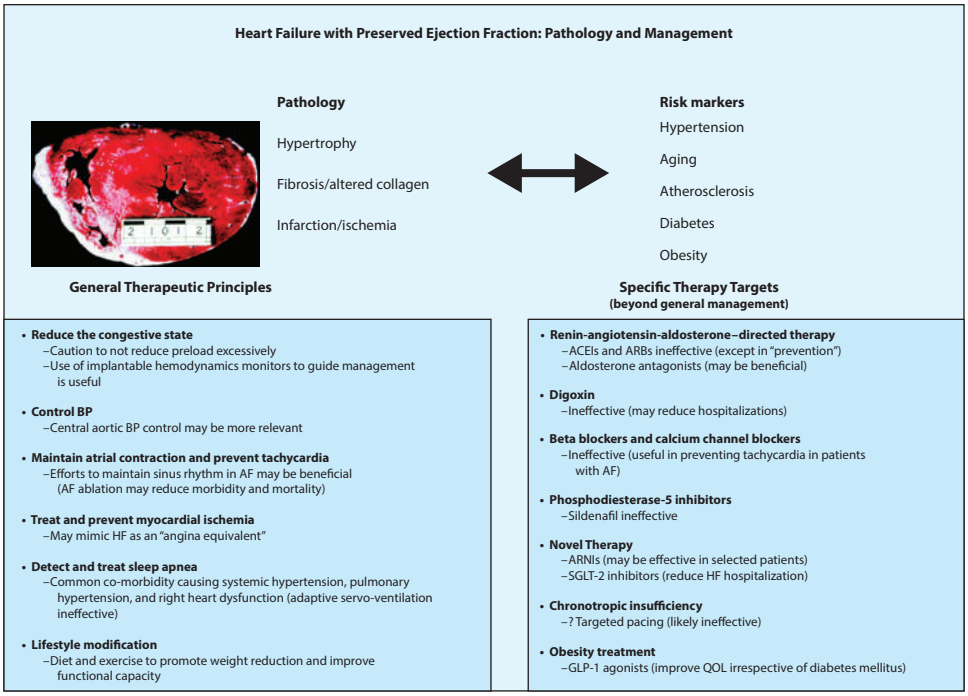

FIGURE 20-5 Pathophysiologic correlations, general therapeutic principles, and results of specific "directed" therapy in HF with preserved ejection fraction. QOL, quality of life. (Reproduced with permission from Desai A, Mehra MR. Heart failure: Management, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

MANAGEMENT OF CHRONIC HFpEF

HFpEF is managed mostly by controlling comorbidities contributing to the HF, with few drugs proven useful for outcomes (Fig. 20-5).

- Quick reference for HFpEF management
  - SGLT-2Is for all patients
  - Consider mineralocorticoid receptor antagonists (MRAs)
  - Consider ARNIs in patients with EF < 60%
  - Control risk factors and comorbidities
- The overall goal is to control congestion, stabilize the heart rate and BP, control risk factors, and improve exercise tolerance
- Clinical trials of RAAS inhibitors, digoxin, β-blockers, and ARNIs have been conducted for HFpEF, but none has conclusively demonstrated a mortality reduction
- Variable benefits, measured in the form of reduced HF hospitalizations, have been seen with MRAs, ARBs, and ARNIs, but benefits are principally confined to those with LVEF below the normal range (< 60%), leading to recommendations for HFmrEF to be treated the same as HFrEF
- In the absence of specific pharmacologic therapies proven to improve clinical outcomes, management of patients with HFpEF has historically been focused on
  - Improvement of symptoms and effort tolerance through lifestyle modification
  - Control of congestion with diuretics
  - Stabilization of heart rhythm (particularly in those with AF)
  - Control of BP to guideline-recommended targets
  - Management of comorbidities
- More recently, however, targeted pharmacologic therapy is emerging, with clinical trials of SGLT-2Is supporting the use of these agents to reduce cardiovascular mortality and HF hospitalizations in HFmrEF and HFpEF
- Trials of ARNIs and GLP-1 agonists (in obese patients) also suggest potential benefits in selected HFpEF patients

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SGLT-2Is

- Benefits from the EMPEROR-REDUCED [5] trial for SGLT-2Is in HFrEF have been extended to HFpEF patients from observed reductions in the composite cardiovascular death or HF hospitalizations in trials with HFpEF (DELIVER and EMPEROR-PRESERVED) [6]
- These results have driven updates to treatment guidelines in the United States and Europe, which now *embrace the use of SGLT-2Is as foundational therapy in patients with symptomatic HF regardless of EF*

MINERALOCORTICOID RECEPTOR ANTAGONISTS

- A weak recommendation for HFpEF patients, as there are some conflicting results from trials
- In patients with HF and a preserved EF, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF

ARNIs

- In patients with HFpEF but a lower EF (< 60%), ARNIs reduced NT-proBNP levels more than valsartan, and may improve clinical benefits, but results were modest
- This has led to the consideration of ARNIs for patients with HFpEF and an EF < 60%

ADJUNCT THERAPIES

- Nitrates are *not* recommended
  - In patients with HFpEF and mild to moderate (NYHA II–III) symptoms, the addition of the long-acting nitrate isosorbide mononitrate appears to hinder rather than improve activity level
  - Patients on nitrate therapy had a borderline significant reduction in total activity units as well as a ~20-min absolute reduction in activity time per day
  - There was no effect of nitrate therapy on 6-min walk distance, quality of life, or clinical biomarkers
- Weight loss if obese
  - Several trials have found weight loss improves quality of life, including use of semaglutide in patients with a BMI of ≥ 30 and HFpEF
- There are several novel targets being tested, but further testing needs to be performed

COMPLICATIONS

- Kidney damage or failure (cardiorenal syndrome)
- Worsening valvular disease
- Dysrhythmias, especially AF
- Cardiac cirrhosis
- Cor pulmonale
- Acute pulmonary edema
- Recurrent hospitalizations

PROGNOSIS

- In primary care, the overall 5-year survival following the diagnosis of HF is ~ 50%
- For patients with severe HF, the 1-year mortality may be as high as 40%
- Most of these patients die of cardiovascular causes, most commonly progressive HF or sudden cardiac death
- A number of clinical and laboratory parameters are independent predictors of mortality (**Table 20-6**)
- Following an HF admission, mortality rates range from 8–14% at 30 days to 26–37% at 1 year to up to 75% at 5 years, with a short-term mortality of 5% while hospitalized
- Readmission with HF is also common, ranging from 20–25% at 60 days to ~ 50% at 6 months, and the risk of death rises with each subsequent admission
- There are racial disparities in outcomes, with Black persons having higher case-fatality rates compared with White persons
- Men have higher age-adjusted mortality rates for death related to HF than women
- Despite these statistics, the overall prognosis for patients with HF is improving due to treatment of risk factors and increased use of guideline-directed therapies

PATHOPHYSIOLOGY

HF PATHOPHYSIOLOGY OVERVIEW

- Chronic hemodynamic changes lead to stress on the myocardium, cascading a series of events of ventricular remodeling until systolic and diastolic dysfunction occur (**Fig. 20-6**)

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TABLE 20-6 Independent Predictors of Adverse Outcomes in HF

Clinical	Male sex
	Older age
	Diabetes mellitus
	CKD
	CAD
	Advanced NYHA class
	Presence of third heart sound or elevated JVP
	Decreased exercise capacity
	Cardiac cachexia
	Depression
Structural	Reduced LV ejection fraction
	Reduced RV ejection fraction
	Increased ventricular volumes and mass
	Secondary mitral or tricuspid regurgitation
Hemodynamic	Elevated pulmonary capillary wedge pressure
	Reduced cardiac index
	Reduced peak oxygen consumption
	Pulmonary hypertension
	Diastolic dysfunction
Biochemical	Worsening renal function
	Hyponatremia
	Hyperuricemia
	Elevated cardiac biomarkers (troponin and natriuretic peptides)
	Elevated plasma neurohormones (norepinephrine, renin, aldosterone, and endothelin-1)
Electrophysiologic	Tachycardia
	Widened QRS interval or LBBB
	AF
	Ventricular ectopic activity
	Ventricular tachycardia and sudden death

LBBB, left bundle branch block. Reproduced with permission from Givertz MM, Mehra MR. Heart failure: Pathophysiology and diagnosis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- HF is a progressive disease
- May be asymptomatic for years until an index event damages myocardium → ↓ force generation
  - Causes: acute MI, chronic pressure/volume overload, or hereditary factors
  - All result in reduced cardiac pump capacity
- Frank-Starling relationship
  - Failing heart → ↓ contractility with exertion → preload ↑ but stroke volume fails to rise → symptoms of HF
    - Tachycardia compensates for ↓ stroke volume

VENTRICULAR REMODELING

- Remodeling is well characterized in HFrEF but poorly understood in HFpEF
- Ventricular remodeling in HFrEF occurs in response to excess cardiac workload
  - Concentric hypertrophy: pressure overload (e.g., hypertension, aortic stenosis) → wall thickening and increased wall stress
  - Eccentric hypertrophy: volume overload (e.g., valve regurgitation) → ventricular chamber dilation
- Ventricular remodeling in HFrEF is accompanied by
  - Cellular changes: myocyte hypertrophy and fibrosis
  - Protein alterations: altered calcium handling and cytoskeletal changes
  - Molecular changes: reactivation of fetal genes

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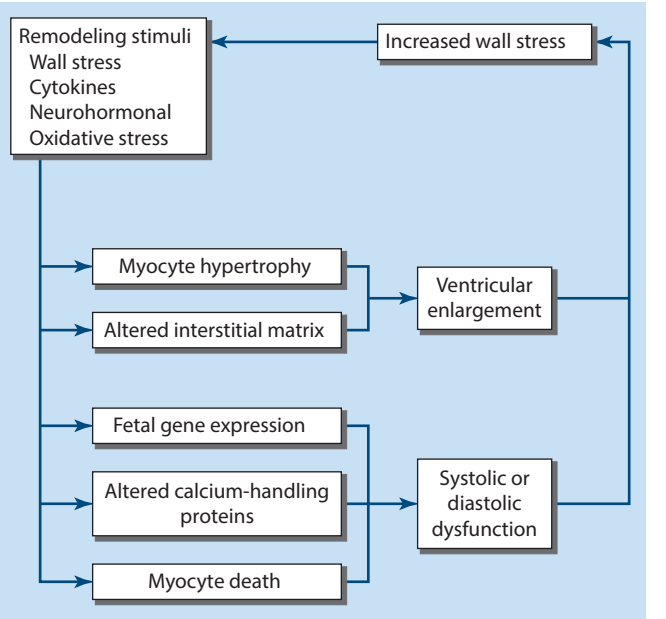

FIGURE 20-6 Remodeling stimuli in heart failure. Chronic hemodynamic stimuli such as pressure and volume overload lead to ventricular remodeling through increases in myocardial wall stress, inflammatory cytokines, signaling peptides, neuroendocrine signals, and oxidative stress. The myocardium responds with adaptive as well as maladaptive changes. Re-expression of fetal contractile proteins and calcium handling proteins may contribute to impaired contraction and relaxation. Myocytes unable to adapt might be triggered to undergo programmed cell death (apoptosis). The net result of these changes is further impairment in pump function and increased wall stress, thus completing a vicious cycle that leads to further progression of myocardial dysfunction. (Reproduced with permission from Givertz MM and Colucci WS. Heart failure. In: Libby P, editor. *Essential Atlas of Cardiovascular Disease*. Philadelphia: Current Medicine; 2009.)

- Cell loss from necrosis/apoptosis → worsens cardiac function
- Systemic vasoconstriction and neurohormonal dysfunction → afterload mismatch → ↓ pump efficiency
- HFpEF
  - Impaired calcium uptake → poor relaxation
  - Contributors include vascular stiffness, renal dysfunction, sodium retention, inflammation, oxidative stress, ↓ NO signaling, and insulin resistance

MECHANISMS OF DISEASE PROGRESSION

- Neurohormonal activation
  - Renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) increase their activity initially to maintain cardiac output (salt/water retention, vasoconstriction, ↑ endothelin; see Fig. 20-7)
  - Chronic activation of RAAS and SNS → excessive vasoconstriction, volume overload, renal/electrolyte issues, baroreceptor dysfunction, myocardial toxicity, and dysrhythmias
    - Targets of therapies to combat excessive RAAS and SNS activity
    - ACE-I/ARB/ARNI (target RAAS overactivity)
    - Mineralocorticoid receptor antagonists (target RAAS overactivity)
    - β-Blockers (target SNS overactivity)
    - Diuretics (target RAAS overactivity)
  - Leads to remodeling of heart, vessels, and kidneys
  - ↑ SGLT-2 activity → sodium/water retention
    - Target of SGLT-2Is
- Vasodilatory counterregulation
  - Atrial natriuretic peptide (ANP), BNP, prostaglandin E_2, prostacyclin, bradykinin, adrenomedullin, and NO oppose overactivated RAAS/SNS effects

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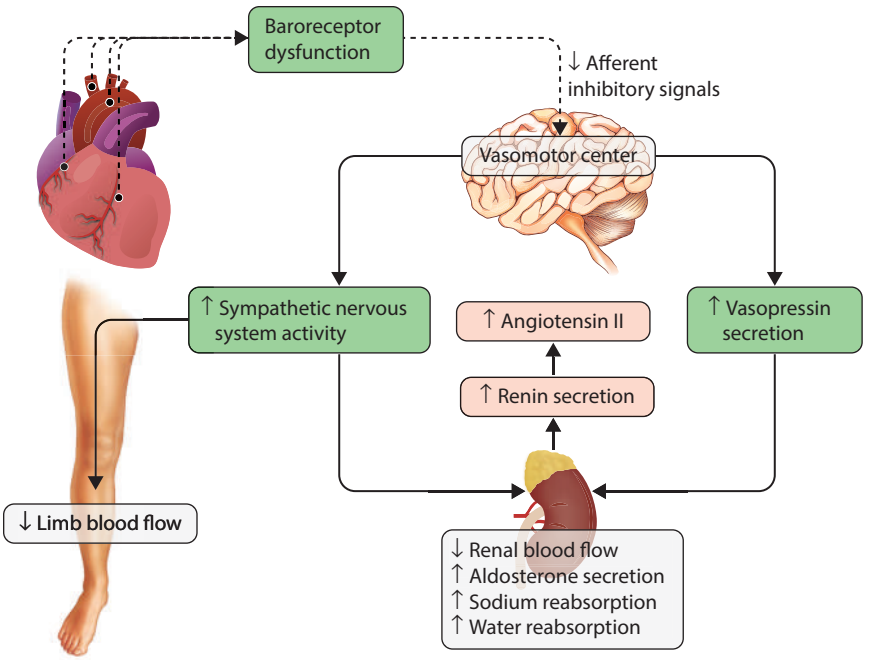

FIGURE 20-7 Activation of neurohormonal systems in HF. Decreased cardiac output in HF results in an "unloading" of high-pressure baroreceptors (*circles*) in the LV, carotid sinus, and aortic arch, which in turn causes reduced parasympathetic tone. This decrease in afferent inhibition results in a generalized increase in efferent sympathetic tone and nonosmotic release of arginine vasopressin from the pituitary. Vasopressin is a powerful vasoconstrictor that also leads to reabsorption of free water by the kidney. Afferent signals to the CNS also activate sympathetic innervation of the heart, kidney, peripheral vasculature, and skeletal muscles. Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention, peripheral vasoconstriction, myocyte hypertrophy, cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure and organ perfusion, they also result in end-organ changes in the heart and circulation. (Reproduced with permission from Givertz MM. Mehra MR. Heart Failure: Pathophysiology and Diagnosis, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

        - Cause vasodilation and natriuresis, inhibit renin/aldosterone, and modulate baroreceptors
        - BNP elevation aids HF diagnosis
        - Bradykinin and natriuretic peptides are degraded by neprilysin
            - Target of ARNI therapy
- Endothelin, cytokines, and oxidative stress
    - Endothelin: potent vasoconstrictor → myocyte hypertrophy, fibrosis, pulmonary hypertension, and RV failure
    - Cytokines (tumor necrosis factor α, interleukin 1β) and reactive oxygen species promote ventricular remodeling

CARDIORENAL AND ABDOMINAL INTERACTIONS

- HF is a systemic disease involving multiple organs
- Cardiorenal syndrome: renal dysfunction results from venous congestion, not just a decreased cardiac output
    - Increased abdominal/venous pressures impair renal, hepatic, and splenic function
    - Splanchnic congestion activates hepatorenal/splenorenal reflexes → renal vasoconstriction
    - Decongestion (diuretics, ultrafiltration) reduces volume/abdominal pressure → improves renal function

GUT CONGESTION, MICROBIOME, AND INFLAMMATION

- Gut congestion → ↑ intestinal permeability → ↑ lipopolysaccharide (endotoxin) → immune activation and inflammation

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- Cytokine elevation (tumor necrosis factor α, interleukin 1 [IL-1], IL-6) → ↓ cardiac function and cachexia
- Microbial toxins (indoxyl sulfate) contribute to HF, especially with renal dysfunction
- Bowel ischemia/congestion → bacterial translocation → systemic inflammation and worsening of HF

COMORBIDITIES THAT WORSEN HF

- Diabetes: alters myocardial metabolism, ↑ oxidative stress, lipotoxicity, and RAAS/SNS activation
- Sleep apnea: ↑ afterload, ↓ preload, intermittent hypoxemia, and SNS activation
- Obesity: increases HF risk; paradoxically improves prognosis in established HF compared to patients with HF and low BMI
- Depression: linked to neuroendocrine dysfunction, inflammation, and poor self-care

RISK FACTORS

- Figure 20-8 describes the most common risk factors and their incidence for HF development
- Other risk factors not listed in Figure 20-8 include
  - Older age
  - Men
  - Hyperlipidemia
  - Cocaine, amphetamines
  - Sleep apnea
  - Congenital heart defects
  - Viral infections
  - Alcohol use
  - Tobacco
  - Obesity
  - Dysrhythmias

ADMITTING ORDERS

- Admit to medicine floor or cardiac care unit with telemetry
- Diagnosis: acute decompensated HF
- Condition: guarded
- Vital signs: on admit and q4h, call for respiratory rate > 30 breaths/min, increasing oxygen requirements, systolic BP < 90 mm Hg, urinary output < 100 mL/h
- Nursing: daily weights, strict *I*s/*O*s, oxygen as needed to maintain oxygen saturation > 92%

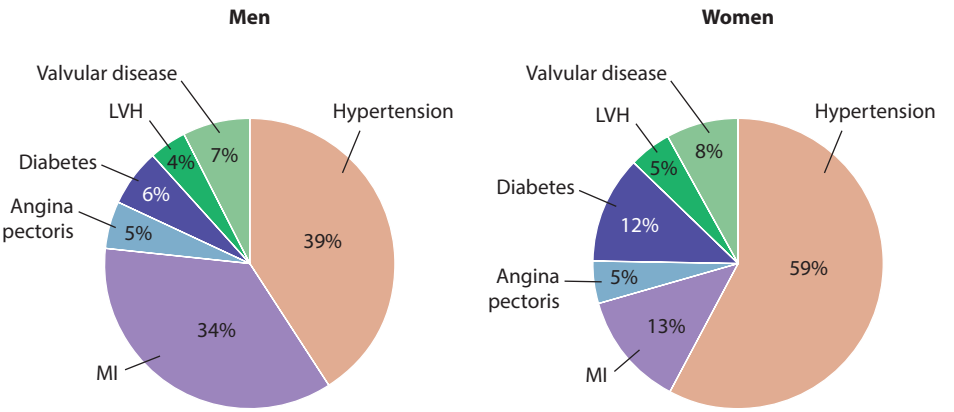

FIGURE 20-8 Population attributable risk of HF incidence. Based on longitudinal data from the Framingham Heart Study, the risk factors contributing most significantly to the population attributable risk (PAR) of HF in men were previous MI and hypertension (in men, both represented equal contributions to HF PAR). In contrast, hypertension was the risk factor accounting for the majority of total PAR in women. In women, previous MI accounted for only 13% of the PAR of HF compared with 34% in men. PAR values are developed based on individual calculations for each variable using hazard ratio and prevalence statistics. Thus, they may not, in aggregate, equal 100%. LVH, LV hypertrophy. (Reproduced with permission from Givertz MM, Colucci WS. Heart failure. In: Libby P, editor. *Essential Atlas of Cardiovascular Disease*. Philadelphia: Current Medicine; 2009.)

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- Diet: 2-g sodium restriction, cardiac diet
- Diagnostic tests
  - CBC
  - CMP
  - Troponins
  - BNP
  - UA
  - TSH
  - Albumin
  - Iron studies
  - ABG if severe respiratory distress
  - ECG
  - CXR
- Medications
  - Furosemide intravenous; initial dose depends on several factors (see Volume Management section)
  - Nitroglycerin, nitroprusside, or nesiritide if hypertensive (situation-dependent; do not always need these agents)
  - Continue their home guideline-directed medical therapy unless the following are present
    - Hold ACE-I/ARB/ARNI/MRA if hypotensive or significantly elevated SCr or potassium above baseline; otherwise, continue their home dose
    - Hold β-blocker if in cardiogenic shock, severely volume overloaded, or if was not taking at home; otherwise, continue home dose
  - Continue or initiate SGLT-2I
  - Dobutamine, dopamine, milrinone, or norepinephrine if cardiogenic shock

DISCHARGE INFORMATION

- Education of low-sodium diet, exercise, and worsening HF symptoms
- Daily weights with furosemide adjustment prn (e.g., doubling the home diuretic dose with weight gain)
- Educate about the importance of medication benefits and adherence to therapy
  - Prescribe discharge medications that are in the Management of HFrEF and HFpEF sections
- Follow-up with a primary care provider within 1 week decreases rehospitalization rates
- Schedule the nearest cardiology appointment available

CASE ANSWERS

1. This patient is presenting with symptoms consistent with an acute HF exacerbation, with a potential precipitating event of not having his medications for the past month. Initial diagnostic tests would include an ECG, CBC, CMP, troponin, BNP, UA, and CXR to help confirm the diagnosis and also to identify if any other potential precipitants are present (e.g., acute myocardial ischemia).
2. Patients presenting with volume overload from acute HF have better outcomes if intravenous diuretics are administered early. Intravenous furosemide with a dose 2–2.5 times higher than his usual home dose would be an appropriate starting medication. You could also consider a vasodilator (e.g., nitroglycerin) because he is hypertensive.
3. The last ejection fraction (EF) this patient had measured on echocardiogram was 35%, indicating he has HFrEF. The four classes of medications that reduce mortality in HFrEF are (1) RAAS inhibitors (ARNI [preferred], ACE-I, or ARB), (2) β-blockers, (3) MRAs, and (4) SGLT-2Is. Additionally, to reduce HF symptoms and hospitalizations, a diuretic should be prescribed at discharge.

LANDMARK TRIALS

[1] McMurray JJV et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371:993, 2014. [PMID: 25176015]
  - *Summary:* The PARADIGM-HF trial showed that among patients with HF with reduced ejection fraction (HFrEF), treatment with an angiotensin receptor–neprilysin inhibitor reduces cardiovascular mortality or HF hospitalizations compared with enalapril. It is also associated with a reduction in all-cause mortality.

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[2] SOLVD Investigators et al. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293, 1991. [PMID: 2057034]
- *Summary:* The SOLVD trial showed that enalapril reduces 4-year mortality by 16% and reduces HF hospitalizations when added to conventional therapy in patients with HFrEF.

[3] Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 353:2001, 1999. [PMID: 10376614]
- *Summary:* The MERIT-HF trial showed that in patients with symptomatic HFrEF with EF ≤ 40%, long-acting metoprolol led to a 34% reduction in all-cause mortality.

[4] Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709, 1999. [PMID: 10471456]
- *Summary:* The RALES trial showed that blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with severe HF.

[5] Packer M et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 383:1413, 2020. [PMID: 32865377]
- *Summary:* The EMPEROR-REDUCED trial showed that among patients receiving recommended therapy for HF, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for HF than those in the placebo group, regardless of the presence or absence of diabetes.

[6] Anker SD et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 385:1451, 2021. [PMID: 34449189]
- *Summary:* The EMPEROR-PRESERVED trial showed that empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HF and a preserved EF, regardless of the presence or absence of diabetes.

FURTHER READING

- Desai A, Mehra MR. Heart failure: Management, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- Givertz MM, Mehra MR. Heart failure: Pathophysiology and diagnosis, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- McGee S. Congestive heart failure, in *Evidence-Based Physical Diagnosis*, 6th ed. Amsterdam, Elsevier, 2026.

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21 Atrial Fibrillation

KEY POINTS

1. Atrial fibrillation (AF) is a cardiac dysrhythmia characterized by disorganized, rapid, and irregular activation of the atrioventricular (AV) node. It is the most common sustained dysrhythmia and is more prevalent with increases in age.
2. AF ranges from asymptomatic to potentially debilitating. Palpitations, dyspnea, fatigue, chest discomfort, and presyncope are common symptoms. An irregularly irregular pulse is found on physical exam.
3. ECG formally diagnoses AF. Continuous telemetry and heart rate/rhythm monitoring devices also may help identify patients with AF. In patients with newly diagnosed AF, a CBC, BMP, TSH, and echocardiogram are indicated. In patients presenting with symptomatic or hemodynamically unstable AF with rapid ventricular response (RVR), troponin and BNP should also be measured.
4. In patients with AF, three primary treatment strategies should be considered: (1) anticoagulation to reduce thromboembolic risk, (2) rate control, and (3) rhythm control. In patients with hemodynamically unstable AF with RVR, electrical or pharmacologic cardioversion is indicated. In patients with hemodynamically stable AF with RVR, IV medications to slow the ventricular rate, with a transition to PO medications, are necessary. All patients should manage underlying medical comorbidities and risk factors.
5. Stroke is the most common and disabling complication of AF. High-output HF from uncontrolled tachycardia and major bleeding from anticoagulation are other commonly observed complications of AF. AF carries a 1.5- to 1.9-fold increased risk of mortality from other comorbidities after controlling for other underlying cardiac diseases.

EPIDEMIOLOGY & DEFINITIONS

AF is a cardiac dysrhythmia characterized by seemingly disorganized, rapid, and irregular atrial activation, resulting in the loss of organized atrial mechanical contraction. These rapid and irregular electrical signals input the atrioventricular (AV) node, which determines ventricular activation and rate. The conducted rate is variable, resulting in an irregular, usually rapid ventricular rate, ranging typically between 110 and 160 beats/min. In some patients, the ventricular rate can exceed 200 beats/min, whereas in others with either high vagal tone or AV nodal conduction disease, the ventricular rate may be excessively slow.

AF is the most common sustained dysrhythmia. The prevalence of AF increases with age, with > 95% of AF patients > 60 years of age. The prevalence > 80 years is ~ 20%. It is slightly more common in men than in women, and more common in White persons than in Black persons. AF is defined by the pattern of episodes and correlates somewhat with the underlying pathophysiology of AF:

Paroxysmal AF: episodes that occur and terminate within a relatively short duration either spontaneously or by pharmacologic or electrical cardioversion, most commonly defined as ≤ 7 days.
Persistent AF: AF that occurs continuously for > 7 days but < 1 year.
Long-standing persistent AF: AF that is persistent for > 1 year.
AF with rapid ventricular response (RVR): AF associated with a ventricular rate ≳ 120 beats/min; can be associated with hemodynamic instability.

CLINICAL VIGNETTE

A 33-year-old man presents to the ED with acute onset (1 h) of shortness of breath associated with a racing heartbeat. He has never had this sensation before. He has no known medical conditions, drinks three cups of coffee daily and three to four alcoholic beverages nightly, and has been a long-distance cyclist for 5 years. A recent visit to his primary care physician revealed a normal BP and hemoglobin A_{1c}. He is afebrile. The heart rate is 168 beats/min, respiratory rate 24 breaths/min, BP 152/84 mm Hg, and oxygen saturation 94% on room air. His physical exam shows normal JVP and clear lung fields without lower extremity edema. An ECG reveals an irregularly irregular rhythm without discernible P waves. The CBC, BMP, troponin, BNP, and TSH are all within normal limits. A CXR is normal.

GUIDING QUESTIONS

1. How would you manage this patient acutely in the ED?
2. Should this patient be initiated on anticoagulation?

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3. What are the different long-term management strategies for this patient, and should one be prioritized over the others?
4. Does this patient have any risk factors that can be modified?

HISTORY

The clinical manifestations of AF result from
1. Symptoms related to the irregular, often rapid but sometimes slow ventricular rates that result
2. The hemodynamic consequences of altered cardiac function
3. The consequences of cardioembolic phenomena, and/or
4. The impact of AF on cardiovascular function over time

AF can range from asymptomatic to symptomatic and hemodynamically unstable. It is commonly present in patients with multiple medical comorbidities, which AF can exacerbate. Some patients cannot feel when they are in AF, but most patients feel palpitations and irregular heartbeat sensations. Symptoms of AF can be debilitating.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - An older male with hypertension, obesity, sleep apnea, and a long history of smoking, who has palpitations
- When did the palpitations begin?
  - Symptom onset can be important for risk stratification if electrical cardioversion can be performed safely without risk of thromboembolic phenomena (see Management section)
- Dyspnea?
  - AF can cause an inadequate ability of the LV to produce an adequate stroke volume, which causes blood to back up into the pulmonary vasculature causing congestion; acutely this can cause pulmonary edema
- Dyspnea on exertion?
  - Same as dyspnea, but can be a sign that adequate long-term rate control is not being achieved
- Angina?
  - AF can cause ischemia because of limited diastolic filling of the coronary arteries
  - Alternatively, myocardial ischemia can precipitate AF
- Fatigue?
  - Can be the same sensation as dyspnea and dyspnea on exertion
- Dizziness, presyncope, or syncope?
  - Dysrhythmia causes irregular blood flow and, therefore, decreased perfusion to the brain
- Slurring of speech?
  - AF is the most common cause of ischemic stroke
- Weakness?
  - Stroke symptom
- Vision changes?
  - Embolization to the optical vessels can occur in AF
- Abdominal pain?
  - Thromboembolic phenomena can embolize to the arteries in the abdomen, causing superior mesenteric artery occlusion and mesenteric ischemia
- Lower extremity edema?
  - Uncontrolled AF over time can cause high-output HF leading to edema

PAST MEDICAL HISTORY

- History of AF?
  - Can you tell when you are in AF? What symptoms do you have when in AF?
    - How is this similar?
    - How is this different?
- History of prior stroke?
  - Was the cause of the stroke from AF?
  - How is this similar and different?
  - Anticoagulation adherence?
- History of cardiac disease?
  - Cardiac disease leads to a greater risk of AF

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- History of COPD?
  - Long-standing lung disease leads to a greater risk of AF

SOCIAL HISTORY
- Use of alcohol and recreational drugs, smoking
- Occupation
- Living situation
- Sexual history

MEDICATIONS
- If they have known AF, ask about adherence to anticoagulation and pharmacologic drugs (either rate or rhythm control)

PHYSICAL EXAM

It is important to perform a thorough cardiac and neurologic exam. AF can be felt on radial pulse palpation as an irregularly irregular rhythm.

- Vital signs
  - Hypotension with rapid ventricular response (RVR) suggests hemodynamic instability
  - Tachypnea and hypoxemia can be seen in pulmonary edema from unstable AF with RVR
- Cardiac
  - Irregularly irregular heart rate
  - Assess the JVP for signs of associated HF exacerbation
- Respiratory
  - Assess for crackles and dullness to percussion (pulmonary edema and pleural effusions)
- Neurologic
  - Assess all cranial nerves
  - Perform a full strength exam
  - Measure deep tendon reflexes bilaterally
  - Unstable AF with RVR can cause altered mental status

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS OF AF
- Premature atrial contractions
  - Patient feels palpitations with an early ventricular contraction—a benign condition
  - P waves are upright with a different morphology than the normal P waves
- Atrial flutter
  - Can feel palpitations and dyspnea; symptoms may be similar to AF
  - Regular tachycardic rhythm with a sawtooth pattern on ECG
- Multifocal atrial tachycardia
  - More common in patients with long-standing lung disease; can have palpitations and tachycardia
  - At least three P-wave morphologies on ECG and a heart rate ≥ 100 beats/min
- Sinus tachycardia
  - No irregularities on ECG, but can have palpitations
- Sinus arrhythmia
  - Different changes in rhythm with inspiration versus expiration—normal variant
- Supraventricular tachycardia
  - Tachycardia with P waves merging with T waves and difficulty measuring the PR interval
- Wolff-Parkinson-White syndrome
  - A younger patient, possibly with recurrent unexplained syncope
  - Tachycardia with delta waves and a short PR interval
- Ventricular tachycardia
  - Tachycardia with an irregular wide QRS complex

ETIOLOGY OF AF

ETIOLOGY OF ACUTE OR NEW-ONSET AF
- Cardiac
  - HF decompensation
  - Myocarditis or pericarditis
  - Myocardial ischemia and infarction

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    - Hypertensive emergency
    - Post–cardiac surgery AF (occurs in ~50% of patients)
    - Sinus node dysfunction
    - Pericardial trauma
- Pulmonary
    - Acute pulmonary disease or hypoxemia (e.g., COPD flare, pneumonia)
    - PE
    - Sleep apnea
- Metabolic
    - High catecholamine states (stress, infection, postop, pheochromocytoma)
    - Thyrotoxicosis
    - Hyperthyroidism or hypothyroidism
- Drugs
    - Alcohol (holiday heart syndrome)
    - Cocaine
    - Amphetamines
    - Theophylline
    - Excessive caffeine
- Neurogenic
    - Subarachnoid hemorrhage
    - Stroke
- Sepsis
- Malignancy
- Anemia

ETIOLOGY OF CHRONIC AF

- Age > 60 years
- Underlying cardiac disease
- Hypertension
- Diabetes
- Family history of AF
- Obesity
- Sedentary lifestyle
- Men who are extreme endurance athletes (cycling and running)
- Thyroid disease
- Sleep-disordered breathing
- Rheumatic heart disease

DIAGNOSTIC TESTS

LABS

- CBC
    - Leukocytosis and low hemoglobin may give clues to precipitants of AF (e.g., infection, anemia)
- BMP
    - Electrolyte abnormalities (e.g., hypokalemia) may cause dysrhythmias
- Troponin and BNP
    - Evaluates for myocardial ischemia as a result of AF, or as a precipitating etiology of AF
    - BNP helps determine if HF is present
- Magnesium
    - Can cause dysrhythmias when deficient
- Lipid panel
    - Additional risk factor for a stroke if have AF
- TSH
    - Hyper- and hypothyroidism are common causes of AF

IMAGING

- ECG
    - Used to diagnose AF (Fig. 21-1)
        - Non-discernible P waves (lack of organized atrial activity)
        - Irregularly irregular ventricular rate

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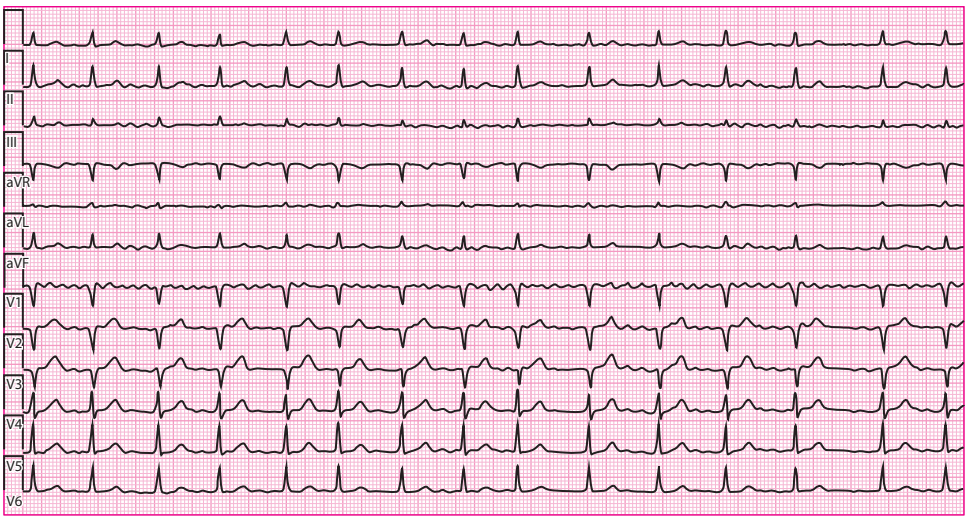

FIGURE 21-1 ECG of an irregularly irregular heart rhythm without discernible P waves. The disorganized atrial activation is best appreciated in lead V_1 for this patient. (Reproduced with permission from Sauer WH et al. Atrial fibrillation, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

  - Atrial flutter may have F waves in a pattern similar to but distinct from AF
  - Helps evaluate any other causes of the patient's symptoms (e.g., MI, multifocal atrial tachycardia)
- CXR
  - To exclude COPD, pneumonia, pneumothorax, PE, etc., for dyspnea evaluation or as precipitants of AF
- Transthoracic echocardiogram
  - Evaluates left atrial size, thrombus in the left atrium, valve disorders, ejection fraction, and the pericardium
- Transesophageal echocardiogram
  - May be indicated to evaluate for the presence of a left atrial thrombus if the patient is being considered for cardioversion when the AF has been present for > 48 h
- Cardiac monitoring devices
  - In the outpatient setting, rhythm monitoring devices (e.g., watches) and heart rate monitors (e.g., Holter monitors) can help identify paroxysmal AF as a cause of a patient's symptoms

MANAGEMENT

INDICATIONS TO ADMIT A PATIENT TO THE HOSPITAL FOR NEW-ONSET AF

- Severe bradycardia after cardioversion
- Treatment of comorbidities that may have caused the new AF (see Etiology section)
- Older patients with several comorbidities
- Further manifestations of HF or hypotension after control of rhythm or rate
- AF with rapid ventricular response
- AF with hemodynamic instability

IMMEDIATE MANAGEMENT OF NEW OR RECENT ONSET AF WITH RVR

- Treatment goals are to
  - Quickly reduce symptom burden with either rate or rhythm control
  - Reverse end-organ dysfunction if present
  - Reduce thromboembolic risk
- Treat the underlying cause if one is identified

HEMODYNAMICALLY UNSTABLE AF WITH RVR

- AF with RVR may require emergent QRS-synchronized electrical cardioversion (200 J, preferably in a sedated patient) if the following are present

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- Hypotension with end-organ damage
- Pulmonary edema
- Evidence of coronary ischemia (angina, ischemic ECG changes, elevated troponin)

- Pharmacologic cardioversion with the class III antiarrhythmic IV ibutilide (0.01 mg/kg) is another option instead of electrical cardioversion
  - Avoid in patients with baseline prolonged QT interval or severe LV dysfunction given the risk of torsades de pointes

HEMODYNAMICALLY STABLE PATIENTS WITH NEW-ONSET AF WITH RVR

- Management focuses on
  - Control of ventricular rate to prevent hemodynamic sequelae by increasing diastolic filling time and improving cardiac output (rate control strategy)
  - Consideration of anticoagulation to mitigate thromboembolic risk
  - Consideration of maintenance of sinus rhythm (rhythm control strategy)
- Rate control is the preferred initial strategy to control ventricular rates, with rhythm control considered after rate control is achieved or if rate control cannot be achieved
- Acute IV rate control options (for dosing, see **Table 21-1**)
  - *No HF history*
    - Calcium channel blockers or β-blockers are preferred
    - If not controlled by IV calcium channel blockers or β-blockers, can add IV digoxin or amiodarone
  - *HF history* (and/or signs of HF exacerbation)
    - IV amiodarone or digoxin are the preferred agents
    - The choice between IV digoxin or amiodarone is usually influenced by practitioner familiarity
    - There is a risk of thromboembolic phenomena if amiodarone converts a patient into sinus rhythm in a patient not anticoagulated when an atrial thrombus is present
  - IV magnesium sulfate 2–4 g
    - As an adjunct to the medications above, infusion of IV magnesium is effective for rate control and modestly effective for restoration of sinus rhythm in rapid AF without clinically significant adverse effects
- Anticoagulation
  - DOAC, heparin infusion, or enoxaparin if anticoagulation is indicated
  - See Management of Chronic AF section for further discussion
- Rhythm control
  - If restoration of sinus rhythm via electrical or pharmacologic cardioversion is being considered acutely, the more immediate risk of thromboembolism must be factored into the management strategy
    - If the presenting episode of AF is > 48 h, or if the episode duration is unknown, there is a risk for precipitating a thromboembolic complication through electrical or pharmacologic cardioversion
      - In this circumstance, the patient should be
        - Initiated on anticoagulation with cardioversion deferred for at least 3 weeks after uninterrupted anticoagulation, or
        - Evaluated to exclude the presence of a left atrial appendage thrombus with a transesophageal echocardiogram (TEE) or, less commonly, high-resolution cardiac CT
          - If no thrombus is found on TEE or CT, then cardioversion can occur
    - If the presenting episode of AF is < 48 h and the patient is not on anticoagulation, it is common practice to cardiovert to normal sinus rhythm (after initiating anticoagulation) unless they have a high risk of stroke due to the following conditions
      - Mitral stenosis
      - Hypertrophic cardiomyopathy
      - Marked left atrial enlargement
  - If opting for electrical or chemical cardioversion, cardiology should guide treatment strategies (class III and IC antiarrhythmics can be used for rapid cardioversion; see Table 21-4)

MANAGEMENT OF CHRONIC AF

- The management goals of chronic AF center on three aims
  - Appropriate mitigation of thromboembolism risk with anticoagulation
  - Control of symptoms through a strategy of rate and/or rhythm control
  - Modification of risk factors for progression of AF

ANTICOAGULATION

- Thromboembolic complications, particularly stroke, are the most significant and potentially life-threatening sequelae of AF, making stroke prevention a key aspect of AF management

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TABLE 21-1 IV Medications for Rate Control in AF

MEDICATION	LOADING DOSE	MAINTENANCE INFUSION DOSE	ADDITIONAL NOTES
No History or Signs of HF			
Diltiazem	0.25 mg/kg IV over 2 min (average adult dosing is 20 mg) If heart rate is not improved in 15 min, administer a repeat bolus dose at 0.3 mg/kg (average adult dosing is 25 mg)	5–15 mg/h	Hypotension is a common side effect When rate control is successful, transition to PO immediate (30–60 mg q6h) or extended-release diltiazem (120–360 mg daily)
Esmolol	500 µg/kg IV over 1 min, then start an infusion If the heart rate response is inadequate, administer a second bolus of 500 µg/kg If the heart rate is still inadequate, administer a third and final bolus of 500 µg/kg	After first bolus, initiate infusion at 50 µg/kg/min If a second bolus is needed, increase infusion to 100 µg/kg/min If a third bolus is needed, increase infusion to 150 µg/kg/min, then increase up to a maximum of 300 µg/kg/min	Hypotension is a common side effect There is no PO esmolol; therefore, when rate controlled is achieved, transition to PO metoprolol tartrate (25–100 mg bid or tid)
Metoprolol	5 mg IV over 2 min Can repeat up to three doses	N/A	Hypotension is a common side effect When rate control is successful, transition to PO metoprolol tartrate
Verapamil	5–10 mg IV over 2 min If heart rate is not improving, can repeat a bolus dose q10–15min as needed and tolerated	Once rate control is achieved with bolus doses, initiate a continuous infusion at 5 mg/h; titrate based on clinical response to a maximum of 20 mg/h	Hypotension is a common side effect When rate control is achieved, transition to either PO verapamil, diltiazem, or metoprolol
History or Signs of HF			
Amiodarone	150 mg IV over 10 min followed by an infusion May repeat 150 mg boluses as needed; do not exceed 6 to 8 additional bolus doses per 24 h	Infusion of 1 mg/min for 6 h, then 0.5 mg/min for 18 h	Pulmonary toxicity, hepatitis, skin discoloration, thyroid dysfunction, corneal deposits, and optic neuropathy are side effects Following infusion, administer 400–1200 mg/d PO in divided doses to complete a total (IV plus PO) loading dose of approximately 10 g The usual PO maintenance dose is 100–200 mg daily A good option if the patient is hypotensive, but caution of conversion to sinus rhythm and risk of potential stroke if an atrial thrombus is present and the patient is not anticoagulated
Digoxin	0.25–0.5 mg IV followed by 0.25 mg q6h for a total loading dose of 0.75 mg to 1.5 mg	NA	Digoxin toxicity and heart block are side effects Following IV pushes, maintenance therapy dosing is 0.125–0.25 mg PO daily Can be added in patients with HF, particularly if the adrenergic state is high, but has been associated with worsening morbidity and mortality in some studies if used long term

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CHA_2DS_2-VASc			HAS-BLED	
Risk Criteria				
Congestive heart failure	1		Hypertension	1
Age > 75	2		Abnormal renal or liver function	1 each
Hypertension	1		Stroke history	1
			Bleeding diasthesis	1
Diabetes mellitus	1		Labile INR (on warfarin)	1
Prior stroke or TIA	2		Elderly (Age > 65)	1
Vascular disease	1		Drugs that predispose to bleeding or alcohol	1 each
Age > 65	1			
Sex category (F)	1			

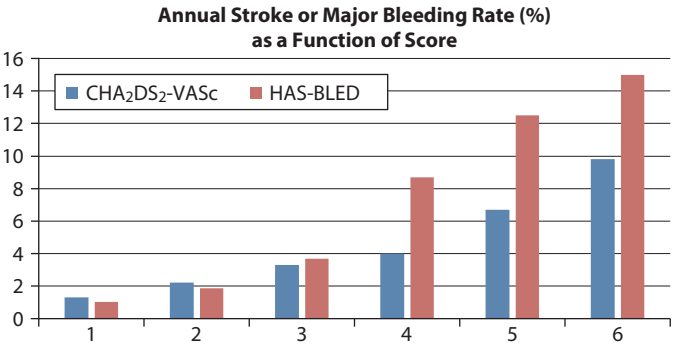

FIGURE 21-2 CHA_2DS_2-VASc and HAS-BLED systems. The CHA_2DS_2-VASc scoring system gives a point for each outlined stroke risk factor, whereas the HAS-BLED scoring system gives a point for each bleeding risk factor, as outlined in the table. In the chart below the table, the corresponding risk of stroke (CHA_2DS_2-VASC) or major bleed event (HAS-BLED) is plotted as a percent risk per annum as a function of score. (Reproduced with permission from Sauer WH et al. Atrial fibrillation, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- *The mainstay of stroke prevention is continuous anticoagulation therapy*
- Especially high-risk patients are those with hypertrophic cardiomyopathy, mitral stenosis, and prior stroke history
  - AF in patients without mitral stenosis is commonly referred to as *nonvalvular AF*
- The decision to give an anticoagulant is based on assessment of stroke risk balanced against bleeding risk
- The CHA_2DS_2-Vasc scoring system (Fig. 21-2) is a widely used tool to estimate an individual patient's annual stroke risk from AF
  - Anticoagulation is recommended for patients with a score of ≥ 1 unless the lone risk factor is female sex
  - If the score is 0, then neither anticoagulation nor antiplatelet therapies are recommended
- The bleeding risk is often assessed with the HAS-BLED scoring system (Fig. 21-2)
- Anticoagulation is recommended if the CHA_2DS_2-Vasc is ≥ 1 and the stroke risk outweighs the bleeding risk
- The approach to anticoagulation is the same regardless of the type of AF (paroxysmal, persistent, long-standing persistent)
  - The perceived burden of AF does not predict stroke risk
- Treatment duration is usually lifelong, but regular assessment of stroke versus bleeding risk is recommended
  - The role of continuous long-term monitoring with implantable loop recorders, pacemakers, or defibrillators in patients with subclinical (asymptomatic AF) to guide anticoagulation is not clear and *not* currently recommended

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TABLE 21-2 Direct Oral Anticoagulants Dosing

ANTICOAGULANT	STANDARD DOSE	REDUCED DOSE	DOSE REDUCTION CRITERIA
Dabigatran	150 mg bid	110 mg bid	Dabigatran 110 mg bid in patients with: age ≥ 80 years, concomitant use of verapamil, or increased bleeding risk
Rivaroxaban	20 mg qd	15 mg qd	CrCl 15–49 mL/min
Apixaban	5 mg bid	2.5 mg bid	At least 2 of 3 criteria: age ≥ 80 years, body weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL (133 mol/L)
Edoxaban	60 mg qd	30 mg qd	If any of the following: CrCl 30–50 mL/min, body weight ≤ 60 kg, or concomitant use of dronedarone, cyclosporine, erythromycin, or ketoconazole

As of publication, four DOACs are available and indicated for stroke prevention for AF. The standard dosing, reduced dosing, and criteria for reduced dosing are shown for each agent. Reproduced with permission from Sauer WH et al. Atrial fibrillation, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- *DOACs* (**Table 21-2**) *are now the preferred agents for patients with nonvalvular AF*
  - Several trials have shown that DOACs are noninferior or superior to warfarin in terms of preventing stroke and systemic VTE risk, and many have been shown to reduce rates of bleeding complications in comparison with warfarin [1]
- Warfarin with heparin bridge until goal INR 2–3 is achieved
  - Used for patients with valvular AF or mechanical heart valves (higher INR goal), or if the patient cannot afford DOAC therapy
  - For valvular AF and mechanical valves, warfarin therapy has led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding
  - Similarly, apixaban and dabigatran have failed to demonstrate noninferiority to warfarin and are less effective than warfarin for the prevention of valve thrombosis or thromboembolism in patients with mechanical valves
  - Warfarin needs frequent INR checks, diet adherence, and potentially frequent dose adjustments
- Antiplatelet agents alone are *generally not sufficient to decrease the stroke risk of AF* [2]
  - Antiplatelets should only be used in AF if indicated for the treatment of another condition, such as a newly placed coronary stent or vascular disease
- If chronic anticoagulation is *contraindicated* due to bleeding risk
  - Because most atrial thrombi likely originate in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery
  - Percutaneously deployed devices that occlude or ligate the left atrial appendage are available, appear to be noninferior to warfarin in reducing stroke risk and are considered in patients at high risk of thromboembolism but serious bleeding risk
    - Watchman devices provide stroke prevention comparable to warfarin, with additional significant reductions in major bleeding, particularly hemorrhagic stroke, and all-cause mortality
    - Patients subsequently still need to take clopidogrel for 6 months after device implantation, with aspirin lifelong therapy
    - Watchman devices also appear to be noninferior to DOACs in preventing major AF-related cardiovascular, neurologic, and bleeding events

RATE CONTROL

- The goal of chronic rate control is to alleviate symptoms and prevent deterioration of ventricular function from excessive rates
  - β-Blockers and calcium channel blockers are often used either alone or in combination
- Exertion-related symptoms are often a sign of inadequate rate control
- The initial heart rate goal is < 80 beats/min at rest, and < 100 beats/min with light exertion
  - However, if this cannot be achieved, it is acceptable to allow the heart rate to be up to 110 beats/min at rest as long as it does not cause symptoms and the ventricular function is normal [3]
    - If allowing the heart rate at rest to be lenient at < 100 beats/min, periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy
- Commonly used agents for rate control
  - Metoprolol tartrate, 25–100 mg PO bid or tid
  - Metoprolol succinate, 25–100 mg PO daily or bid (indicated when HFrEF is also present)

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    - Propranolol, 80–240 mg/d divided in equal doses
    - Verapamil, 120–360 mg/d divided in equal doses
    - Diltiazem, 120–360 mg/d divided in equal doses
    - Digoxin, 0.125–0.375 mg daily
        - Can be added in select patients with hypotension and inadequate rate control despite β-blockers or calcium channel blockers, but long-term use is associated with worsening morbidity and mortality
- If a patient has tachycardia-induced cardiomyopathy, HF, or LVEF < 40%, a more stringent rate control should be targeted (heart rate 60–80 beats/min at rest)
- Atrioventricular (AV) node ablation with pacemaker insertion can be considered in patients with very difficult-to-manage rates
    - Patients become dependent on the pacemaker to support their ventricular rate, and it may cause dyssynchronous ventricular activation (an induced left bundle branch block [LBBB]) that can depress ventricular function
    - Biventricular pacing or direct pacing of the LBBB area may be used to minimize the degree of ventricular dyssynchrony
- AV nodal ablation and cardiac resynchronization therapy have been demonstrated to be superior to pharmacologic therapy in improving quality of life and in reducing the development of HF, HF hospitalizations, and all-cause mortality in patients with permanent AF and a narrow QRS, irrespective of their baseline LVEF

RHYTHM CONTROL

- In general, patients who maintain sinus rhythm have better survival than those who continue to have AF
    - In previous randomized trials, patients with nonvalvular AF had no survival benefit between rate and rhythm control, but rhythm control trended toward increased mortality with increased hospitalizations
    - However, patient selection bias may have influenced these results and introduced disappointing efficacy and toxicities of antiarrhythmics, and discontinuation of anticoagulation, in the rhythm control arms
    - In 2020, a randomized trial evaluating an early rhythm control strategy (within 1 year of initial presentation) compared with standard rate control demonstrated a reduction in cardiovascular events, including death from cardiovascular causes and stroke [4]
        - This trial included both pharmacologic and catheter ablation strategies
    - In patients with HFrEF (EF < 40%), a catheter ablation–based strategy to maintain sinus rhythm appears to provide all-cause mortality benefit compared with a medical rhythm control strategy [5]
- A rhythm control strategy is usually selected for patients with
    - Symptomatic paroxysmal AF
    - Recurrent episodes of symptomatic persistent AF
    - AF with a difficult rate to control
    - AF that has resulted in depressed ventricular function or that aggravates HF
- Rhythm control is more likely favored in young patients than in sedentary patients or older patients in whom rate control is more easily achieved
- Anticoagulation according to the CHA_2DS_2-VASc stroke risk profile is still indicated even if rhythm control is achieved
- Catheter ablation (**Table 21-3**) is considered first-line therapy over pharmacologic
    - Trials have demonstrated superiority of ablation over medications for maintenance of sinus rhythm
    - Successful catheter ablation can allow the patient to avoid drug toxicities and complications, but procedural risks and efficacy are operator-dependent
    - Ablation can be used for patients with untreated paroxysmal AF and is clearly superior when compared with antiarrhythmic therapy for patients who have recurrent paroxysmal AF despite drug therapy
    - Ablation is less effective in patients with persistent and long-standing persistent AF due to the fibrosis that has already developed in those classes
    - Complications of catheter ablation include
        - Stroke (0.5–1%)
        - Cardiac tamponade (1%)
        - Phrenic nerve paralysis
        - Bleeding from femoral access sites
        - Fluid overload with HF
        - Ablation of the pulmonary vein leading to pulmonary vein stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis
        - Esophageal ulcer and fistula
            - The esophagus abuts the posterior wall of the left atrium, and esophageal ulcers can form immediately after the procedure

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TABLE 21-3 Recommendations for Catheter Ablation in Patients with AF

CLASS	LEVEL OF EVIDENCE	RECOMMENDATIONS
1	A	In patients with symptomatic AF in whom antiarrhythmic drugs have been ineffective, contraindicated, not tolerated, or not preferred, and in whom continued rhythm control is desired, catheter ablation is useful to improve symptoms.
1	A	In selected patients (generally younger with few comorbidities) with symptomatic paroxysmal AF in whom rhythm control is desired, catheter ablation is useful as first-line therapy to improve symptoms and reduce progression to persistent AF.
1	A	In patients with symptomatic or clinically significant atrial flutter, catheter ablation is useful for improving symptoms.
2a	B	In patients who are undergoing ablation for AF, ablation of additional clinically significant supraventricular dysrhythmias can be useful to reduce the likelihood of future dysrhythmia.
2a	B	In patients (other than younger with few comorbidities) with symptomatic paroxysmal or persistent AF who are being managed with a rhythm-control strategy, catheter ablation as first-line therapy can be useful to improve symptoms.

Reproduced with permission from JA Joglar et al: 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2024; 83:109.

        - This rarely leads to a fistula between the left atrium and esophagus (< 0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure
        - Diagnosed via chest CT and water soluble-oral and IV contrast
        - Immediate surgical repair is indicated
- Pulsed field ablation
    - Uses electric fields generated by short pulses of high energy and has shown promise by specifically targeting the myocardium without generating heat or damaging adjacent tissues
- Pharmacologic therapy for maintaining sinus rhythm (Table 21-4)
    - Risks and side effects of antiarrhythmic drugs are a major consideration in selecting therapy
    - An appropriate anticoagulation strategy must be in place prior to initiation, as conversion to sinus rhythm can cause thromboembolic phenomenon
    - β-Blockers and calcium channel blockers can convert AF to sinus rhythm but have low efficacy for preventing or terminating AF episodes
    - Class I agents (e.g., flecainide, propafenone, disopyramide) are options for patients without significant structural heart disease but should be avoided in patients with CAD or HF
    - Class III agents (e.g., sotalol, dofetilide) can be administered in patients with CAD or structural heart disease but have ~3% risk of inducing excessive QT prolongation and torsades de pointes
        - These agents should be initiated only in the hospital with ECG and telemetry monitoring of the QT interval
    - Amiodarone can be administered in patients with HF and CAD, but > 40% of patients experience amiodarone-related toxicities during long-term therapy
        - Monitoring of potential toxicities, including skin, liver, lung, and thyroid abnormalities, must accompany this therapy
        - Amiodarone additionally has severe drug–drug interactions
    - Dronedarone should be avoided, as it increases mortality in patients with HF or long-standing persistent AF

MANAGEMENT OF MODIFIABLE RISK FACTORS

- Aggressive treatment of risk factors (specifically sedentary lifestyle, obesity, hypertension, smoking, alcohol use, and sleep apnea) is indicated in all patients and can substantially reduce AF episodes in some patients
- Exercise
    - The amount of exercise has a complex relation to the risk of AF development
    - In men, sedentary individuals and endurance athletes have the highest risk of AF, with individuals who have a moderate exercise regimen having the lowest risk
    - In contrast, in women the risk of AF decreases continuously with increasing exercise activity
- Caffeine intake
    - Excessive intake of caffeine is a risk factor for the development of AF or as a trigger of AF
    - A modest caffeine intake decreases AF risk

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TABLE 21-4 Commonly Used Antiarrhythmic Medications

DRUG	LOADING DOSE	MAINTENANCE DOSE	SIDE EFFECTS
Class IA			
Quinidine		PO: 300–600 mg q6h	Diarrhea, tinnitus, QT prolongation, hypotension, anemia, thrombocytopenia
Procainamide	IV: 15 mg/kg over 60 min	IV: 1–4 mg/min	Nausea, lupus-like syndrome, agranulocytosis, QT prolongation
		PO: 500–1000 mg q4h	
		PO: 1000–2500 mg q12h (sustained release)	
Disopyramide		PO: 100–300 mg q6–8h	Myocardial depression, AV block, QT prolongation anticholinergic effects
		PO: 200–400 mg q12h (sustained release)	
Class IB			
Lidocaine	IV: 1–3 mg/kg at 20–50 mg/min	IV: 1–4 mg/min	Confusion, seizures, respiratory arrest
Mexiletine		PO: 150–300 mg q8–12h	Nausea, tremor, gait disturbance
Class IC			
Flecainide		PO: 50–200 mg q12h	Nausea, exacerbation of ventricular dysrhythmia, prolongation of PR and QRS intervals
Propafenone		PO: 150–300 mg q8h	
Class II			
Metoprolol	IV: 5 mg over 3–5 min × 3 doses	PO: 25–100 mg q6h	Bradycardia, AV block, HF, bronchospasm
Esmolol	IV: 500 µg/kg over 1 min	IV: 50 µg/kg/min	
Class III			
Amiodarone	PO: 800–1600 mg qd × 1–2 weeks, then 400–600 mg qd × 3 weeks	PO: 100–400 mg qd	Thyroid abnormalities, pulmonary fibrosis, transaminitis, bluish skin
	IV: 150 mg over 10 min	IV: 1 mg/min × 6 h, then 0.5 mg/min for 18 h	
Ibutilide	IV (≥ 60 kg): 1 mg over 10 min, can repeat after 10 min	—	Torsades de pointes, hypotension, nausea
Dofetilide		PO: 125–500 µg bid	Torsades de pointes, headache, dizziness
Sotalol		PO: 80–160 mg q12h	Fatigue, bradycardia, exacerbation of ventricular dysrhythmia
Dronedarone		PO: 400 mg q12h	Bradycardia, AV block, prolonged QT, exacerbation of HF, GI discomfort
Class IV			
Verapamil	IV: 5–10 mg over 3–5 min	IV: 2.5–10 mg/h	AV block, HF, hypotension, constipation
		PO: 80–120 mg q6–8h	
Diltiazem	IV: 0.25 mg/kg over 3–5 min (max 20 mg)	IV: 5–15 mg/h	
		PO: 30–60 mg q6h	
Other			
Digoxin	IV: 0.25 mg q2h until 1 mg total	IV, PO: 0.125–0.25 mg qd	Nausea, AV block, ventricular and supraventricular dysrhythmias
Adenosine	IV: 6-mg rapid bolus; if no effect then 12-mg bolus	—	Transient hypotension or atrial standstill

AV, atrioventricular. Reproduced with permission from Jameson JL et al. Tachyarrhythmias, in *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). New York, McGraw Hill Education, 2020.

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COMPLICATIONS

- Stroke (AF causes ~25% of strokes)
  - AF has been detected in up to 8.9% of patients within 6 months following cryptogenic stroke using insertable cardiac monitors
  - MRI has detected asymptomatic embolic infarcts in patients with AF
    - A possible cause of the higher incidence of dementia in AF patients
- Development of HF
- Dementia (higher incidence of dementia in patients with AF)
- Bleeding associated with anticoagulation use
  - The most serious adverse effect of anticoagulation is hemorrhage
    - Administer the reversal agent protamine sulfate if hemorrhage is associated with heparin or enoxaparin
    - If associated with dabigatran, idarucizumab is approved by the U.S. Food and Drug Administration as an effective and rapidly acting reversal agent
    - If associated with warfarin, the most effective agent is prothrombin complex concentrate, but minor bleeding can be managed with fresh frozen plasma and/or IV/PO vitamin K or stopping the warfarin and observation depending on the situation
    - If associated with rivaroxaban, apixaban, or edoxaban, four-factor prothrombin complex concentrate (4F-PCC) should be considered for reversal

PROGNOSIS

- AF carries a 1.5 to 1.9-fold increased risk of mortality after controlling for underlying cardiac disease
- Patients with HF and AF carry a worsened morbidity and mortality than those without AF

PATHOPHYSIOLOGY

- AF tends to be a progressive condition with, at this point, no definitive cure that will completely eliminate AF durably in a predictable fashion
- The pathophysiology of AF remains incompletely understood
- Most data support a multifactorial process that leads to development of AF
- The proposed pathway suggests a "final common pathway" of risk factors (see Risk Factors section) to electrophysiologic changes in atrial tissues
- Alterations in membrane channels result in abnormal electrical excitability
- Additional cellular and tissue remodeling results in abnormal conduction properties in the atria, including shortening of atrial tissue refractory periods
- Further remodeling leads to the development of fibrosis and left atrial enlargement
- Multiple foci in the atria, usually near the pulmonary veins, fire continuously in a chaotic pattern, causing an irregular rapid ventricular rate
  - There is variable cardiac displacement and contraction, resulting in the sensation of palpitations and awareness of heartbeat
- The atria quiver and do not contract efficiently
  - The cardiac output loses the atrial systole contribution and, with irregular ventricular rates, a variable stroke volume results from variable ventricular filling
  - The resultant decrease in cardiac output may result in exercise intolerance, fatigue, weakness, presyncope, and dyspnea
  - With the loss of atrial contraction, blood stasis may promote in situ thrombosis (primarily in the left atrial appendage) that, when embolized, may result in a range of clinical consequences—most importantly, stroke
- Paroxysmal AF
  - Initiated by small re-entrant or rapidly firing foci in sleeves of atrial muscle that extend into pulmonary veins
- Persistent AF
  - Also initiated by re-entrant foci near the pulmonary veins, but also commonly includes areas near the superior vena cava, coronary sinus, and the posterior wall of the atrium
  - Involves more areas of fibrosis that uncouple atrial fibers, promoting further reentry pathways
- Long-standing persistent AF is associated with significant fibrosis
- Chronic tachycardia from AF can lead to depressed ventricular function with cardiomyopathy

RISK FACTORS

- Age > 60 years
- Underlying cardiac disease

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- Hypertension
- Diabetes mellitus
- Family history of AF
- Obesity
- Sedentary lifestyle
- Men who are extreme endurance athletes (cycling and running)
- Thyroid disease
- Sleep-disordered breathing
- Male sex
- Caucasian
- Rheumatic heart disease
- Identifiable precipitants of acute AF
    - Acute PE
    - Alcohol intoxication
    - MI
    - Hyperthyroidism
    - Cardiac surgery (AF occurs in up to 50% of patients postoperatively)
    - Excessive caffeine intake

ADMITTING ORDERS

- Admit to telemetry or the cardiac ICU
- Diagnosis: AF
- Vital signs: q2h × 4, then decreased to q4h
- Nursing: oxygen to maintain oxygen saturation > 92% and apply continuous telemetry
- Diet: nothing by mouth (if preparing for electrical cardioversion) or cardiac diet
- Diagnostic tests
    - ECG
    - BMP
    - CBC
    - Troponin
    - BNP
    - TSH
    - CXR
    - Transthoracic echocardiogram
- Medications
    - If AF with rapid ventricular response (RVR) is
        - Hemodynamically unstable
            - Prepare for urgent cardioversion and prepare sedating medications before cardioversion
        - Hemodynamically stable
            - Consider IV diltiazem, metoprolol, esmolol, verapamil, digoxin, or amiodarone; then transition to a PO rate control option when adequate rate control has been achieved
    - Anticoagulation with a DOAC (preferred) if the CHA_2DS_2-VASc score is ≥ 1
        - If the patient has mitral stenosis or a mechanical heart valve, use warfarin with a heparin bridge

DISCHARGE INFORMATION

- Discharge when the heart rate and symptoms are controlled
- Follow up with primary care clinician and cardiology to assess potential rhythm control strategies
- If discharged on anticoagulation, educate about bleeding risk
- Educate on the signs and symptoms of stroke
- If AF is associated with HF, ensure the patient is on adequate guideline-directed medical therapy
- Manage and discuss the importance of risk factor modification and management

CASE ANSWERS

1. This patient is presenting with new-onset AF with rapid ventricular response (RVR) causing dyspnea and palpitations. He does not have vital sign abnormalities or findings of end-organ damage, classifying this episode as hemodynamically stable AF with RVR. Because he does not have a history or signs of HF, IV diltiazem, 0.25 mg/kg over 2 min, would be a reasonable first-line choice to control the ventricular rate. If this does not improve the heart rate, a repeat bolus dose at 0.3 mg/kg can be administered with a continuous infusion started afterward at 5 mg/h.

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Alternatively, since this episode of AF is acute (onset < 48 h), a QRS-synchronized electrical cardioversion to restore the rhythm to normal sinus can be considered.

2. The CHA_2DS_2-VASc scoring system helps identify which patients should receive anticoagulation to reduce the annual risk of stroke from AF. This patient's CHA_2DS_2-VASc score is 0, indicating a very low risk of stroke from AF. Therefore, anticoagulation is not indicated for this patient.
3. The two main aspects of AF management besides reducing the annual stroke risk are either a rate or rhythm control strategy. Given that this patient is young, active, and does not have long-standing AF, a rhythm control strategy may be favored. This may include electrical cardioversion, catheter ablation, or antiarrhythmic therapy.
4. In men, excessive exercise is a risk factor for AF. While exercise with long-distance cycling has many health benefits, it may be a contributing factor to his new AF if performed in excess. The patient should additionally reduce his excessive caffeine and alcohol intake, as they likely contribute to the AF.

LANDMARK TRIALS

[1] Patel MR et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365:883, 2011. [PMID: 21830957]
- *Summary:* The ROCKET AF trial showed that among patients with nonvalvular AF, rivaroxaban is noninferior to warfarin in preventing stroke and systemic thromboembolism.

[2] Connolly SJ et al. Apixaban in patients with atrial fibrillation. N Engl J Med 364:806, 2011. [PMID: 21309567]
- *Summary:* The AVVEROES trial showed that in patients with AF thought to be unsuitable candidates for anticoagulation with a vitamin K antagonist, apixaban significantly reduced the risk of stroke and systemic embolism without increasing the risk of major bleeding or intracranial hemorrhage compared with aspirin.

[3] Van Gelder IC et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 362:1363, 2010. [PMID: 20231232]
- *Summary:* The Race II trial showed that among patients with permanent AF, lenient rate control (< 110 beats/min) is as effective as strict rate control (heart rate < 80) in preventing cardiovascular-related deaths, hospitalization for HF and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events.

[4] Kirchhof P et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med 383:1305, 2020. [PMID: 32865375]
- *Summary:* The EAST-AFNET 4 trial showed that early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early atrial fibrillation and cardiovascular conditions.

[5] Marrouche NF et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 378:417, 2018. [PMID: 29385358]
- *Summary:* The CASTLE-AF trial showed that in patients with AF and symptomatic (NYHA II–IV) systolic HF (LV ejection fraction ≤ 35%), catheter ablation was associated with a 16.1% absolute reduction in death or hospitalization for HF compared with medical therapy (rate or rhythm control). This difference was driven by both a 11.6% absolute risk reduction in death and a 15.2% absolute reduction in hospitalization for HF. Catheter ablation was also associated with greater improvement in LV ejection fraction and long-term maintenance of sinus rhythm.

FURTHER READING

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22 Syncope

KEY POINTS

1. Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow; onset is rapid, duration is brief, and recovery is spontaneous and complete. There are three types of syncope: neurally mediated (vasovagal), orthostatic, and cardiac.
2. Gathering a thorough and detailed history is the most important component in evaluating a patient with syncope. Ideally, both the patient and a witness can corroborate the activity and posture of the patient before, during, and after the incident. Precipitating factors, prodromes, postictal states, and associated symptoms also are important to elicit. Measurement of the patient's vital signs, including orthostatic vitals, and cardiac exam for murmurs and dysrhythmias are important on physical exam.
3. An ECG quickly evaluates a patient for cardiac conditions that can cause syncope. If the patient has obvious neurally mediated syncope, routine evaluation of bloodwork is not recommended. In patients with concern for other causes of syncope, a point-of-care glucose, CBC, BMP, and troponin should be measured. If a murmur is discovered on physical exam, or if there is concern for a structural cardiac cause of syncope, an echocardiogram is indicated.
4. Management of syncope depends entirely on the underlying cause. Neurally mediated syncope is managed with avoidance of triggers and isometric counterpressure maneuvers. Orthostatic hypotension is managed with education of staged movements, isometric counterpressure maneuvers, an abdominal binder, and medications. Cardiac syncope is managed based on the underlying cause.
5. Syncope can cause falls resulting in orthopedic and head/neck trauma (including intracranial hemorrhage). Cardiac syncope can result in life-threatening dysrhythmias and sudden cardiac death.

EPIDEMIOLOGY & DEFINITIONS

Syncope is a prevalent disorder, accounting for ~3% of ED visits and 1% of hospital admissions each year in the United States. Up to 40% of the population may experience a syncopal event during their lifetime. The annual cost of syncope-related hospitalization in the United States is ~$2.4 billion. Although most causes of syncope are benign, this symptom presages a life-threatening event in a small subset of patients.

CLINICAL VIGNETTE

A 64-year-old woman presents to the ED with several episodes of loss of consciousness in the last 2 weeks. Her daughter is at the bedside to corroborate some of the episodes. A few episodes occurred as she stood from a seated position; during these, she had lightheadedness, dizziness, weakness, and the feeling that her knees were buckling prior to falling backward into her chair as she lost consciousness. According to the daughter, her mother's loss of consciousness is ~10 s in duration, after which she quickly awakens without confusion. During one of these episodes, she had jerking movements and loss of urinary continence, but no loss of fecal continence, and she never had bleeding in her mouth. The other episodes have occurred while sitting, when she feels her heart racing and then slumps over in the chair, recovering quickly without postictal confusion. Her past medical history includes Parkinson's disease (treated with carbidopa-levodopa), AF (treated with apixaban and metoprolol), and type 2 diabetes mellitus (managed with empagliflozin). Her ECG in the ED reveals AF with heart rates ranging from 80 to 120 beats/min. Her orthostatic vital signs reveal a 30–mm Hg decrease in the systolic BP after 3 min of standing from a seated position.

GUIDING QUESTIONS

1. Besides causes of syncope, what is on your differential for transient loss of consciousness?
2. What historic features would help differentiate syncope versus seizure?
3. What diagnostic tests would you order?
4. Does this patient need to be admitted to the hospital?
5. Based on the history and physical exam, what two types of syncope should be considered in this patient?

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HISTORY

The history is the most important aspect of syncope assessment. In cases of presyncope or syncope, knowing about the patient's activity and posture before, during, and after the incident—ideally from both the patient and a witness—is important. Precipitating factors, prodromes, postictal states, and associated symptoms are important. Knowing whether the patient hit their head and where the patient fell is key to determining if cranial imaging is necessary. It is important to discover if the patient has a history of seizures, narcolepsy, and/or diabetes. Several medications have been implicated in precipitating syncope. Several clues in history can help determine the type of syncope and help differentiate seizure from syncope.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Depends on the class of syncope (neurally mediated, orthostatic, or cardiac), but all have a transient loss of consciousness that is brief with spontaneous and complete recovery
- Activity and posture before, during, and after the incident
  - Helps determine whether the syncope was exertionally or posturally related, or if the patient was at rest
  - Helps narrow the differential diagnosis of the syncopal event
- How long were they unconscious?
  - Longer time unconscious (> 5 min) is more likely to be a seizure
- What were they like when they woke up?
  - Prolonged confusion after waking up is more likely a seizure
  - Rapid recovery is more likely syncope
- Precipitating factors
  - Exertion: aortic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension
  - Positional change: orthostatic hypotension
    - Orthostatic and neurally mediated syncope rarely occur when patients are recumbent
  - Stressors: sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, and pain are associated with neurally mediated syncope
    - Compared with syncope, seizures are rarely evoked by emotions or pain
  - Neurocardiogenic: nausea or vomiting, cough, micturition, defecation, swallowing
  - Carotid sinus hypersensitivity: head turning or shaving, wearing a tight tie
  - Subclavian steal: arm activity prior to syncope
- Prodromes
  - Neurally mediated syncope
    - More likely if symptoms last > 5 s before a syncopal event
    - Common symptoms: diaphoresis, nausea, blurry vision, and warm sensation
  - Cardiac syncope
    - More likely if symptoms (e.g., chest pain, palpitations) last < 5 s before a syncopal event
- Associated symptoms
  - Chest pain?
  - Palpitations?
  - Neurologic symptoms?
  - Postictal status (seizures, confusion)
  - Bowel/bladder incontinence?
    - Loss of bladder continence can occur in either syncope or seizures
    - Fecal incontinence occurs during seizures, but only rarely occurs in syncope
  - Convulsive activity for < 10 s may occur in syncope, mimicking seizure activity
- Muscle aches after waking
  - Can occur in both seizures and syncope after awakening
  - However, last longer and are more severe with seizures
- On insulin therapy?
  - Hypoglycemia is a differential for syncope, and these patients present with
    - Tremor
    - Palpitations
    - Anxiety
    - Diaphoresis
    - Hunger
      - Hunger is not a typical symptom of syncope
    - Paresthesias
    - Fatigue, weakness, dizziness, cognitive/behavioral symptoms due to impaired neuronal function

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- High-risk features in the history
  - New onset of chest discomfort, abdominal pain, shortness of breath, or headache
  - Syncope during exertion or while supine
  - Sudden onset of palpitations followed by syncope
  - Severe coronary artery or structural heart disease

TYPICAL HISTORY BASED ON THE TYPE OF SYNCOPE

- Neurally mediated syncope
  - Dizziness, lightheadedness
  - Fatigue
  - Premonitory features of autonomic activation
    - Diaphoresis
    - Pallor
    - Palpitations
    - Nausea
    - Hyperventilation
    - Yawning
  - Proximal and distal myoclonus
    - May occur during syncopal event, raising concern of seizure instead
    - Myoclonus lasting < 30 s is more likely syncope than seizure
  - Eyes
    - Remain open
    - Usually deviate upward
    - May have roving movements
    - Pupils are dilated
  - Grunting, moaning, snorting, and stertorous breathing may be present
  - Urinary incontinence may occur, raising concern of seizure instead
  - Fecal incontinence and postictal confusion: rare in syncope
- Orthostatic hypotension
  - Light-headedness, dizziness, and presyncope occurring in response to sudden postural change
  - Nonspecific symptoms may be present, including
    - Generalized weakness
    - Fatigue
    - Cognitive slowing
    - Leg buckling
    - Headache
  - Visual blurring may occur, likely because of retinal or occipital lobe ischemia
  - Neck pain in the suboccipital, posterior cervical, and shoulder region (the "coat hanger headache")
    - Most likely due to neck muscle ischemia
    - May be the only symptom
  - May report
    - Orthostatic dyspnea (ventilation-perfusion mismatch due to inadequate perfusion of ventilated lung apices)
    - Angina (due to impaired myocardial perfusion even with normal coronary arteries)
- Cardiac syncope
  - Palpitations, either with brady- or tachycardic dysrhythmias
  - Chest pain associated with syncope
  - Exertional dyspnea and possibly angina with valvular diseases
  - May have syncope at rest or while lying supine

PAST MEDICAL HISTORY

- History of prior syncope?
  - What happened that time?
  - How is this similar? How is this different?
- History of previous cardiac or neurologic disorders?
  - Dysrhythmias? Structural or functional cardiac disease?
  - Parkinson's disease?
- History of diabetes?
  - Can lead to autonomic dysfunction and predispose to orthostatic hypotension

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SOCIAL HISTORY

- Use of alcohol or recreational drugs, smoking
- Occupation
- Living situation
- Sexual history

FAMILY HISTORY

- Cardiomyopathies (hypertrophic)?
- Sudden cardiac death (long QT syndrome)?
- Syncope?

MEDICATIONS

The following medications have been implicated in precipitating syncope:

- Cardiac medications
  - α-Blockers
  - β-Blockers
  - ACE-Is/ARBs
  - Calcium channel blockers
  - Class Ia, Ic, or III antiarrhythmics that prolong the QT interval
  - Diuretics
  - Hydralazine
  - Ganglion-blocking agents
  - Nitrates
- Psychiatric medications
  - Antidepressants
  - Antipsychotics
  - Barbiturates
  - Benzodiazepines
  - Phenothiazines

PHYSICAL EXAM

Vital signs (especially orthostatic vital signs) are important in syncope, as they can help diagnose the problem at hand. Other major organ systems to evaluate are cardiac, vascular, and neurologic. Common clinical clues of the syncopal event and its suggested cause are described in Table 22-1. An approach to the diagnostic workup and management of syncope from the historic features, initial vitals, and ECG are described in Figure 22-1.

TABLE 22-1 Historic Features of a Syncopal Event and its Suggested Causes

HISTORIC FEATURE OF SYNCOPAL EPISODE	SUGGESTED CAUSE(S)
Exertional	Aortic stenosis or mitral stenosis, HOCM, pulmonary hypertension
Associated with chest pain	Myocardial ischemia, PE, aortic dissection
Associated with palpitations	Tachy- or bradydysrhythmias
Patient with history of CAD or cardiomyopathy	Ventricular tachydysrhythmia
Family history of syncope or sudden death	Hereditary long QT syndrome, HOCM
Associated with emotional stress, pain, unpleasant auditory or visual stimuli	Vasovagal syncope
Following cough, micturition, or defecation	Situational syncope (form of vasovagal)
After arising from lying or sitting position	Orthostatic hypotension, hypovolemia, autonomic dysfunction
After turning head, during shaving, wearing a tight tie	Carotid sinus hypersensitivity
Associated with lying supine or bending forward	Atrial myxoma or "ball valve" thrombus
Diuretic medication use	Hypovolemia
Antiarrhythmic or antipsychotic medication use	Ventricular tachydysrhythmia
Parkinson's disease and diabetes mellitus	Autonomic insufficiency
Syncopal event after eating a large meal	Postprandial hypotension

HOCM, hypertrophic obstructive cardiomyopathy.

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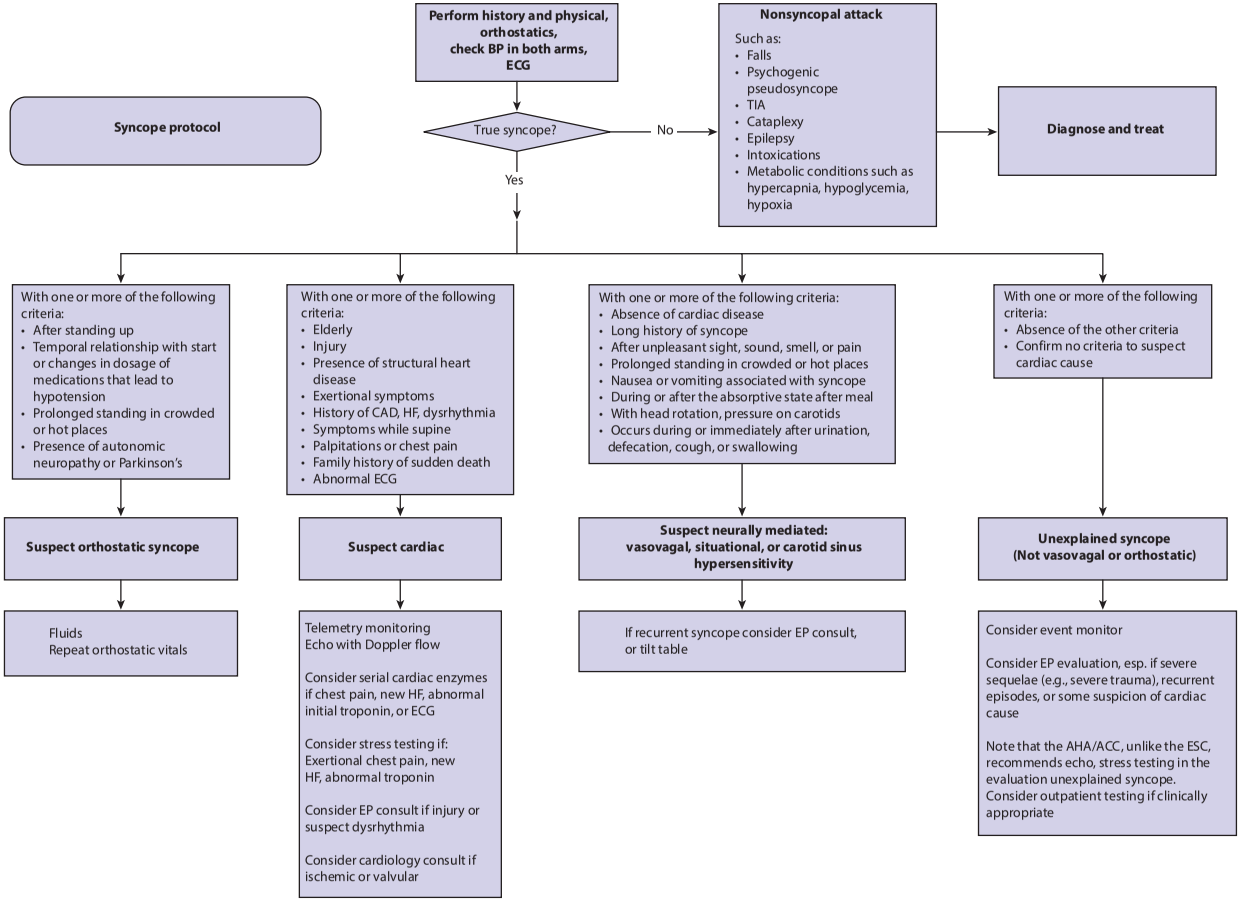

FIGURE 22-1 Overview of syncope evaluation. AHA/ACC, American Heart Association/American College of Cardiology; EP, electrophysiology; ESC, European Society of Cardiology. (Reproduced with permission from Corrigan FE III et al. Syncope, in *Principles and Practice of Hospital Medicine,* 2nd ed, SC McKean et al (eds). New York, McGraw Hill, 2017.)

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- Vital signs
  - Orthostatic vital signs, BP, heart rate, and oxygen saturation
  - Orthostatic vital signs are positive when there is a reduction in systolic BP of at least 20 mm Hg or diastolic BP of at least 10 mm Hg after 3 min of sitting or standing or the patient develops presyncopal symptoms
  - Supine hypertension may be present in orthostatic patients
- Cardiac
  - Assess the JVP and point of maximal impulse
  - Evaluate for the presence of S_3, murmurs, and RV heave with increased P_2 (pulmonary hypertension)
  - Assess for valvular disorders that may cause syncope (e.g., aortic stenosis, hypertrophic cardiomyopathy)
- Vascular
  - Evaluate for symmetric pulses and carotid, vertebral, and subclavian bruits
  - Perform a carotid sinus massage to assess for carotid hypersensitivity (if no bruits or suspected carotid stenosis is present) in patients > 40 years of age with recurrent syncope of unknown etiology
    - Assess for hypotension (systolic BP drop by 50 mm Hg) and bradycardia or asystole for 3 s
- Neurologic
  - Focal neurologic abnormalities may be present (e.g., pill rolling tremor in Parkinson's)
  - Assess for bleeding from the tongue, which may suggest a seizure
- High-risk features on physical exam
  - Unexplained systolic BP < 90 mm Hg
  - Suggestion of GI hemorrhage
  - Previously undiagnosed systolic murmur

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL

Other causes of transient loss of consciousness need to be distinguished from syncope:

- Seizure
  - Long postictal confused state
  - Tongue bites
  - Full tonic-clonic movements lasting > 5 min
  - Loss of bowel/bladder function
- TIA/stroke from vertebrobasilar ischemia
  - Presence of focal neurologic abnormalities, including
    - Unilateral weakness
    - Tingling
    - Slurring of speech
    - Abnormal reflexes
    - Dizziness
- Hypoglycemia
  - Patient takes insulin or intentionally took other hypoglycemic drugs in abundant amounts
  - Hypoglycemia is found on glucose testing
- Hypoxemia and/or hypercapnia
  - Associated with an acute cardiopulmonary condition
- Narcolepsy
  - History of suddenly falling asleep or sudden loss of consciousness with stress
- Cataplexy
  - An abrupt partial or complete loss of muscular tone triggered by strong emotions, typically anger or laughter
  - No premonitory symptoms
  - Consciousness is maintained throughout the attacks, which typically last between 30 s and 2 min
- Psychogenic pseudosyncope
  - Psychiatric history
    - Generalized anxiety disorder
    - Panic disorders
    - Major depression
    - Somatization disorder
  - Patients rarely have prodromal symptoms and rarely become injured despite numerous falls
  - Positive drop arm test may be seen during a syncopal event
- Intoxication
  - From use of alcohol and other drugs

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ETIOLOGY

- Neurally mediated syncope (most common cause of syncope)
  - Vasovagal
    - Provoked fear, anxiety, intense emotion
    - Sight of blood
    - Unpleasant sights and odors
    - Orthostatic stress
  - Situational reflex syncope
    - Pulmonary: cough, wind instrument player's syncope, weightlifter's syncope, "mess trick" (hyperventilation for ~1 min, followed by sudden chest compressions) and "fainting lark" (hyperventilation [~20 breaths] in a squatting position, rapid rise to standing, then Valsalva maneuver), sneeze syncope, airway instrumentation
    - Urogenital: postmicturition syncope, prostatic massage, urogenital tract instrumentation
    - GI: swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, rectal exam, defecation syncope
    - Cardiac: Bezold-Jarisch reflex, cardiac outflow obstruction
    - Carotid sinus: carotid sinus hypersensitivity, carotid sinus massage
    - Ocular: ocular pressure, ocular examination, ocular surgery
- Orthostatic hypotension
  - Primary autonomic failure due to idiopathic central and peripheral neurodegenerative disease—the "synucleinopathies"
    - Synucleinopathies: Parkinson's disease, Lewy body dementia, pure autonomic failure
    - Multiple system atrophy (Shy-Drager syndrome)
  - Secondary autonomic failure due to autonomic peripheral neuropathies
    - Diabetes
    - Amyloidosis (hereditary or primary)
    - Hereditary sensory and autonomic neuropathy
    - Idiopathic immune-mediated neuropathy
    - Autoimmune autonomic ganglionopathy
    - Sjögren's syndrome
    - Paraneoplastic autonomic neuropathy
    - HIV neuropathy
  - Postprandial hypotension
    - Dizziness, lightheadedness, and syncope after heavy carbohydrate meals
  - Iatrogenic from medications (see Medications in History section)
  - Volume depletion (e.g., dehydration, hemorrhage)
- Cardiac syncope
  - Dysrhythmias
    - Sinoatrial (SA) node dysfunction (sinus arrest or SA block)
    - Atrioventricular (AV) node dysfunction (e.g., Mobitz second degree type II)
    - Tachy-brady syndrome
    - Stokes-Adams syndrome (syncope due to bradycardia or asystole)
    - Supraventricular and ventricular tachycardia
    - Inherited channelopathies (long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia)
  - Cardiac structural disease
    - Valvular disease (aortic stenosis and mitral stenosis especially)
    - Obstructive cardiomyopathies (e.g., hypertrophic cardiomyopathy)
    - Atrial myxoma
    - Pericardial effusions and tamponade
    - Anomalous coronary artery
    - Pulmonary hypertension
  - Massive MI
  - PE
    - In patients admitted for first episode of syncope, 17% were found to have PE after a standardized, guideline-based inpatient evaluation
    - PE was identified in 13% of patients with an alternative etiology for syncope and 25% of patients who did not
    - PE was identified in 25% of patients without typical signs or symptoms [1]
- Cerebrovascular disease
  - TIA or ischemic stroke of vertebrobasilar circulation may rarely lead to syncope

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DIAGNOSTIC TESTS

LABS

- Baseline lab blood tests are rarely helpful in identifying the cause of syncope
- Blood tests should be performed when specific disorders (e.g., MI, anemia, secondary autonomic failure) are suspected
- Point-of-care glucose
  - Hypoglycemia is a life-threatening condition
  - Low threshold to order this test
- CBC
  - Evaluate for anemia
- BMP
  - Check for sodium, calcium, potassium, and magnesium abnormalities, which can cause altered mental status (mimicking syncope) or dysrhythmias that cause syncope
- Troponin
  - Assess for myocardial ischemia

IMAGING

- ECG
  - Evaluate for acute myocardial ischemia, old MI, brady- and tachydysrhythmias, atrioventricular (AV) block, long QT interval, bundle branch blocks
- Transthoracic echocardiogram in patients with a history of cardiac disease, or if abnormalities are found on physical exam or the ECG
  - Patients with murmurs, family history of sudden cardiac death, syncope during exertion or supine position, abnormal ECG (long QRS, AV block type II, sinus pauses, inappropriate bradycardia, nonsustained ventricular tachycardia, Brugada pattern, Q waves suggesting prior MI, negative T waves in right precordial leads), and sudden onset of palpitations before syncope should receive an echocardiogram
  - Evaluates for aortic stenosis, mitral stenosis, hypertrophic obstructive cardiomyopathy, cardiac tumors, aortic dissection, and pericardial tamponade
  - Echocardiography also has a role in the risk stratification for sudden cardiac death based on the LVEF
- EEG if you suspect seizures in the differential
- CT angiogram or MR angiogram of neck/brain vasculature if you suspect neurocardiogenic (vertebrobasilar insufficiency) syncope
- Carotid ultrasound (not commonly performed for syncope, however)
  - Can perform in the hospital, but not commonly done inpatient unless there are carotid bruits
- Ambulatory ECG monitor if a dysrhythmia is suggested but not recorded on ECG or during hospitalization (Holter monitor, event recorder, loop recorder)
- Treadmill exercise testing with ECG and BP monitoring
  - Should be performed in patients who have experienced syncope during or shortly after exercise
  - Treadmill testing may help identify exercise-induced dysrhythmias (e.g., tachycardia-related AV block) and exercise-induced exaggerated vasodilation
- Tilt-table test
  - Examines for vasovagal syncope if it is not cardiac syncope, but the syncope is recurrent
  - Not needed if syncope is obviously vasovagal in nature
  - Can help differentiate orthostatic hypotension due to autonomic failure from the hypotensive bradycardic response of neurally mediated syncope
  - Performed in outpatient setting
- Invasive electrophysiologic studies
  - Indicated in patients with structural heart disease and ECG abnormalities in whom noninvasive investigations have failed to yield a diagnosis
  - Have low sensitivity and specificity and should be performed only when a high pretest probability exists
  - Rarely performed to evaluate patients with syncope

MANAGEMENT

CRITERIA FOR ADMISSION

- Patients with structural heart disease (HF, MI, CAD, valvular disease)
- ECG shows a dysrhythmia, myocardial ischemia, or prolonged QT interval
- Comorbid reasons (risk factors)

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TABLE 22-2 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope
Chest pain suggesting coronary ischemia
Features of HF
Moderate or severe valvular disease
Moderate or severe structural cardiac disease
Electrocardiographic features of ischemia
History of ventricular dysrhythmias
Prolonged QT interval (> 500 ms)
Repetitive SA block or sinus pauses
Persistent sinus bradycardia
Bi- or trifascicular block or intraventricular conduction delay with QRS duration ≥ 120 ms
AF
Nonsustained ventricular tachycardia
Family history of sudden death
Preexcitation syndromes
Brugada pattern on ECG
Palpitations at time of syncope
Syncope at rest or during exercise

SA, sinoatrial. Reproduced with permission from Freeman R, Raj SR. Syncope, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- Syncope at rest, with exertion, or while supine
- Recurrent syncope
- Table 22-2 indicates a more thorough discussion of the high-risk features indicating a need for hospitalization to evaluate syncope
- The following are low-risk features that suggest a benign condition in patients with syncope at the initial evaluation in the ED (and can usually be discharged from the ED)
    - Associated with prodrome typical of reflex syncope (e.g., lightheadedness, feeling of warmth, sweating, nausea, vomiting)
    - After a sudden unexpected sight, sound, smell, or pain
    - After prolonged standing or in a crowded, hot environment
    - During a meal or postprandial
    - Triggered by cough, defecation, or micturition
    - With head rotation or pressure on the carotid sinus (e.g., tumor, shaving, tight collars)
    - Standing from a supine/sitting position

MANAGEMENT OF NEURALLY MEDIATED (VASOVAGAL) SYNCOPE

- Cornerstones of management
    - Reassurance
    - Education
    - Avoidance of provocative stimuli
    - Plasma volume expansion with fluid and salt intake
- Isometric counterpressure maneuvers (tensing of the abdominal and leg muscles, leg crossing, or handgrip and arm tensing) may raise BP by increasing central blood volume and cardiac output
    - Abdominal and leg muscle tensing most effective
    - Physical counterpressure maneuvers
        - Are a risk-free, effective, and low-cost treatment method in patients with vasovagal syncope and recognizable prodromal symptoms
        - Should be advised as first-line treatment in patients presenting with vasovagal syncope with prodromal symptoms [2]
- Fludrocortisone, vasoconstricting agents (e.g., midodrine), and β-adrenoreceptor antagonists are widely used by experts to treat refractory patients
    - Of these, only midodrine has been shown to be effective
        - Midodrine can reduce the recurrence of syncope in healthy, younger patients with a high syncope burden [3]
- Dual-chamber pacemaker insertion
    - Sham-controlled studies

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        - Showed that syncope recurrence was decreased with dual-chamber pacemakers with a closed-loop stimulation algorithm
        - However, the trial restricted enrollment to older patients (> 40 years)
    - Uncertainty remains about using in patients with cardioinhibitory syncope response during tilt-table testing

MANAGEMENT OF ORTHOSTATIC HYPOTENSION

- Remove reversible causes, such as
    - Ganglion-blocking agents
    - Vasodilators
    - Diuretics
    - Nitrates
    - α-Adrenoreceptor antagonists used to treat hypertension and prostatic hypertrophy
    - Antihypertensives
    - Tricyclic antidepressants
    - Phenothiazines
- Education regarding
    - Staged moves from supine to upright
    - Warning about the hypotensive effects of large meals
    - Instructions about isometric counterpressure maneuvers (especially abdominal and leg tensing)
    - Raising the head of the bed to reduce supine hypertension and nocturnal diuresis
- Increase fluid and salt intake
    - Rapid ingestion of 500 mL of plain water can often act as a short-term pressor response in these patients
    - In some patients, IV fluids may be trialed to see if symptoms result from volume depletion
- Abdominal binder and compression stockings application
- If the above measures do not work, can initiate pharmacologic therapy
    - Fludrocortisone acetate
        - Initiated at 0.05 mg daily in the morning
        - Titrated up to 0.2 mg daily
    - Midodrine
        - Titrated to 2.5–10 mg two to three times daily
        - Avoid if severe heart disease, uncontrolled supine hypertension, or urinary retention is present
    - L-dihydroxyphenylserine (droxidopa) 100 mg tid, then titrated up to 600 mg tid, also can be considered for patients with autonomic dysfunction
    - Patients with intractable symptoms may require additional therapy with
        - Supplementary pyridostigmine, especially if supine hypertension is present
        - Atomoxetine
        - Yohimbine
        - Octreotide
        - Desmopressin acetate (DDAVP)
        - Erythropoietin

MANAGEMENT OF CARDIAC SYNCOPE

- Treat the underlying disorder
    - Automated implantable cardioverter defibrillator (AICD) for hypertrophic obstructive cardiomyopathy and ventricular tachycardias when indicated
    - Cardiac pacing for bradycardia (including sinoatrial and atrioventricular nodal diseases)
    - Ablation, antiarrhythmic drugs, and cardioverter-defibrillators for atrial and ventricular tachydysrhythmias
    - Valve replacement for aortic stenosis and mitral stenosis
    - β-Blockers or calcium channel blockers for SVTs
    - Revascularization if syncope is ischemia related
- Continuous cardiac ambulatory electrocardiographic (Holter) monitoring
    - May be needed for patients who experience frequent syncopal episodes (e.g., daily or almost daily)
    - Loop recorders
        - Continually record and erase cardiac rhythm
        - Indicated for patients with suspected dysrhythmias with low risk of sudden cardiac death

COMPLICATIONS

- Falls with injury leading to orthopedic and head/neck injuries (including intracranial bleeding)
- Sudden cardiac death from dysrhythmia-related syncope

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PROGNOSIS

- Excellent for syncope of noncardiac and unexplained origin in younger individuals; life expectancy is unaffected
- Risk of sudden cardiac death and mortality from other causes are increased in cardiac syncope from structural heart disease or a primary dysrhythmic disorder
- Mortality rate also increased in individuals with syncope due to orthostatic hypotension related to age and the associated comorbid condition

PATHOPHYSIOLOGY

- Most syncopal events occur in the upright position, usually from standing
- Normal response to standing
  - Standing results in the pooling of 500–1000 mL of blood in the lower extremities, buttocks, and splanchnic circulation
  - The dependent pooling leads to a decrease in venous return to the heart and reduced ventricular filling that results in diminished cardiac output and BP
  - These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, resulting in increased outflow and decreased vagal nerve activity that allows the pooled blood to redistribute to the rest of the body
  - The reflex increases peripheral resistance, venous return to the heart, and cardiac output, and this limits the fall in BP
- Syncope occurs from the failure of cerebral blood flow autoregulation mechanisms (Fig. 22-2)
  - Myogenic factors, local metabolites, and autonomic neurovascular control are responsible for the autoregulation of cerebral blood flow
  - The normal autoregulatory response is 5–10 s, with cerebral blood flow measuring 50–60 mL/min per 100 g brain tissue
  - Cessation of blood flow to the brain for 6–8 s will result in loss of consciousness, while impairment of consciousness ensues when blood flow decreases to 25 mL/min per 100 g brain tissue

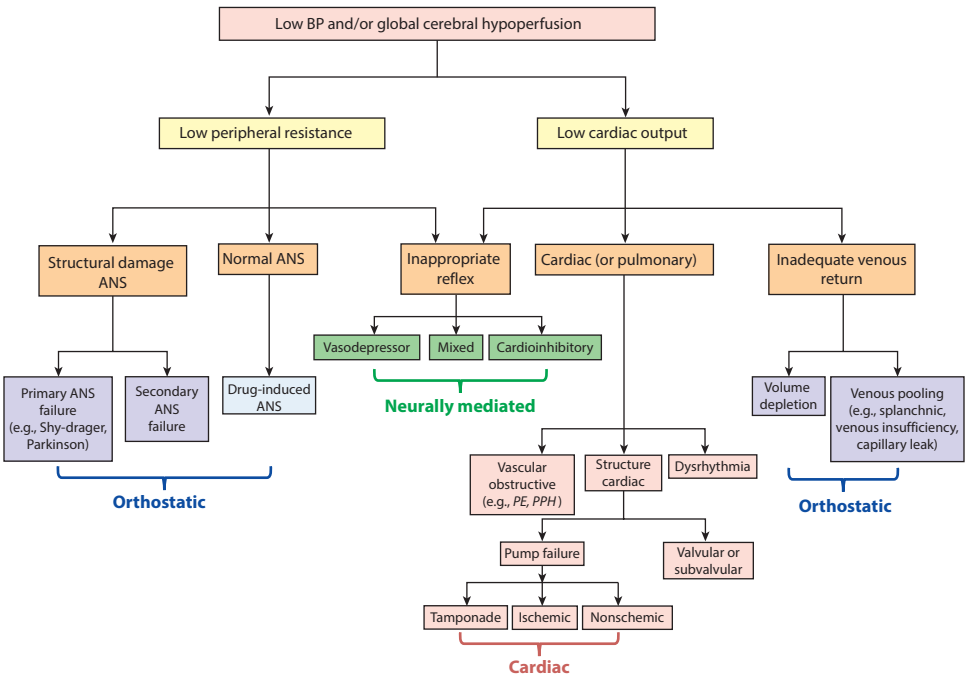

FIGURE 22-2 Pathophysiologic basis of syncope. ANS, autonomic nervous system; PPH, primary pulmonary hypertension. (Reproduced with permission from Corrigan III FE, Agrawal K, Pittman Jr. JR, Dressler DD. Syncope, in *Principles and Practice of Hospital Medicine*, 2nd ed, SC McKean et al (eds). McGraw Hill, 2017.)

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- A fall in systemic BP to ~50 mm Hg or lower results in syncope (enough to cause cessation of blood flow to the brain for 6–8 s)
  - This occurs from a decrease in cardiac output and/or systemic vascular resistance (the determinants of BP)
  - Common causes of impaired cardiac output include decreased effective circulating blood volume, increased thoracic pressure, massive PE, brady- and tachydysrhythmias, valvular heart disease, and myocardial dysfunction
  - Decreased systemic vascular resistance may be caused by central and peripheral autonomic nervous system diseases, by sympatholytic medications, and transiently during neurally mediated syncope
  - Increased cerebral vascular resistance, most frequently due to hypocarbia from hyperventilation, also may contribute to the pathophysiology of syncope
- As baroreceptor dysfunction occurs with decreased BP, loss of sympathetic activity and parasympathetic deactivation leads to further decreased venous return to the heart and brain, resulting in global cerebral hypoperfusion

- Neurally mediated syncope
  - Transient changes in the reflexes responsible for maintaining cardiovascular homeostasis (above) result in syncope
  - Episodic vasodilation (or loss of vasoconstrictor tone), decreased cardiac output, and bradycardia occur in varying combinations, resulting in temporary failure of BP control
- Orthostatic hypotension
  - As opposed to neurally mediated syncope, there is chronic autonomic failure, where the above reflexes are chronically impaired, leading to failure of BP control mechanisms with change in position
- Cardiac syncope
  - Bradydysrhythmias: a prolonged pause limits cerebral blood flow
  - Ventricular tachycardia
    - Dependent in part on the ventricular rate (rates < 200 beats/min are less likely to cause syncope) and ventricular function (a patient with poor ventricular function is more likely to have syncope at a given ventricular rate)
    - The compromised hemodynamic function during ventricular tachycardia is caused by ineffective ventricular contraction, reduced diastolic filling due to abbreviated filling periods, loss of atrioventricular synchrony, and concurrent myocardial ischemia
  - Long QT syndromes: associated with prolonged cardiac repolarization and a predisposition to ventricular dysrhythmias that can lead to torsades de pointes that may degenerate into ventricular fibrillation
  - Structural heart disease (e.g., valvular disease, myocardial ischemia, hypertrophic and other cardiomyopathies, cardiac masses such as atrial myxoma, and pericardial effusions)
    - May lead to syncope by compromising cardiac output
    - Structural heart diseases may predispose to other mechanisms of syncope by
      - Predisposing to arrhythmogenesis
      - Aggressive treatment of cardiac failure with diuretics and/or vasodilators that may lead to orthostatic hypotension
      - Inappropriate reflex vasodilation that may occur with structural disorders such as aortic stenosis and hypertrophic cardiomyopathy, possibly provoked by increased ventricular contractility

RISK FACTORS

- Neurally mediated syncope
  - Motionless upright posture
  - Warm ambient temperature
  - Intravascular volume depletion
  - Alcohol ingestion
  - Hypoxemia
  - Anemia
  - Pain
  - The sight of blood and venipuncture
  - Intense emotion
- Cardiac and orthostatic syncope
  - Older age
  - Women > men

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- Dehydration
- Certain medications
- Patients who are institutionalized
- Cardiac disease
- Dysrhythmias
- Neurologic disease
- Diabetes mellitus

ADMITTING ORDERS

- Admit to telemetry
- Diagnosis: syncope
- Condition: guarded
- Vital signs: telemetry routine, orthostatic BP measurement
- Activity: fall risk, up with assistance only
- Nursing: oxygen to maintain oxygen saturation > 92%, daily weights
- Diet: regular or tailored to comorbidities
- Fluids: if indicated
- Diagnostic tests
  - CBC
  - BMP, including glucose
  - Troponins if indicated
  - ECG
  - Echocardiogram if indicated
- Medications
  - Hold medications that can cause syncope (BP medications, diuretics, antidepressants, antianginals, analgesics, CNS depressants, etc.)
  - Other medications are situation dependent
    - For example, β-blockers to control the rate of supraventricular tachydysrhythmias (including AF)

DISCHARGE INFORMATION

- Holter monitor outpatient if indicated
- Education on avoidance of provocative stimuli, plasma volume expansion with fluid and salt intake, and sitting-to-standing counterpressure maneuvers if neurally mediated or orthostatic syncope
- Follow up with primary care physician

CASE ANSWERS

1. Causes of transient loss of consciousness include
   a. Seizure
   b. TIA/stroke from vertebrobasilar ischemia
   c. Hypoglycemia
   d. Hypoxemia and hypercapnia
   e. Narcolepsy
   f. Cataplexy
   g. Psychogenic pseudosyncope
   h. Intoxication (use of alcohol and other drugs)
2. Seizure and syncope can present similarly. *Seizure* is more likely if
   a. Tonic-clonic movements are prolonged (> 30 s)
   b. Loss of consciousness is > 5 min with a prolonged postictal drowsiness and disorientation
   c. Fecal incontinence occurred
   d. Tongue biting was present

Syncope, on the other hand, is more likely when

a. Tonic-clonic movements resolve quickly
b. Loss of consciousness is short-lived with rapid recovery

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c. Fecal incontinence is absent (bowel incontinence can occur in syncope) *and*

d. Tongue biting is absent

3. A point-of-care glucose test is a rapid test that can rule out life-threatening hypoglycemia mimicking syncope. Given this patient has multiple comorbidities and some episodes that occurred while at rest, a CBC, BMP, and troponin should be ordered.
4. Patients with syncope do not always need to be admitted to the hospital. However, as this patient had some syncopal episodes that occurred at rest and she has an underlying cardiac dysrhythmia, she meets the criteria to be hospitalized to further evaluate for cardiac syncope. Table 22-2 in the Management section describes indications for hospital admission.
5. The history describes two separate syncopal events: syncope after standing and syncope while sitting in a chair. Syncope after standing with associated symptoms of lightheadedness, dizziness, weakness, knee buckling sensation, and exam findings of a 30-mm Hg decrease in the systolic BP after 3 min of standing from a seating position are all findings of orthostatic hypotension. Further supporting this diagnosis is the medical history of Parkinson's disease (a synucleinopathy leading to autonomic failure) and type 2 diabetes mellitus. Additionally, the patient also describes syncope while sitting in a chair after palpitations occurred. The ECG reveals her known AF with a variable heart rate. Taking these separate events, both orthostatic hypotension and cardiac syncope should be evaluated and managed while admitted to the hospital.

LANDMARK TRIALS

[1] Prandoni O et al. Prevalence of pulmonary embolism among patients hospitalized for syncope. N Engl J Med 375:1524, 2016. [PMID: 27797317]
- *Summary:* Of inpatients admitted for first episode of syncope, 17% were found to have PE after a standardized, guideline-based inpatient evaluation. PE was identified in 12.7% of patients who had an alternative etiology for syncope and 25.4% of patients who did not. PE was identified in 25% of patients without typical signs or symptoms.

[2] van Dijk N et al. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: The Physical Counterpressure Manoeuvres Trial (PC Trial). J Am Coll Cardiol 48:1652, 2006. [PMID: 17045903]
- *Summary:* Physical counterpressure maneuvers are a risk-free, effective, and low-cost treatment method in patients with vasovagal syncope and recognizable prodromal symptoms and should be advised as first-line treatment in patients presenting with vasovagal syncope with prodromal symptoms.

[3] Sheldon R et al. Midodrine for the prevention of vasovagal syncope: A randomized clinical trial. Ann Intern Med 174:1349, 2021. [PMID: 34339231]
- *Summary:* Midodrine can reduce the recurrence of syncope in healthy, younger patients with a high syncope burden.

FURTHER READING

- Corrigan FE III et al. Syncope, in *Principles and Practice of Hospital Medicine*, 2nd ed, SC McKean et al (eds). New York, McGraw-Hill Education, 2017.
- Freeman R, Raj SR. Syncope, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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23 Gastrointestinal Bleeding

KEY POINTS

1. Gastrointestinal bleeding (GIB) is categorized as overt (with hematemesis, melena, and/or hematochezia) or occult (non-obvious bleeding but symptoms of blood loss). Additionally, categorizing the location of the bleed (e.g., upper, small intestinal, or lower) is important to guide the diagnostic work-up and management.
2. In overt GIB, the patient will report obvious bleeding from vomit or in the passage of stool. Occult bleeding will present with symptoms of anemia and may include lightheadedness, syncope, angina, or dyspnea. The physical exam can help determine the severity of the bleed (e.g., tachycardia, hypotension, orthostatic hypotension), and to identify potential bleeding etiologies (e.g., caput medusae and spider angioma may suggest cirrhosis with esophageal variceal bleeding). A digital rectal exam is indicated in most cases of GIB to detect the presence of hemorrhoids, hematochezia, and/or melena.
3. Overt GIB is diagnosed via the history and physical exam. Occult GIB is diagnosed with a CBC showing anemia in the clinical context of symptoms consistent with chronic blood loss. An iron panel is useful in the evaluation of occult GIB. Endoscopy (either EGD or colonoscopy) identifies the bleeding location and lesion.
4. All patients with GIB, regardless of the location, should have two large-bore IVs, fluid boluses, and a blood transfusion when indicated (hemoglobin is ≤ 7 g/dL). In upper GIB (UGIB) patients, IV proton pump inhibitor therapy is indicated. In patients with cirrhosis presenting with an UGIB, IV ceftriaxone and an octreotide infusion should additionally be administered. GI consultation for advanced endoscopic therapies is indicated for most patients.
5. Recurrent bleeding and hospitalizations, decompensation of chronic medical conditions, and death are complications of GIB. During hospitalizations, the case fatality rate is ~2%. Patients generally die from decompensation of other underlying illnesses rather than exsanguination. Patients with esophageal variceal bleeds have poorer outcomes than patients with other sources of UGIBs.

EPIDEMIOLOGY & DEFINITIONS

Gastrointestinal bleeding (GIB) presents as either overt or occult bleeding.

Overt GIB is manifested by

- Hematemesis
- Melena, and/or
- Hematochezia

Occult GIB may present with symptoms of chronic blood loss or anemia such as

- Lightheadedness
- Syncope
- Angina
- Dyspnea with iron-deficiency anemia, or
- A positive fecal occult blood test on colorectal cancer screening

GIB is the most common gastrointestinal condition leading to hospitalization in the United States, accounting for ~530,000 admissions annually with a case fatality rate of ~2%. Patients generally die from decompensation of other underlying illnesses rather than exsanguination.

Hematemesis: vomiting red blood or "coffee-grounds" material—usually results from an upper GIB (UGIB).

Melena: black tarry stool—usually results from a UGIB.

Hematochezia: passage of red or maroon blood from the rectum—usually results from a lower GIB.

Upper GI bleed (UGIB): intraluminal blood loss from the oropharynx to the ligament of Treitz.

Lower GI bleed (LGIB): intraluminal blood loss from ligament of Treitz to the anus.

Small-intestinal bleed: with improved diagnostics, ~75% of GIBs labeled as "obscure" are now estimated to originate in the small intestine beyond the extent of a standard upper endoscopic exam.

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CLINICAL VIGNETTE

A 63-year-old man with cirrhosis due to alcohol use presents to the ED vomiting bright red blood for the past 2 h. He recently relapsed with alcohol due to losing his job. On physical exam, he appears uncomfortable. He is afebrile and tachycardic at 120 beats/min, BP is 94/62 mm Hg, and oxygen saturation is 96% on room air. Caput medusae and spider angiomata are present on abdominal and chest examination, respectively. Initial lab data reveal a hemoglobin of 9.4 g/dL (baseline hemoglobin is 10–11 g/dL), albumin of 2.4 g/dL, PT 16.5 seconds, INR 2.4, and creatinine of 2.4 mg/dL. He is not currently vomiting bright red blood.

GUIDING QUESTIONS

1. What type of IV access is indicated for this patient?
2. In addition to administering IV fluid boluses, would you transfuse this patient with PRBCs?
3. What medications would you administer to this patient?

HISTORY

A quick history to discover where the gastrointestinal bleed (GIB) is originating from and how much blood has been lost is vital to understanding how unstable a patient with a GIB is, and how to proceed with evaluation and management. Assess risk factors for certain conditions that can cause bleeding. For example, does the patient have cirrhosis and, if so, any history of varices or prior bleeding episodes, and medications that could disrupt the mucosal barrier (e.g., antiplatelets/anticoagulants, NSAIDs, steroids)?

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/*s*ymptoms—or use your preferred mnemonic)
  - Patients can present with overt bleeding with hematemesis, hematochezia, or melena
  - Alternatively, can present with an occult GIB with the only complaint being a low hemoglobin on routine blood work
  - Other symptoms may also be present
    - Fatigue
    - Dyspnea
    - Pallor
    - Abdominal pain
    - Anorexia
    - Change to stool caliber
- Acute or chronic bleeding?
  - Acute has a higher risk of complications and a life-threatening etiology
  - Chronic is less likely to be life-threatening in the immediate scenario
- How much blood has been lost?
  - Can change the immediate management
- Hematemesis?
  - Vomiting blood
  - Only sign or symptom that definitively reveals an upper GIB (UGIB)
- Vomiting before hematemesis (Mallory-Weiss tear)?
  - Recent alcohol use or binge? Vomiting after eating (bulimia)?
- Coffee-ground emesis?
  - Suggests an UGIB source with a slower bleeding rate than hematemesis
- Melena?
  - Black, tarry, liquid, foul-smelling stool
  - Caused by degradation of hemoglobin by bacteria in the colon
  - Presence of melena indicates that blood has remained in the GI tract for ≥ 14 h and as long as 3–5 days
  - Dark stools can also result from bismuth, iron, spinach, charcoal, and licorice
  - 90% of the time, true melena is from an UGIB
- Hematochezia?
  - Bright red blood per rectum; usually represents a lower GIB source (typically left colon or rectum)
  - It may also result from a massive UGIB that is briskly bleeding
- Pain?
  - Where is it?

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- How severe is it?
- Radiation?
- Description of pain?

- Dyspnea?
  - Either overt or occult GIB can present with dyspnea from reduced oxygen-carrying capacity of the blood
- Recent weight loss?
  - How much?
  - Unintended?
  - Potential sign of colon cancer if associated with GIB
- Anorexia?
  - What happens when you eat?
  - Pain with eating (may suggest a gastric ulcer)?
- Change in stool caliber?
  - What did it used to be like?
  - What is it like now?
- Prior abdominal radiation?
  - Can cause GIB, as the GI cells turn over quickly

PAST MEDICAL HISTORY

- Prior GIBs?
  - Was the source found?
  - What was done to stop it?
  - How many times has this happened?
  - Is this the same as those other times?
- Other GI disease?
  - Can help in diagnosis
  - How was your GI disease diagnosed and how is it being treated?
- History of coagulopathy?
  - Can have clots forming in GI vessels and causing acute ischemia with bleeding
  - Can have bleeding diatheses that make GIB more common
- History of cirrhosis?
  - Known esophageal varices?
  - Prior EGD?
- Risk factors for cirrhosis?
  - Hepatitis B/C?
  - α_1 Antitrypsin deficiency?
  - Wilson's disease?
  - Hemochromatosis?
  - Autoimmune hepatitis?
  - Primary biliary cirrhosis?
- History of *Helicobacter pylori* infection?
  - Risk of upper GIB from ulcers
- History of cancer?
  - Esophageal, gastric, and colon cancer

SURGICAL HISTORY

- Prior GI or aortic surgeries?
  - Post–abdominal aortic aneurysm repair
    - Ischemic colitis is common
    - Causes bloody diarrhea and petechial bleeding, insufficient blood supply especially to watershed areas of colon (splenic flexure)
    - Prior abdominal aortic aneurysm repair can cause a fistula to form between the aorta and bowel, causing an aortoenteric fistula with brisk bleeding

SOCIAL HISTORY

- Use of alcohol and recreational drugs, smoking
- Occupation
- Living situation
- Sexual history

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MEDICATIONS

- Antiplatelets/NSAIDs?
  - Risk of peptic ulcers and bleeding as they inhibit the formation of prostaglandins, which are a mucosal protective barrier
- Anticoagulants?
  - Warfarin, heparin, and DOACs all predispose to bleeding
- Glucocorticoids?
  - Inhibit the proper formation of a protective mucosal lining in the stomach

PHYSICAL EXAM

Vital signs and the ABCs are important in cases of gastrointestinal bleed (GIB). Visualization of the blood, if present, is very helpful to establish a likely site of bleeding. Signs of peritonitis should be evaluated in case emergent surgery is necessary. Rectal exam is indicated if no obvious frank bleeding is occurring at the present time. Examine for signs of cirrhosis.

- Vital signs
  - Heart rate and BP, orthostatic vital signs
    - Clinically significant bleeding leads to postural changes in heart rate or BP
    - Eventually, significant bleeding leads to recumbent hypotension
    - Patients with a slow, chronic GIB may have normal heart rates and BP despite low hemoglobin due to hemodynamic compensation over time
- HEENT
  - Evaluate for epistaxis (can be confused with hematemesis)
  - Assess for oropharyngeal trauma
- Cardiac
  - Evaluate the JVP and capillary refill time for a volume status exam
  - Hammond's crunch (a crunching or bubbling sound detected during cardiac auscultation synchronous with the heartbeat suggesting the presence of air in the mediastinum) may indicate Mallory-Weiss tear and esophageal rupture
- Abdominal and rectal
  - Assess for localizable pain, peritoneal signs, hepatosplenomegaly, ascites, and caput medusae
  - Hyperactive bowel sounds may be a sign of an upper GIB (UGIB)
  - Assess for hemorrhoids, anal fissures, stool appearance, color, and presence of occult blood
- Skin
  - Pallor suggests anemia and chronicity of bleeding
  - Jaundice suggests cirrhosis or hemolytic anemias
  - Telangiectasias: caput medusa and hemorrhoids are signs of cirrhosis
  - Spider angiomas: sign of cirrhosis

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

UPPER GI BLEED

- Peptic ulcer disease (gastric and duodenal) (**Fig. 23-1** and **2**)
  - Burning retrosternal epigastric or chest pain that then bleeds, with common risk factors of NSAIDs and *H. pylori*
  - Responsible for ~50% of upper GI bleed (UGIB) hospitalizations
- Mallory-Weiss tear
  - Self-limiting hematemesis, usually following vomiting/retching/coughing in a patient with a recent alcohol binge or in patients with bulimia nervosa
  - Responsible for ~2–10% of UGIB hospitalizations
- Esophageal varices (**Fig. 23-3**)
  - Hematemesis in a patient with cirrhosis; can be hemodynamically unstable at presentation
  - Responsible for ~2–40% of UGIB hospitalizations, with the wide range being variable depending on the population
- Gastric, small and large intestine varices, and portal hypertensive gastropathy
  - Portal hypertension (usually in a patient with cirrhosis) is usually responsible for these conditions
- Erosive disease (**Fig. 23-4**)
  - Erosions of the mucosal layer that do not cause major bleeding (no arteries or veins in the mucosal layer)
  - May occur in the esophagus, stomach, or duodenum and are primarily from GERD, gastritis, or duodenitis
  - Responsible for ~30% of UGIB hospitalizations

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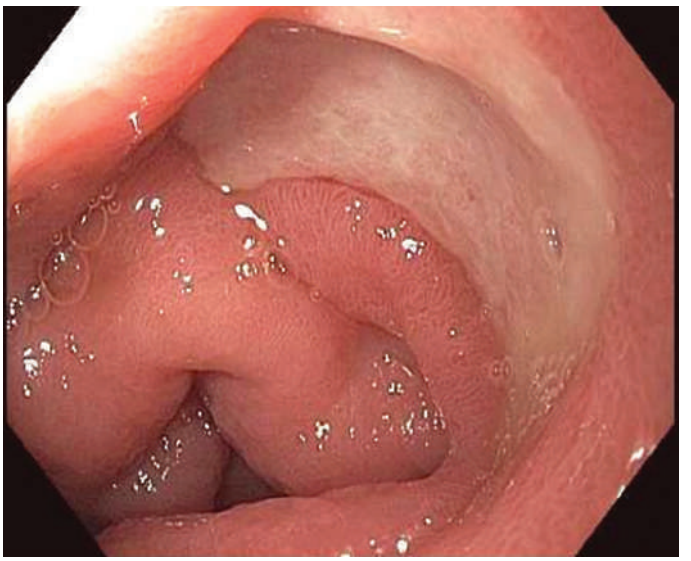
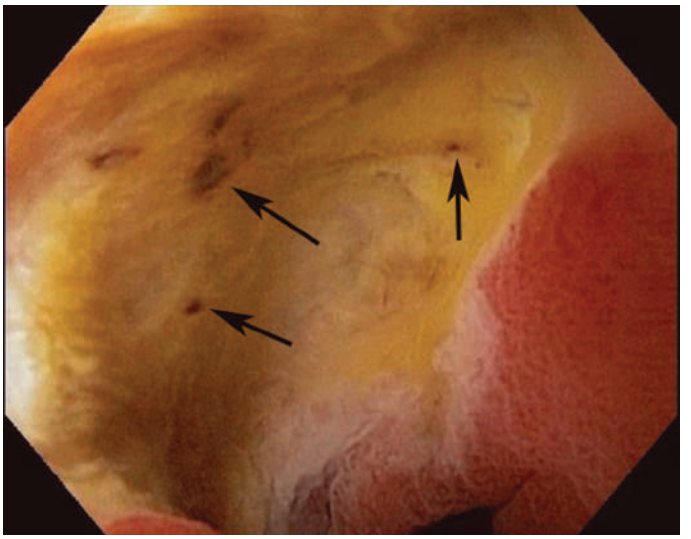


FIGURE 23-1 Gastric ulcer (benign) in the antrum. (Modified with permission from Song LMWK et al. Gastrointestinal endoscopy, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

  - The most important cause is NSAID use: up to ~50% of patients who chronically ingest NSAIDs may have gastric erosions
  - Other causes include alcohol intake, *H. pylori* infection, and stress-related mucosal injury
- Esophageal rupture
  - Very sick patient with mediastinitis, subcutaneous air in the mediastinum (Hamman's crunch), fever, and leukocytosis
  - Does not present with GI bleed very often, but comparable to Mallory-Weiss tears



A

FIGURE 23-2 (A–D). Stigmata of hemorrhage in peptic ulcers. *A.* Duodenal ulcer with flat pigmented spots (*arrows*). ***B.*** Duodenal ulcer with a dense adherent clot. ***C.*** Duodenal ulcer with a pigmented protuberance/visible vessel (*arrow*). ***D.*** Duodenal ulcer with active spurting (*arrow*). (Used with permission from Song LMWK et al. Gastrointestinal endoscopy, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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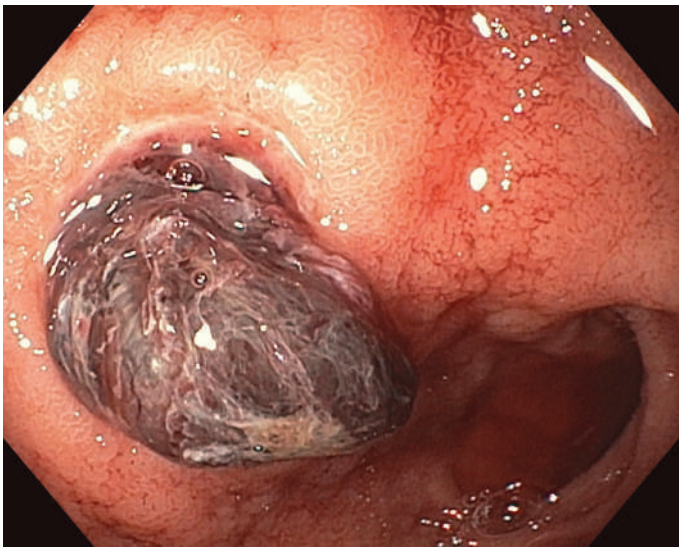
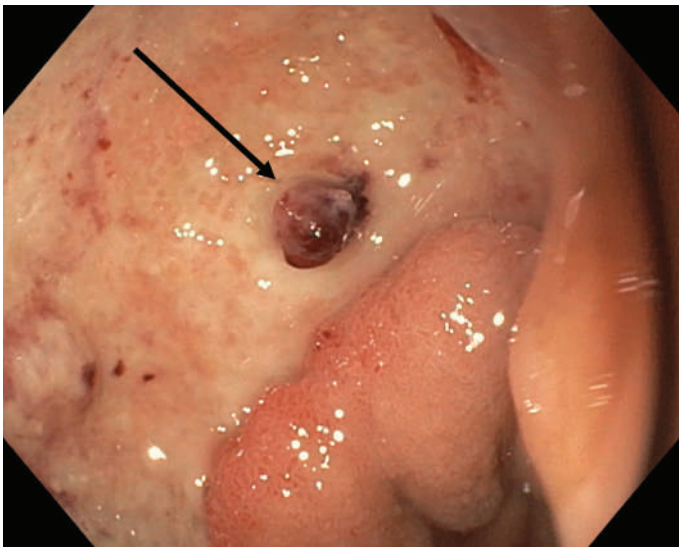


B



C

FIGURE 23-2 (*Continued*)

- Other causes of UGIB
  - Dieulafoy's lesion: an aberrant vessel in the mucosa that bleeds from a pinpoint mucosal defect; asymptomatic then painless bleeding
  - Neoplasms: esophageal and gastric carcinomas
  - Vascular ectasias: thin-walled vessels in the mucosal and submucosal layers of the GI tract that cause painless bleeding
  - Gastric antral vascular ectasia (GAVE; "watermelon stomach")
  - Prolapse gastropathy: prolapse of proximal stomach into esophagus with retching
  - Aortoenteric fistulas: usually have inflammatory bowel disease or prior abdominal aortic aneurysm repair (graft), where a fistula forms between the aorta and bowel causing brisk bleeding

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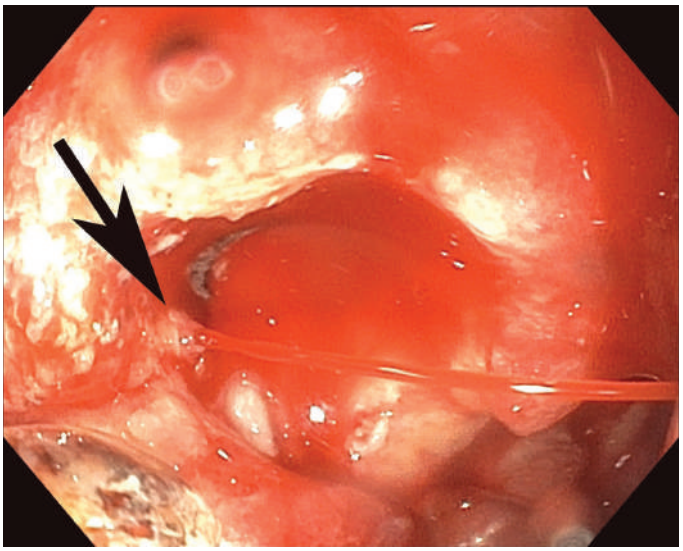

D

FIGURE 23-2 (*Continued*)

- Hemobilia
- Hemosuccus pancreaticus: bleeding from the bile duct or pancreatic duct
- Heyde's syndrome: upper GI arteriovenous malformations in someone with aortic stenosis

SMALL-INTESTINAL BLEEDING

- With improved diagnostics, ~75% of GIBs labeled as "obscure" are now estimated to originate in the small intestine beyond the extent of a standard upper endoscopic exam
- Small-intestinal GIB may account for ~5% of GIBs
- Etiologies
  - Vascular ectasias
  - Neoplasms: GI stromal tumor, carcinoid, adenocarcinoma, lymphoma, metastases
  - NSAID-induced erosions
  - Ulcers
  - Other less common causes of small-intestinal GIB: Crohn's disease, infection, ischemia, vasculitis, small-bowel varices, diverticula, intussusception, Dieulafoy's lesions, aortoenteric fistulas, and duplication cysts

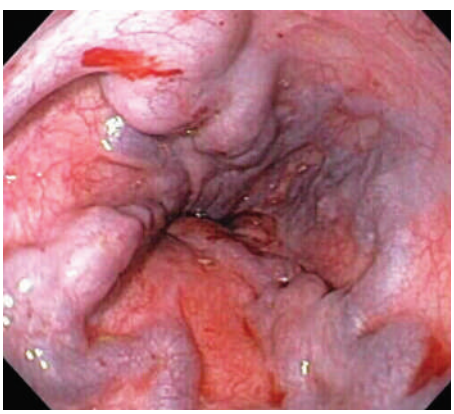

FIGURE 23-3 Esophageal varices. (Used with permission from Song LMWK et al. Gastrointestinal endoscopy, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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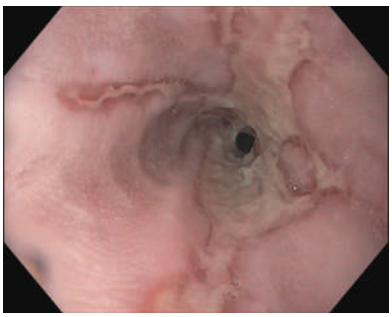

FIGURE 23-4 Severe reflux esophagitis with mucosal ulceration and friability. (Used with permission from Song LMWK et al. Gastrointestinal endoscopy, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

LOWER GI BLEED

- Hemorrhoids and anal fissures
  - Hemorrhoids are probably the most common cause of lower GIB (LGIB)
  - Rarely requires hospitalization
- Diverticular disease
  - Most common cause of LGIB requiring hospitalization
  - Diverticulosis is associated with painless bleeding, occurring abruptly, sometimes massive in quantity, and often from the right colon
    - Chronic or occult bleeding is not common
  - Spontaneously stops in ≥ 90% of cases
  - Diverticulitis is painful but does not bleed as often
- Colonic vascular ectasias
  - May be overt or occult, but tends to be chronic and only occasionally hemodynamically significant
  - Usually stops spontaneously
- Neoplasms
  - Weight loss, anemia (iron deficiency), and changes to stool caliber; fecal occult blood testing positive
  - A lower GI source of bleeding in a patient > 40 is colon cancer until proven otherwise
  - Primarily adenocarcinomas
- Colitis
  - Bloody diarrhea, fever, and leukocytosis are common
  - Can be from infections, ischemia, Crohn's disease, ulcerative colitis, NSAID-induced colitis, or ulcers
- Ischemic colitis
  - Peripheral vascular disease, CAD, stroke history, AF, post–abdominal aortic aneurysm repair, with bloody bowel movements and pain out of proportion to exam
  - Acute mesenteric ischemia: severe, acute, nonremitting abdominal pain that is strikingly out of proportion to the physical findings
    - Can be embolic or thrombotic in nature, and the mortality rate is > 50%
  - Chronic mesenteric ischemia: insidious symptoms with recurrent episodes of acute, dull, crampy, postprandial epigastric pain, fear of eating resulting in weight loss, and chronic diarrhea that causes malnourishment
- Postpolypectomy bleeding
- Radiation proctopathy
- Other rare causes
  - Solitary rectal ulcer syndrome
  - Rectal varices
  - Lymphoid nodular hyperplasia
  - Vasculitis
  - Trauma
  - Aortocolic fistulas

DIAGNOSTIC TESTS

LABS

- CBC

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    - Hemoglobin does not fall immediately with acute GI bleed (GIB) due to proportionate reductions in plasma and red cell volumes ("people bleed whole blood")
    - Thus, hemoglobin may be normal or only minimally decreased at initial presentation of a severe bleeding episode
        - As extravascular fluid enters the vascular space to restore volume (via RAAS activation), the hemoglobin falls, but this process may take up to 72 h
    - Check a CBC q2–4h at first, then space out if stable
        - Helps you determine how brisk the bleeding is
- Type and screen on admission
    - In case the patient needs an urgent transfusion now or in the future
- CMP
    - Evaluate liver function tests for cirrhosis signs (INR, SCr, sodium, albumin, bilirubin) and electrolyte imbalances that may need fixing
    - BUN:SCr ratio
        - Ratio > 36 classically occurs in upper GIB (UGIB) due to volume depletion and blood proteins absorbed in the small intestine
        - In the absence of renal disease, a high BUN suggests GI bleeding
- Iron studies
    - Iron-deficiency anemia in patients with occult GI bleed suggests colon cancer
- PT/PTT/INR
    - Helps to determine if they are properly or overly anticoagulated (if on warfarin or other anticoagulation), and can help to identify if cirrhosis may be present or decompensated
    - May identify a new or existing bleeding diathesis
- Lactic acid
    - Can be severely elevated in acute mesenteric ischemia
    - Elevated in any GIB source that causes hemorrhagic shock
- *H. pylori* testing (rapid urease, histology, culture, serology, or stool antigen testing)
    - Common cause of peptic ulcer disease, and an infection for which antibiotics can help cure the underlying etiology
- Fecal occult blood testing
    - Positive test only means bleeding is present; does not say if it is an upper or lower GIB
    - However, this test is studied only for colon cancer screening and should not be performed to assess for acute GIB (it is often performed by emergency room providers, however, for the assessment of GIB)

IMAGING

- Duplex ultrasound or CT angiography of mesenteric vessels if suspicious for mesenteric ischemia

PROCEDURES

- Nasogastric tube with lavage (not performed often)
    - Fresh blood → active UGIB
    - Coffee grounds → recent UGIB
    - Non-bloody bile → lower source, but does not exclude active UGIB
    - Also helps you quantify how much bleeding there is
- EGD
    - Performed within 24 h for UGIB
    - May be first step for a lower GIB (LGIB) that is hemodynamically unstable
    - May be diagnostic and therapeutic
- Colonoscopy
    - Primarily for LGIB
    - May be a second step if no source is found on EGD
    - May be diagnostic and therapeutic
- Diagnostic tests to pursue based on bleeding site
    - Hematemesis: an upper endoscopy is the initial test
    - Hematochezia
        - First rule out an anorectal cause (e.g., hemorrhoids)
        - Colonoscopy should then be the initial test unless hemodynamically unstable
    - Melena
        - Upper endoscopy is usually the initial test because the most likely bleeding site is in the upper GI tract
        - Perform a colonoscopy if no bleeding site is identified from the endoscopy

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- Occult blood
  - Colonoscopy is the initial test in most cases (colon cancer is the main concern)
  - Perform an upper endoscopy if no bleeding site is identified from the colonoscopy

DIFFERENTIATING UGIB FROM LGIB

- Hematemesis indicates UGIB
- Melena indicates blood has remained in the GI tract for ≥ 14 h and as long as 3–5 days; the more proximal the bleeding site, the more likely melena will occur (and therefore, melena is most often an UGIB)
- Hematochezia usually represents LGIB
  - Exception is a source of UGIB that may bleed so briskly that blood transits the bowel before melena develops; these patients present with hemodynamic instability and dropping hemoglobin
- Small bowel bleeds may present as melena or hematochezia
- Elevated BUN:SCr ratio > 36 classically occurs in UGIB due to volume depletion and blood proteins absorbed in the small intestine
- Nasogastric (NG) tube aspirate is not commonly performed now, as a nonbloody NG aspirate may be seen in ~15% of patients with UGIB who present with clinically serious hematochezia

MANAGEMENT

WHEN TO ADMIT TO THE HOSPITAL

The Glasgow-Blatchford score (GBS) helps determine the risk of rebleeding and death for patients presenting with an upper GI bleed (UGIB) (Table 23-1). Patients with a score of 0–1 can be discharged home, as their risk of needing transfusion, requiring hemostatic intervention, or death is ~1%. Patients at high risk for rebleeding and death include those with

- Hemodynamic compromise (tachycardia or hypotension)
- Older age
- A GBS score > 1
- Medical comorbidities

For a lower GI bleed (LGIB), the Oakland scoring system can help identify patients with a low-risk LGIB for safe discharge from the ED (scores ≤ 8 have a 95% probability of safe discharge). Patients with an Oakland score > 8 usually require admission for further workup and management due to the higher risk. Clinical judgment should guide both scoring systems.

TABLE 23-1 Glasgow-Blatchford Score

RISK FACTORS AT ADMISSION	SCORE
BUN (mg/dL)	
18.2 to < 22.4	2
22.4 to < 28.0	3
28.0 to < 70.0	4
≥ 70.0	6
Hemoglobin (g/dL)	
12.0 to < 13.0 (men); 10.0 to < 12.0 (women)	1
10.0 to < 12.0 (men)	3
< 10.0	6
Systolic BP (mm Hg)	
100–109	1
90–99	2
< 90	3
Heart rate (beats per minute)	
≥ 100	1
Melena	1
Syncope	2
Hepatic disease	2
HF	2

Modified with permission from Laine L. Gastrointestinal bleeding, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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WHAT LEVEL OF CARE TO ADMIT THE PATIENT TO

- ICU
  - Positive orthostatic vital signs in clinically apparent GIB
  - Frankly hypotensive or the presence of shock
  - Ongoing obvious hemorrhage requiring multiple transfusions urgently
  - Patients with cirrhosis with bleeding esophageal varices who require acute resuscitation (mortality rate is high in these patients)
- Medical floor
  - Patients with UGIB and a Glasgow-Blatchford score ≥ 1 without the above criteria
  - Patients with LGIB who are hemodynamically stable

BASIC PRINCIPLES OF THE MANAGEMENT OF EVERY GI BLEED

- At least two large-bore IVs (18-gauge or larger)
- IV fluid boluses (at least 2 L of LR or NS)
- Oxygen supplementation if oxygen saturations are < 90%
- Nothing by mouth
- Type and cross, and transfuse as needed (using a restrictive transfusion strategy [Hb > 7 g/dL])
  - Among patients with acute upper GI bleeding (UGIB), a restrictive transfusion strategy (Hb ≥ 7 g/dL) was associated with reduced mortality at 45 days compared with a liberal transfusion threshold (Hb ≥ 10 g/dL) [1]
    - These trials excluded major GIB, so if a patient has a major hemodynamically unstable bleed with ongoing hemorrhage, a liberal transfusion is warranted until stabilization
- IV proton pump inhibitor (PPI) twice daily or continuous infusion *(unless clearly a lower GIB)*
  - There is a 70% reduction in rebleeding with IV omeprazole in patients with active UGIB [2]
  - Pre-endoscopic PPI therapy modestly decreases the need for endoscopic therapy due to a reduction in high-risk ulcer stigmata but does not improve clinical outcomes such as further bleeding or death
  - Several randomized controlled trials document that high-dose PPIs given to reduce intragastric acid, thereby enhancing clot stability, decrease further bleeding and mortality in patients with high-risk ulcers (active bleeding, nonbleeding visible vessels, adherent clots) when given after endoscopic therapy
  - A systematic review and meta-analysis compared intermittent PPI therapy to an IV bolus plus continuous infusion for patients with bleeding ulcers and high-risk endoscopic findings. Noninferiority of IV intermittent dosing was seen compared with IV bolus and continuous infusion for 3 days.
- GI consultation for consideration of either EGD or colonoscopy, depending on clinical history and exam

MANAGEMENT OF UGIB

- IV PPI twice daily
- Consult GI
- If performing endoscopy, erythromycin, 250 mg IV ~30–90 min prior to the procedure helps with visualization
  - Ordered by GI consultant prior to endoscopy; reduces the need for repeat endoscopy and hospital stay
- *Patients with cirrhosis with UGIB should also receive*
  - Ceftriaxone
    - Dose: IV 2 g/d for 5–7 days
    - Among cirrhotic patients with UGIB, ceftriaxone reduces the rate of bacterial infections, rebleeding and number of transfusions needed, and mortality [3]
  - Octreotide
    - Dose: 50 μg IV × 1, then 50 μg/h IV infusion × 2–5 days
    - Vasoactive medications improve control of bleeding in the first 12 h after presentation [4]
- Upper endoscopy (**Tables 23-2** through **23-5**)
  - Findings on upper endoscopy dictate
    - Risk of rebleeding
    - What endoscopic and medical therapies should be employed
    - What diet should be ordered post-endoscopy
    - What level of care is needed post-endoscopy
    - Estimated hospital length of stay
  - EGD should be performed within 24 h in most patients with UGIB
    - In patients with acute UGIB who were at high risk for further bleeding or death, endoscopy performed within 6 h after GI consultation was not associated with lower 30-day mortality than endoscopy performed between 6 and 24 h after consultation
      - Some observational trials even suggest increased mortality in high-risk patients when endoscopy is performed within 6–12 h of presentation

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TABLE 23-2 Endoscopic Features and Management of Ulcers

Endoscopic features	Active bleeding or visible vessel	Adherent clot	Flat pigmented spot	Clean base
Endoscopic therapy	Yes	Consider	No	No
Medical therapy	High-dose PPI therapy[a]	High-dose PPI therapy[a]	Once-daily PPI therapy	Once-daily PPI therapy
Diet[b]	Clear liquids ~2 days	Clear liquids ~2 days	Clear liquids ~1 day	Regular diet
Hospital stay[c]	3 days	3 days	~1–2 days	Discharge after endoscopy

[a]IV bolus (80 mg) followed by infusion (8 mg/h) or by intermittent oral or intravenous doses (e.g., 40 mg 2–4 times per day) for 3 days.
[b]Diet after endoscopy, assuming no nausea or vomiting.
[c]Duration after endoscopy assuming patient stable without further bleeding or concurrent medical conditions requiring hospitalization.
PPI, proton pump inhibitor.
Data from Laine L. Gastrointestinal bleeding, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- Early endoscopy within 6–12 h of presentation may be indicated in low-risk patients (e.g., hemodynamically stable without severe comorbidities) to identify low-risk lesions (e.g., clean-based ulcers, erosions, nonbleeding Mallory-Weiss tears) that allow discharge in ≥ 40% of patients, reducing hospital stay and costs

MANAGEMENT OF PEPTIC ULCER DISEASE (~50% OF UGIB) (TABLE 23-2)

- Proton pump inhibitor (PPI) therapy
  - High-dose IV PPI on presentation
  - Then either continuing high-dose IV PPI twice daily post-endoscopy or transitioning to oral standard-dose PPI depending on ulcer type
- EGD + endoscopic therapy
  - With bipolar electrocoagulation, heater probe, injection therapy, clips, and/or topical hemostatic powder (for high-risk lesions)
  - 20% of patients with bleeding ulcers have the highest-risk findings of active bleeding or a nonbleeding visible vessel (determined by the Forrest classification)
    - These patients need continued high-dose IV PPI twice-daily therapy and
    - Several days of monitoring in the ICU and/or medical floor prior to discharge with oral PPI therapy
- Biopsies of ulcers to test for *H. pylori* and malignancy
  - Eradicate *H. pylori* if present
- Clean-based ulcers have nearly a 0% rate of serious rebleeding
  - These patients can be discharged home post-endoscopy with oral PPI therapy if no other reason for hospitalization
- NSAIDs should be avoided
  - If NSAIDs must be given, a cyclooxygenase 2–selective NSAID (celecoxib) plus a PPI is recommended
- Aspirin
  - Patients with established cardiovascular disease who develop bleeding ulcers while taking low-dose aspirin for *secondary* prevention should not discontinue aspirin, but, if aspirin is held, it should be restarted once hemostasis is confirmed

TABLE 23-3 Endoscopic Features and Management of Esophageal Varices

Endoscopic therapy	Endoscopic ligation
Medical therapy	Vasoactive drug (e.g., octreotide[a]) + antibiotic (e.g., ceftriaxone)
Diet[b]	Clear liquids ~2 days
Hospital stay[c]	~3–5 days

[a]IV 50-µg bolus followed by 50-µg/h infusion for 2–5 days.
[b]Diet after endoscopy, assuming no nausea or vomiting.
[c]Duration after endoscopy assuming patient stable without further bleeding or concurrent medical conditions requiring hospitalization.
Data from Laine L. Gastrointestinal bleeding, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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TABLE 23-4 Endoscopic Features and Management of a Mallory-Weiss Tear

Endoscopic features	Active bleeding	No active bleeding
Endoscopic therapy	Yes	No
Medical therapy	Antiemetic if ongoing nausea	Antiemetic if ongoing nausea
Diet[a]	Clear liquids ~1 day	Regular diet
Hospital stay[b]	~1–2 days	Discharge after endoscopy

[a]Diet after endoscopy, assuming no nausea or vomiting.
[b]Duration after endoscopy assuming patient stable without further bleeding or concurrent medical conditions requiring hospitalization.
Modified with permission from Laine L. Gastrointestinal bleeding, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

        - Immediate reinstitution of aspirin was associated with a lower 8-week mortality (1.3% vs 12.9%) compared with not restarting aspirin
    - In contrast, aspirin should be stopped in patients taking aspirin for *primary* prevention of cardiovascular disease who develop an UGIB; restart aspirin once bleed has stabilized

MANAGEMENT OF ESOPHAGEAL VARICES (TABLE 23-3)

- Fluid resuscitation
- IV PPI twice daily
- Avoid overtransfusion in patients with esophageal varices
    - Increased variceal pressure from transfusions may cause worsened bleeding
- Ceftriaxone
    - Dose: IV 2 g/d for 5–7 days
    - Among cirrhotic patients with UGIB, ceftriaxone reduces the rate of bacterial infections, rebleeding, number of transfusions needed, and mortality [3]
- Vasoactive medications
    - Octreotide, 50 μg IV × 1, then 50 μg/h IV infusion × 2–5 days
    - Splanchnic vasoconstrictor shunts blood away from esophageal varices, reducing variceal pressure
    - Improves control of bleeding in the first 12 h after presentation [4]
- Combination of endoscopic and medical therapy is superior to either therapy alone in decreasing rebleeding
    - Endoscopic ligation and banding of varices
    - Nonselective β-blockers
        - Start on day 5 after initial bleeding episode if hemostasis has been achieved—e.g., carvedilol, 3.125 mg bid; nadolol, 20 mg once daily; propranolol, 20 mg bid
        - Carvedilol is becoming the non-selective β-blocker of choice for esophageal varices
            - Has additional anti–α_1-adrenergic vasodilating properties
            - More effectively lowers portal pressure
            - Does not require heart rate goals
            - Emerging data suggest it can prevent hepatic decompensation and improve survival
        - If taking a nonselective β-blocker on presentation, stop the medication on admission until the bleeding is controlled, then restart
- Transjugular intrahepatic portosystemic shunt (TIPS)
    - Recommended in patients who have persistent or recurrent bleeding despite endoscopic and medical therapy

TABLE 23-5 Endoscopic Features and Management of Erosions

Endoscopic therapy	No
Medical therapy	Once-daily PPI therapy
Diet[a]	Regular diet
Hospital stay[b]	Discharge after endoscopy

[a]Diet after endoscopy, assuming no nausea or vomiting.
[b]Duration after endoscopy assuming patient stable without further bleeding or concurrent medical conditions requiring hospitalization.
PPI, proton pump inhibitor.
Data from Laine L. Gastrointestinal bleeding, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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- Also suggested for acute variceal bleeding in patients with advanced liver disease
  - Child-Pugh class B with score 8–9 and active bleeding at endoscopy or
  - Child-Pugh class C with score 10–13
- In these patients with cirrhosis who were hospitalized for acute variceal bleeding and at high-risk for treatment failure, the early use of TIPS was associated with significant reductions in treatment failure and in mortality [5]
- Patient selection for TIPS is critical with the following *absolute* contraindications
  - HF
  - Severe tricuspid regurgitation or pulmonary hypertension
  - Polycystic liver disease
  - Active systemic infection
- *Relative* contraindications to TIPS include
  - Hepatic tumors
  - Hepatic vein obstruction
  - Hepatic encephalopathy
  - Significant thrombocytopenia
- Encephalopathy occurs in as many as 20% of patients after TIPS and is particularly problematic in older patients and in patients with preexisting encephalopathy

MANAGEMENT OF MALLORY-WEISS TEARS (TABLE 23-4)

- Bleeding usually stops spontaneously
- Protracted bleeding may respond to
  - Endoscopic local epinephrine or cauterization therapy
  - Endoscopic clipping
  - Angiographic embolization
- Surgery is rarely necessary

MANAGEMENT OF GASTRIC, SMALL, AND LARGE INTESTINE VARICES, AND PORTAL HYPERTENSIVE GASTROPATHY

- Caused by portal hypertension
- Treated with endoscopic injection of tissue adhesives (e.g., *n*-butyl cyanoacrylate), transhepatic intrajugular portosystemic shunt, or retrograde transvenous obliteration

MANAGEMENT OF EROSIVE GASTRITIS (TABLE 23-5)

- Medications
  - Omeprazole, 20 mg by mouth daily for 4–8 weeks
  - Avoid NSAIDs, alcohol, and glucocorticoids
- Treatment of *H. pylori*
  - Current regimens consist of a PPI and two or three antimicrobial agents given for 10–14 days
  - First-line recommended regimens for most of the world include
    - Omeprazole, bismuth subsalicylate, tetracycline, and metronidazole
    - Omeprazole, amoxicillin, clarithromycin, and tinidazole, or
    - Omeprazole, amoxicillin, and levofloxacin
  - Optimal regimens vary in different parts of the world, depending on known rates of primary antibiotic resistance in most *H. pylori* strains in a particular locale

MANAGEMENT OF ESOPHAGEAL RUPTURE

- Provide broad-spectrum antibiotics and IV PPI therapy
- GI and surgery consult for possible EGD versus surgery
- Esophageal rupture can be a life-threatening condition

MANAGEMENT OF LGIB

- If you are initially unsure if the bleeding is from an upper or lower GIB
  - If the patient has cirrhosis, administer an octreotide infusion and ceftriaxone as above
  - IV PPI twice daily
  - Continue these therapies until endoscopy is performed
  - If not a UGIB source, can discontinue these medications
- The initial strategy of endoscopic therapy or imaging depends on the clinical context (Fig. 23-5)
  - If hemodynamically stable → prepare with colonoscopy using oral lavage solution (polyethylene glycol 4 L solution until stools are clear; may need to add more if stools not clear)

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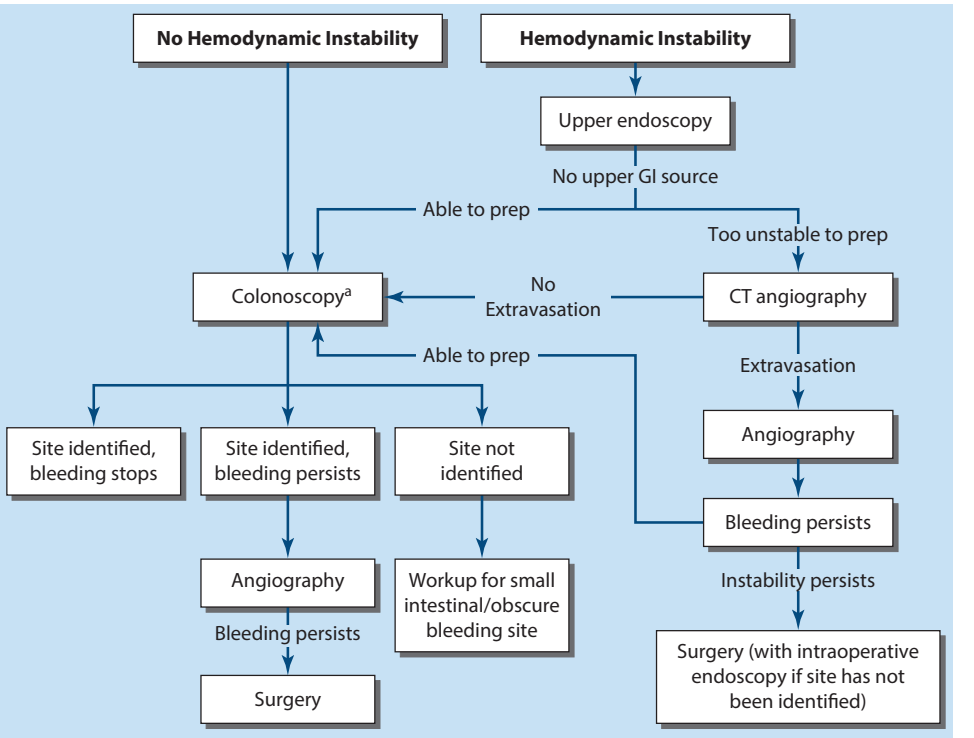

FIGURE 23-5 Suggested algorithm for patients with acute lower GI bleeding (hematochezia). [a]For patients < 35 years old with minor bleeding (e.g., blood on toilet paper), normal BP and heart rate, normal hemoglobin and iron panel, and no family history of colorectal cancer, some would suggest flexible sigmoidoscopy is adequate. (Modified with permission from Laine L. Gastrointestinal bleeding, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- If hemodynamically unstable → upper endoscopy
  - Administer colon prep for colonoscopy if no bleeding source is identified on upper endoscopy
    - Perform CT angiography if too unstable to prep for colonoscopy
  - If a bleeding site is identified on colonoscopy but bleeding persists, perform CT angiography to identify the bleeding vessel for possible embolization therapy
  - If the bleeding site is not identified, evaluate for small intestinal/obscure bleeding
- If the bleeding site is identified but bleeding persists despite therapies, consult surgery for surgical intervention

MANAGEMENT OF DIVERTICULAR DISEASE (MOST COMMON CAUSE OF LGIB)

- Spontaneously stops in ≥ 90% of cases
- Endoscopic therapy
  - Case series suggest endoscopic therapy may decrease recurrent bleeding in the uncommon case when colonoscopy identifies the specific bleeding diverticulum
  - Effective methods to prevent rebleeding or need for emergent surgery include
    - Colonoscopic ligation with banding
    - Placement of a detachable snare
    - Over-the-scope hemoclips
- Transcatheter arterial embolization by superselective technique
- Prevents further bleeding in most patients when diverticular bleeding is found at angiography
  - With coil embolization, the rate of colonic ischemia is < 10%, and the risk of acute rebleeding is < 25%
- Segmental surgical resection
  - Recommended if
    - Bleeding is refractory to angiographic or endoscopic treatments

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    - The patient is hemodynamically unstable, or
    - The patient has required large-volume transfusion
- Dietary fiber should be increased with fruits, vegetables, and supplementary fiber

MANAGEMENT OF COLONIC VASCULAR ECTASIAS

- Bleeding usually stops spontaneously
- Endoscopic hemostatic therapy may be used
- Transcatheter arterial embolization also may be attempted for persistent bleeding from vascular ectasias
- Surgical therapy is required for major persistent or recurrent bleeding

MANAGEMENT OF NEOPLASMS

- Cancer-directed therapies
- Surgical resection when indicated

MANAGEMENT OF ISCHEMIC COLITIS

- Acute mesenteric ischemia
    - Arterial embolus: anticoagulation, broad-spectrum antibiotics, and early laparotomy or embolectomy
    - Arterial thrombosis: anticoagulation, broad-spectrum antibiotics, resuscitation, and endovascular, endarterectomy, thrombectomy, or bypass surgery
- Chronic mesenteric ischemia: endovascular, open surgical, or hybrid revascularization in addition to aggressive risk factor modification

POSTPOLYPECTOMY BLEEDING

- For persistent bleeding from postpolypectomy bleeding the following may be attempted
    - Endoscopic hemostatic therapy or
    - Transcatheter arterial embolization

MANAGEMENT OF SMALL-INTESTINAL BLEEDS

- PPI IV twice daily
- Consult GI for EGD, push enteroscopy, or video capsule study
- Small-intestinal vascular ectasias
    - Endoscopic therapy
    - Rebleeding is common
        - Administration of thalidomide showed reductions in bleeding episodes, transfusions, and hospitalizations
    - Monthly intramuscular injections of octreotide long-acting release also are recommended
- For other isolated lesions, such as tumors, surgical resection is generally required

COMPLICATIONS

- Recurrent bleeding and hospitalizations
- Decompensation of chronic medical comorbidities
- Transfusion-related reactions
- Volume overload from transfusions
- Gastric MALT lymphoma and gastric cancer from *H. pylori* infection
- Death

PROGNOSIS

- During hospitalizations, the case fatality rate is ~2% for GI bleed
- Patients generally die from decompensation of other underlying illnesses rather than exsanguination
- Patients with variceal bleeds have poorer outcomes than patients with other sources of UGIBs
- The risk of rebleeding depends on the etiology but is highest in esophageal varices, high-risk ulcers, and acute mesenteric ischemia

PATHOPHYSIOLOGY

Selected disease pathophysiology processes:

■ ULCERS

- Breaks in the mucosal surface > 5 mm in size, with depth to the submucosa
- Average basal and nocturnal gastric acid secretion is increased in duodenal ulcers, and the bicarbonate secretion is decreased

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- Gastric acid output is normal or decreased in gastric ulcers
  - Impairment of mucosal defense factors may be present in the presence of decreased acid secretion
- *H. pylori* and acid peptic disorders
  - A gram-negative, microaerophilic rod living in gastric mucus; adapts to the acidic environment
  - Colonization and survival
    - Starts in the antrum, may spread proximally
    - Can form a dormant coccoid state under stress
  - Virulence factors
    - Hop proteins, urease, VacA toxin, and cag-PAI enable colonization and injury
    - cag-PAI injects CagA → alters cell signaling, increasing cytokines
    - Urease is converted to ammonia, which neutralizes acid but damages cells
    - Proteases, phospholipases, adhesins, and other enzymes weaken mucosal defense
  - Pathogenesis
    - Causes epithelial apoptosis, inflammation, and immune activation (neutrophils, lymphocytes, cytokines: interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor α, interferon γ)
    - Can inhibit parietal cell acid secretion
  - Clinical outcomes
    - Infection nearly always causes chronic active gastritis
    - Only 10–15% develop peptic ulcers
    - Disease outcome (gastritis, peptic ulcer disease, MALT lymphoma, gastric cancer) depends on host and bacterial factors and *H. pylori* strain virulence

ESOPHAGEAL VARICES

- Develops over time from portal hypertension
- When clinically significant portal hypertension develops (defined as a hepatic venous pressure gradient ≥ 10 mm Hg), there is a substantial risk of decompensation with variceal bleeding
- Increased venous pressures from the portal venous system cause esophageal veins to dilate and weaken over time, leading to increased risk of rupture and bleeding

DIVERTICULOSIS

- Diverticula occur at the point where the nutrient artery, or vasa recta, penetrates through the muscularis propria, resulting in a break in the integrity of the colonic wall
- Diverticula are most commonly encountered in the sigmoid colon
  - This anatomic restriction may be a result of the relatively high-pressure zone within the muscular sigmoid colon
- Higher-amplitude contractions combined with constipated, high-fat-content stool within the sigmoid lumen in an area of weakness in the colonic wall result in the creation of these diverticula
- Consequently, the vasa recta is compressed or eroded, leading to either perforation or bleeding

RISK FACTORS

- Antiplatelets, anticoagulants, NSAIDs, and steroids
- Alcohol
- *H. pylori* infection
- Hepatitis B/C
- Low-fiber diet
- Stress ulcers from critical illness in the ICU
- COPD
- CKD
- Tobacco use
- CAD
- Diabetes
- Cancer
- Older age

ADMITTING ORDERS

- Admit to
  - ICU for upper GI bleed (UGIB) or lower GI bleed (LGIB) with active hemorrhage requiring multiple transfusions, hemodynamic instability, and/or positive orthostatic vital signs
  - Otherwise admit to the general medical floor

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- Diagnosis: UGIB or LGIB
- Condition
  - UGIB: guarded
  - LGIB: stable/guarded
- Vital signs
  - UGIB: per ICU/floor routine, call for heart rate > 100 beats/min, systolic BP < 100 mm Hg
  - LGIB: q2h × 2, then q4h if stable; call for heart rate > 100 beats/min, systolic BP < 100 mm Hg
- Activity
  - UGIB: bedrest, advance as tolerated
  - LGIB: as desired with fall precautions
- Nursing
  - Maintain two 18-gauge or larger IVs at all times
  - Strict inputs and outputs
  - DVT prophylaxis with sequential compression devices
  - Administer oxygen if O_2 saturation < 90%
- Diet
  - UGIB: nothing by mouth
  - LGIB: clear liquids then nothing by mouth overnight with bowel prep (if pursuing colonoscopy)
- Fluids
  - UGIB: LR or NS bolus 2 L
  - LGIB: LR or NS bolus as needed for hemodynamic changes
- Diagnostic tests
  - CBC q4h, then space out if stabilizing
  - CMP
  - Iron studies
  - PT/PTT/INR
  - Lactic acid
  - Type and screen blood products
- Medications
  - UGIB
    - Pantoprazole, 40 mg IV bid
    - Avoid NSAIDs
    - Continue aspirin if taking for secondary prevention of cardiovascular disease and not hemodynamically unstable
      - Stop aspirin if hemodynamically unstable or taking for primary prevention of cardiovascular disease
    - If varices or cirrhosis
      - Octreotide, 50-μg bolus, then 50-μg/h infusion
      - Ceftriaxone, 2 g/day
      - Discontinue their home β-blocker until bleeding is controlled, then restart
    - Erythromycin, 250 mg IV ~30–90 min before endoscopy (ordered by GI prior to EGD)
  - LGIB
    - GoLytely prep for colonoscopy

DISCHARGE INFORMATION

- With no evidence or rebleeding for 48–72 h for high-risk lesions
- Education on proton pump inhibitor therapy (if prescribed)
- Avoid NSAIDs, alcohol, and steroids if possible
- Increase dietary fiber for diverticular disease
- Education about the risk of rebleeding based on the identified lesion found on endoscopy
- Aggressive treatment of modifiable risk factors

CASE ANSWERS

1. All patients presenting with significant GI bleed (GIB) require adequate IV access. This includes at least two large-bore IVs (18- gauge or higher). Large-bore IVs allow multiple fluids and medications to be administered simultaneously and quickly for patients with hemodynamically unstable GIBs.

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2. In this patient presenting with hematemesis and a history of cirrhosis, it should be assumed until proven otherwise that the bleeding is from esophageal varices. While this patient's bleeding is life-threatening, the hemoglobin of 9.4 g/dL is well above a restrictive transfusion threshold (≤ 7 g/dL). In this scenario, administering a transfusion could increase the esophageal variceal pressure and cause more bleeding. If the patient were having active hemorrhage, transfusion would be indicated regardless of the hemoglobin level.
3. All patients with an upper GIB require IV proton pump inhibitor therapy. In patients with cirrhosis and concern for bleeding esophageal varices, IV antibiotics (e.g., ceftriaxone) and vasoactive medications (e.g., octreotide) also should be administered.

LANDMARK TRIALS

[1] Villanueva C et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 368:11, 2013. [PMID: 23281973]
- *Summary:* Among patients with acute upper GI bleeding (GIB), a restrictive transfusion threshold (Hb ≥ 7) was associated with reduced mortality at 45 days compared with a liberal transfusion threshold (Hb ≥ 10).

[2] Lau JY et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 343:310, 2000. [PMID: 10922420]
- *Summary:* In patients with bleeding peptic ulcers and signs of recent bleeding, treatment with omeprazole decreases the rate of further bleeding and the need for surgery.

[3] Fernández J et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage trial. Gastroenterology 131:1049, 2006. [PMID: 17030175]
- *Summary:* Among patients with cirrhosis with GIB, ceftriaxone reduces the rate of bacterial infection by 67% but does not confer an increased survival benefit compared with norfloxacin. Norfloxacin prevents bacterial infection in patients with cirrhosis with GI hemorrhage.

[4] Corley DA et al. Octreotide for acute esophageal variceal bleeding: A meta-analysis. Gastroenterology 120:946, 2001. [PMID: 11231948]
- *Summary:* The results suggest that octreotide is more effective than vasopressin or terlipressin in the control of esophageal variceal bleeding, and that it is a safe and effective adjuvant therapy after variceal obliteration techniques.

[5] García-Pagán JC et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 362:2370, 2010. [PMID: 20573925]
- *Summary:* In patients with cirrhosis who were hospitalized for acute variceal bleeding and at high risk for treatment failure, the early use of transjugular intrahepatic portosystemic shunt was associated with significant reductions in treatment failure and in mortality.

FURTHER READING

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24 Cirrhosis & Its Complications

KEY POINTS

1. Cirrhosis is a condition characterized by fibrosis and architectural distortion of the liver, resulting in a decrease in liver function and hepatic blood flow.
2. Clinical presentation of cirrhosis varies depending on the severity of the disease. Symptoms may include fatigue, right upper quadrant pain, jaundice, and peripheral edema. Decompensated cirrhosis may present with hematemesis, melena, abdominal swelling (ascites), peripheral edema, and encephalopathy. Physical exam may reveal hepatomegaly, splenomegaly, palmar erythema, spider angiomas, caput medusae, and ascites.
3. Diagnosis of cirrhosis involves a thorough evaluation of the patient's medical history, physical exam, and lab tests. Imaging tests such as ultrasound and CT scan can help confirm the diagnosis. Liver biopsy may be performed to assess the severity of fibrosis. In patients with decompensated cirrhosis, broad infectious cultures (blood, urine, sputum), CBC, CMP, coagulation studies, CXR, and a paracentesis (when ascites is present) are indicated.
4. Management of compensated cirrhosis focuses on treating underlying causes and prevention of complications. Treatment may include lifestyle modifications (e.g., alcohol abstinence), medications to control symptoms and complications, and, in severe cases, liver transplantation. Esophageal variceal bleeding should be managed with fluid resuscitation, octreotide, antibiotics, and endoscopic management. Spontaneous bacterial peritonitis is managed with antibiotics and albumin. Hepatic encephalopathy management includes treatment of the underlying cause, lactulose, and rifaximin. Hepatorenal syndrome, after an albumin challenge, is managed with terlipressin and continuation of albumin (alternatives to terlipressin including norepinephrine, midodrine, and octreotide).
5. The prognosis of cirrhosis depends on the cause and extent of liver damage. Without treatment, patients with decompensated cirrhosis have a poor prognosis, but the prognosis can be improved with appropriate management. Variceal hemorrhage has a 20–30% mortality rate with each episode. Patients with ascites have a < 50% survival rate after 2 years once ascites develops. Spontaneous bacterial peritonitis has a 25% in-hospital mortality.

EPIDEMIOLOGY & DEFINITIONS

Cirrhosis is a condition that is defined histopathologically (progressive fibrosis with distortion of the hepatic architecture and the formation of regenerative nodules) and has a variety of clinical manifestations and complications, some of which can be life-threatening. Previously, cirrhosis was thought to be irreversible; however, it is now apparent that when the underlying insult causing the cirrhosis is removed, there can be reversal of fibrosis.

A patient labeled with *decompensated* cirrhosis has developed ascites, hepatic encephalopathy, or variceal bleeding; these patients should be referred for liver transplant, especially if the decompensation is poorly controlled.

According to the Centers for Disease Control and Prevention (CDC), cirrhosis accounted for ~ 52,600 deaths and was the eighth leading cause of death in the United States in 2023. In addition, there were an estimated 12,700 deaths due to liver cancer, which often occurs in the setting of cirrhosis. Mortality rates related to cirrhosis have been rising and are estimated at 21.7 per 100,000 individuals in the United States. There was an increase in the prevalence of cirrhosis in 2017 compared with 1990 in both men and women, with 5.2 million cases of cirrhosis and chronic liver disease occurring in 2017. Disability-adjusted life-years due to cirrhosis ranked sixteenth among all diseases and seventh in people aged 50–74 years in 2019.

There are many complications of cirrhosis (Table 24-1). This chapter will focus on the complications that patients are more commonly hospitalized for and are, therefore, more life-threatening.

CLINICAL VIGNETTE

A 40-year-old woman presents to the ED with fatigue, fullness in her stomach, weight gain, leg swelling, and her skin turning yellow. She has gained 4.5 kg in the past month, and friends said her skin was yellow starting 2 weeks ago. She has mild shortness of breath for which she states it feels like she cannot take a full deep breath in due to her abdominal swelling, and the dyspnea worsens with sitting upright. Occasionally, her friends have told her she seems confused. She denies any fevers or chills, headache, dysphagia, hemoptysis/hematemesis, cough, chest pain, diarrhea, melena, or dysuria. Her mother has a chronic liver disease of which she doesn't know the etiology, and her father died of pancreatic

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TABLE 24-1 Complications of Cirrhosis

Portal hypertension
Gastroesophageal varices
Portal hypertensive gastropathy
Splenomegaly, hypersplenism
Ascites
SBP
AKI-HRS
CKD-HRS
Hepatic encephalopathy
Hepatopulmonary syndrome
Portopulmonary hypertension
Malnutrition
Coagulopathy
Factor deficiency
Fibrinolysis
Thrombocytopenia
Bone disease
Osteopenia
Osteoporosis
Osteomalacia
Hematologic abnormalities
Anemia
Hemolysis
Thrombocytopenia
Neutropenia

HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis. Reproduced with permission from Befeler AS, Bacon BR. Cirrhosis and its complications, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

cancer 5 years ago. She reports a 20-pack-year smoking history, alcohol use (8 beers daily for 15 years), and injection drug use intermittently over the past 10 years. She takes no medications.

On physical exam, she is afebrile, with a heart rate of 98 beats/min, respiratory rate of 20 breaths/min, BP of 106/61 mm Hg, and oxygen saturation of 95% on room air. She is in no acute distress and has mild pallor with scleral and subungual icterus. She becomes more dyspneic with sitting upright but is not hypoxemic. There are decreased breath sounds at the bases of her lungs. Her abdomen is markedly distended with a positive fluid wave, and she has 2+ pitting edema to her knees bilaterally. Spider angiomas are present on her chest. Asterixis is present, and she is disoriented to the date and year. A digital rectal exam reveals small internal hemorrhoids but does not show melena or hematochezia.

A CXR shows bilateral small pleural effusions. Her lab data are as follows:

- Hemoglobin: 9.4 g/dL
- Platelets: 75,000 cells/μL
- Mean corpuscular volume: 98 fL
- WBC count: 6500 cells/μL
- Total bilirubin: 6.0 mg/dL
- Sodium: 128 mEq/L
- Potassium: 3.2 mEq/L
- SCr: 1.4 mg/dL
- Albumin: 2.4 g/dL
- INR: 2.4

GUIDING QUESTIONS

1. What is on your differential for the etiology of this patient's cirrhosis?
2. Does she have compensated or decompensated cirrhosis?

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3. What other diagnostic tests would you order?
4. Would you perform any procedures, and if so, what tests would you order from the procedure?
5. Are there any medications you would order?

HISTORY

When someone presents to the hospital with decompensated cirrhosis, causes of decompensation should be investigated:

1. Infection
2. Bleeding (e.g., bleeding esophageal varices, caput medusa, hemorrhoids)
3. Fluid status (e.g., ascites and hyper- or hypovolemia)
4. Medication nonadherence

Figure 24-1 depicts the clinical effects of cirrhosis.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/*s*ymptoms—or use your preferred mnemonic)
  - Depends on the clinical scenario; patients can come in with acute infection, hyper- or hypovolemia, encephalopathy, GI bleeding, or a combination of several conditions

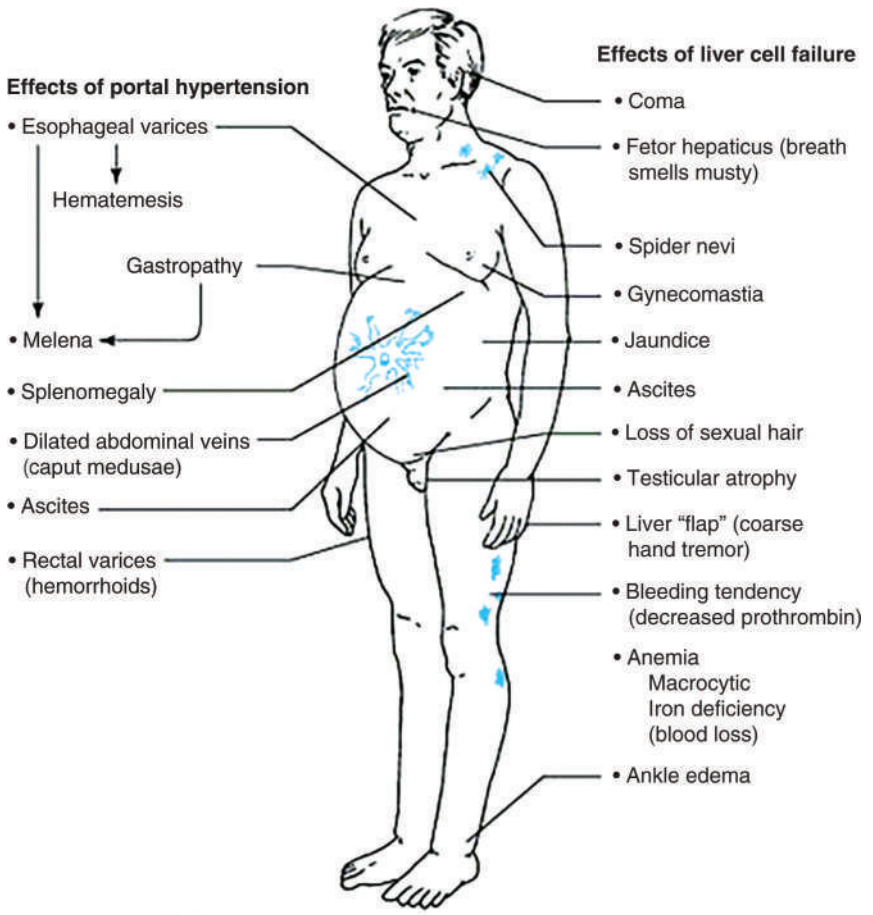

FIGURE 24-1 Clinical effects of cirrhosis. (Reproduced with permission from Chandrasoma P, Taylor CE. *Concise Pathology*, 3rd ed. Appleton & Lange: The McGraw-Hill Companies, Inc; 1998.)

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- Fever or chills?
  - Spontaneous bacterial peritonitis (SBP) can be life-threatening, and any infection can cause decompensation
- Abdominal swelling or pain?
  - Ascites and SBP are possible
  - Paracentesis may need to be performed
- Edema?
  - Patients with cirrhosis are prone to edema from hypoalbuminemia
  - Medication nonadherence, portal vein thrombosis, decompensation from other complications, and any other cause of edema need to be considered
- Anorexia?
  - Ascites with gut edema may present with symptoms of early satiety and anorexia
- Change in mental status?
  - Hepatic encephalopathy or infections that can cause encephalopathy should be considered
- Nausea and vomiting? Blood in vomit?
  - Varices or any cause of upper GI bleeding, and whether they can tolerate oral medications
- Melena? Hematochezia?
  - Variceal bleeding and peptic ulcer disease can present as melena (variceal bleeds, if active, present as hematemesis)
  - Hemorrhoidal bleeding from portal hypertension can present with hematochezia
- Dyspnea?
  - Hepatic hydrothorax, hepatopulmonary syndrome (platypnea and orthodeoxia), and other causes of dyspnea should be considered
- Dark urine?
  - Cholestasis causes the body to excrete refluxed conjugated bilirubin into the urine, leading to dark urine
  - Evaluate for liver or biliary disease and/or hemolytic anemia
- Light stools?
  - No bilirubin reaches the GI tract (due to reflux into the bloodstream from cholestasis); therefore, urobilinogen causes decreased stercobilin and light stool
- Itching?
  - Bile acids deposit in the skin and cause pruritus
  - However, levels of bilirubin in the bloodstream and the severity of pruritus do not appear to be highly correlated
- Fatigue?
  - Common symptom of cirrhosis; can be an early sign of hepatic encephalopathy
- Diarrhea?
  - From cholestasis and cirrhosis or medications (e.g., lactulose)
- Jaundice?
  - Buildup of bilirubin in the bloodstream; usually around 2–3 mg/dL is when jaundice appears (first appearance is under the tongue)

PAST MEDICAL HISTORY

- History of cirrhosis?
  - When was it diagnosed?
  - How severe is it (do they know their compensated Model for End-Stage Liver Disease [MELD] score)?
  - How is it being treated?
- History of chronic hepatitis B or C?
  - Common causes of cirrhosis
- History of HF?
  - Right HF can cause hepatomegaly and liver injury; it can mimic cirrhosis with ascites, peripheral edema, and abdominal pain, and/or eventually lead to cardiac cirrhosis
- History of Wilson's disease?
  - An uncommon cause of cirrhosis
- History of hemochromatosis?
  - How and when was it diagnosed?
  - How is it being treated?
- History of α_1-antitrypsin deficiency?
  - Cause of cirrhosis

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SURGICAL HISTORY

- Have they had a transjugular intrahepatic portosystemic shunt (TIPS)?
  - Hepatic encephalopathy is common side effect

SOCIAL HISTORY

- Long-term heavy alcohol use
  - Men: 5 or more drinks on any day or 15 or more drinks per week
  - Women: 4 or more drinks on any day or 8 or more drinks per week
- Smoking
- Use of recreational drugs (injection drugs; risks of hepatitis B and C)
- Occupation
- Living situation
- Sexual history
- Recent travel? Different types of infections can cause cirrhosis; see Etiology

FAMILY HISTORY

- Wilson's disease?
- Hemochromatosis?
- α_1-Antitrypsin deficiency?
- Cystic fibrosis?

MEDICATIONS

- Adherence to furosemide and spironolactone, nonselective β-blocker, lactulose and/or rifaximin, and any other medications

PHYSICAL EXAM

Knowing the physical exam findings in cirrhosis can help you make the clinical diagnosis of cirrhosis in a patient without a known diagnosis or can help you determine if the patient has decompensated cirrhosis. There are exam findings that are important to look for in every patient with cirrhosis, as these findings may point to decompensation that needs immediate medical attention.

Likelihood ratios for individual positive or negative findings on physical exam can be clinically useful in determining whether cirrhosis exists. When a finding can be either positive or negative, then the likelihood ratios are called the *positive likelihood ratio* (PLR) or the *negative likelihood ratio* (NLR). A finding that has a PLR > 1 indicates that the positive finding is associated with the presence of cirrhosis; a finding that has an NLR of < 1 indicates that the finding is associated with the absence of cirrhosis. The further either ratio is from 1, the more likely cirrhosis is either present or absent. For example, a PLR of 3 = 20% probability patient has condition, a PLR of 4 = 25% probability patient has condition, a PLR of 5 = 30% probability patient has condition, and a PLR of 10 = 45% probability patient has condition.

- Vital signs
  - Tachycardia can be present for many reasons in decompensated cirrhosis
  - Baseline low BP and increased pulse pressure are common in patients with late stage cirrhosis
  - Fever can be a sign of spontaneous bacterial peritonitis (SBP) or other infections
  - Orthodeoxia in patients with dyspnea and hypoxemia
    - Defined as either decrease in arterial oxygen tension (by > 4 mm Hg) or arterial oxyhemoglobin desaturation (variably defined as a change of > 3% or 5%) when patient moves from a supine to an upright position, then improved by returning to the recumbent position
    - Sign of hepatopulmonary syndrome
- HEENT
  - Blood in the mouth
    - Can be a sign of bleeding esophageal varices
  - Subungual and scleral icterus
    - Findings of jaundice and possible decompensated cirrhosis
  - Parotid gland swelling
    - Usually occurs in alcohol-associated liver disease
    - There is an increase in flow rate, protein, and amylase levels causing hypertrophy of the parotids
  - Fetor hepaticus
    - Breath smells musty
    - Cause: portal hypertension; portosystemic shunting allows thiols (dimethyl sulfide) to pass directly into the lungs (ketones and ammonia involved, too)
  - Kayser-Fleischer rings: copper deposits in the cornea seen in Wilson's disease

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- Respiratory
  - Dullness to percussion in the bases (primarily right side) may indicate hepatic hydrothorax
- Cardiac
  - The Cruveilhier-Baumgarten murmur is a venous hum heard in the epigastric region due to collateral connections forming between the portal system and the periumbilical veins as a result of portal hypertension
- Abdominal
  - Palpate the liver edge (firm liver edge PLR 3.3)
    - The liver is large in early stages of cirrhosis, then small, firm, and nodular in late stages
  - Ascites (PLR 6.6)
    - Fluid wave and bulging flanks (PLR 5.0)
    - Sign of portal hypertension
  - Abdominal pain on palpation may be present (or absent) with SBP
  - Palpate the spleen for splenomegaly
    - Sign of portal hypertension
  - Digital rectal exam
    - To assess for hemorrhoids and to rule out GI bleeding
- Skin, extremity, and musculoskeletal
  - Palmar erythema (PLR 4.2; **Fig. 24-2**)
    - Reddening of the palms at the hypothenar and thenar eminences
    - Caused by increased estrogen and nitric oxide
  - Spider angiomata (PLR 4.6; **Fig. 24-3**)
    - Dilated blood vessels and their corresponding capillaries result from increased estrogen
  - Caput medusa (head of Medusa) (PLR 9.5)
    - Dilated periumbilical collateral veins due to portal hypertension
    - Blood from the portal venous system may be shunted through the periumbilical veins and ultimately to the abdominal wall veins
  - Decreased body hair (PLR 8.8), gynecomastia (PLR 7), and testicular atrophy
    - From increased estrogen
  - Bilateral pitting lower extremity edema
    - When from cirrhosis, is caused by hypoalbuminemia
    - If present, the PLR of also having ascites is 3.8
  - Jaundice (PLR 3.8)
    - Due to hyperbilirubinemia
  - Terry's nails (PLR 10.7)
    - Proximal two-thirds of the nail plate appears white, whereas the distal third is red
  - Muehrcke's nails
    - Paired horizontal white bands separated by normal color



FIGURE 24-2 Palmar erythema. This figure shows palmar erythema in a patient with alcohol-associated cirrhosis. The erythema is peripheral over the palm with central pallor. (Used with permission from Befeler AS, Bacon BR. Cirrhosis and its complications, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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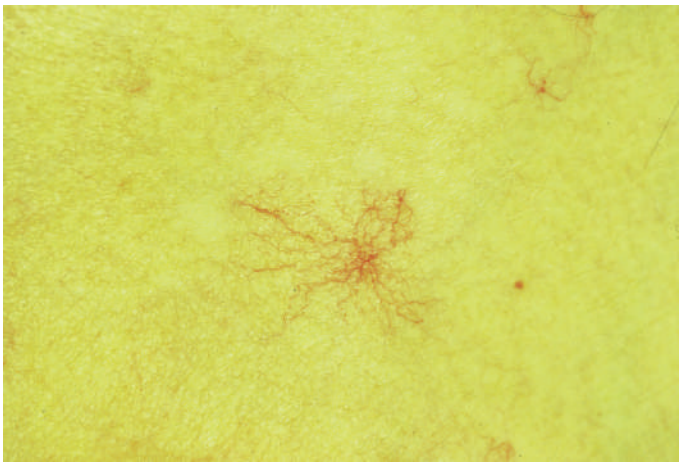

FIGURE 24-3 Spider angioma. This figure shows a spider angioma in a patient with hepatitis C cirrhosis. With release of central compression, the arteriole fills from the center and spreads out peripherally. (Used with permission from Befeler AS, Bacon BR. Cirrhosis and its complications, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Clubbing and cyanosis
        - Helpful findings to diagnose hepatopulmonary syndrome
    - Dupuytren's contractures
        - Thickening of the palm's fascia, forming cords that pull the fingers inward, making them hard to straighten
- Neurologic
    - Mental status exam
        - Assesses for hepatic encephalopathy (PLR 8.8)
    - Asterixis
        - Sign of hepatic encephalopathy
        - Five stages of hepatic encephalopathy based on severity of symptoms
            - 0: No noticeable or minimal symptoms
            - 1: Mild symptoms such as sleep disturbances, mild confusion, and mood changes
            - 2: Disorientation, inappropriate behavior, drowsiness, trouble with basic tasks like math
            - 3: Severe confusion and sleepiness, but still responsive to sleepiness
            - 4: Coma, with no response to stimuli
        - Asterixis is usually present in stages 2 and 3 and is not present in the most severe stage (4) in which the patient is unconscious
        - If asterixis is not present, it does *not* mean that they do not have hepatic encephalopathy
        - Uremia, hypercapnia, and gabapentin toxicity can also cause asterixis
- *Findings to always evaluate for on physical exam*
    - Oral exam for blood in mouth
    - Abdominal exam for ascites, fluid wave, and peritoneal signs
    - Asterixis and mental status exam for hepatic encephalopathy
    - Presence of caput medusa, which signifies severe portal hypertension and possibly bleeding
    - Digital rectal exam to rule out bleeding

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS OF SPECIFIC SIGNS & SYMPTOMS IN CIRRHOSIS

- Edema and ascites
    - HF
        - Peripheral edema, orthopnea, paroxysmal nocturnal dyspnea, cardiac disease history, JVD, high serum-ascites albumin gradient (SAAG) on paracentesis; ascitic protein level is ≥ 2.5 g/dL
    - Nephrotic syndrome
        - Peripheral edema, no liver disease history, hematuria, abnormal UA with proteinuria

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    - Myxedema
        - Will have edema, but will have other features of hypothyroidism (fatigue, obesity, hair thinning, bradycardia, cold intolerance, constipation, delayed relaxation of tendon reflexes, abnormal TSH)
    - Pancreatitis
        - Typical epigastric pain that radiates to the back, alcohol binges, jaundice, nausea and vomiting, elevated lipase
    - Abdominal masses
        - Can cause abdominal swelling
    - See the Diagnostic Tests section for interpretation of the SAAG for a further differential of ascites
- Hepatomegaly
    - Hepatitis
        - Fever, nausea and vomiting with elevated liver function tests (primarily AST/ALT)
    - Hepatocellular carcinoma or liver metastases
        - Weight loss, risk factors for cancer, possibly long-standing undiagnosed cirrhosis, and masses seen on CT
    - Right HF
        - JVD with a positive hepatojugular reflex, peripheral edema, nocturia, and ascites
- Encephalopathy
    - Uremia
        - Nausea and anorexia, fibrinous pericarditis, friction rub, asterixis, encephalopathy, bleeding or bruising (from platelet dysfunction), increased bleeding time only (not from an increased PT/INR as in cirrhosis)
    - Thiamine deficiency
        - Confusion, ophthalmoplegia, ataxia, confabulation, memory loss (i.e., Wernicke-Korsakoff syndrome)
- Upper GI bleeding
    - Peptic ulcer disease
        - Gnawing epigastric pain; possible NSAID, alcohol, or steroid use
    - Mallory-Weiss tear
        - Vomiting before hematemesis, usually after an alcohol binge
    - See **Chap. 23** for additional differential diagnoses of UGIB
- Noncirrhotic causes of portal hypertension
    - Categorized into prehepatic, hepatic, and posthepatic causes
        - Prehepatic: portal vein thrombosis, splenic vein thrombosis, massive splenomegaly (Banti's syndrome)
            - Portal vein thrombosis most often associated with cirrhosis but may be idiopathic or can occur in association with infection, pancreatitis, abdominal trauma, or can be associated with coagulation disorders (polycythemia vera; essential thrombocytosis; protein C, protein S, antithrombin III, factor V Leiden deficiencies; or abnormal prothrombin gene regulating production)
        - Hepatic: categorized into presinusoidal, sinusoidal, and postsinusoidal
            - Presinusoidal: schistosomiasis and congenital hepatic fibrosis
            - Sinusoidal: cirrhosis (overwhelmingly the most common cause of portal hypertension) and alcohol-associated hepatitis
            - Postsinusoidal: hepatic sinusoidal obstruction (veno-occlusive syndrome)
        - Posthepatic: Budd-Chiari syndrome, inferior vena cava caval webs, cardiac causes (restrictive cardiomyopathy, constrictive pericarditis, and severe HF)

ETIOLOGY

- The most common etiologies of cirrhosis are
    - Alcohol-associated liver disease
    - Chronic hepatitis B or C infection
    - Metabolic dysfunction–associated steatohepatitis (MASH)
- **Table 24-2** lists all the etiologies of cirrhosis

DIAGNOSTIC TESTS

LABS

- Broad cultures: perform unless an obvious noninfectious cause of the decompensated cirrhosis is present
    - Blood cultures × 2
    - UA with culture
    - Sputum culture with Gram stain

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TABLE 24-2 Etiologies of Cirrhosis
Alcohol-associated liver disease
Chronic viral hepatitis
Hepatitis B
Hepatitis C
Autoimmune hepatitis
Metabolic dysfunction–associated steatohepatitis (MASH)
Biliary cirrhosis
Primary biliary cholangitis
Primary sclerosing cholangitis
Autoimmune cholangiopathy
Cardiac cirrhosis
Inherited metabolic liver disease
Hemochromatosis
Wilson's disease
α_1-Antitrypsin deficiency
Cystic fibrosis
Cryptogenic cirrhosis

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- CBC
  - Common findings of cirrhosis on CBC include
    - Macrocytic anemia
    - Thrombocytopenia (isolated thrombocytopenia is a common early finding in cirrhosis)
    - Leukopenia
    - Neutropenia
  - Evaluate for leukocytosis for possible spontaneous bacterial peritonitis (SBP) or other infections
- CMP
  - Electrolytes
  - Liver function tests
  - CMP studies help calculate the Model for End-Stage Liver Disease (MELD) score
  - BUN and SCr
    - Increase in SCr can be a sign of acute decompensation, as well as concern for hepatorenal syndrome (HRS)
    - Increase in the BUN:SCr ratio > 36 can indicate an upper GI bleed is present
- PT/PTT/INR
  - Elevated PT and INR are poor prognostic signs of cirrhosis, as all factors except for factor VIII are produced in the liver
- Albumin (included in CMP)
  - Hypoalbuminemia is present because albumin production is decreased in liver dysfunction
  - Used to calculate the serum-ascites albumin gradient (SAAG) when performing a paracentesis
- Ammonia
  - Typically elevated in hepatic encephalopathy, but the correlation between severity of liver disease and height of ammonia levels is often poor
  - Most hepatologists do not rely on ammonia levels to make a diagnosis or follow clinical progress
- Hepatitis panels
  - Hepatitis A IgM/IgG
    - Evaluates for acute or resolved hepatitis A infection
  - HBsAg
    - Detectable during acute infection
    - Persistence after 6 months indicates chronic infection
  - HBeAg
    - Appears after HBsAg during acute infection
    - A marker of viral replication activity
    - Detectable in chronic infections with high infectivity

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    - Anti-HBc IgM
        - Present during acute infection and window phase when both HBsAg and anti-HBs are absent
    - Anti-HBc IgG
        - Detectable along with anti-HBs and anti-Hbe after recovery from acute infection
        - Present without anti-HBs in chronic infection; not present after vaccination (only anti-HBs seen)
    - Anti-HBe
        - Present after recovery from acute infection
        - HBeAg/anti-HBe seroconversion indicates the transition of chronic infection from high to low viral replication and infectivity
    - Anti-HBs
        - Appearance indicates resolution of acute infection and confers long-term immunity
    - Hepatitis C RNA
        - To evaluate whether hepatitis C is present
        - If Hep C RNA is positive, order a total viral load
- Iron studies if anemic
    - Evaluate for hemochromatosis as a possible cause of cirrhosis, or to evaluate what type of anemia is present
    - Hemochromatosis findings
        - Increased serum iron
        - Decreased total iron-binding capacity (TIBC)
        - Increased ferritin
        - Increased transferrin saturation percentage (serum iron/TIBC)
- UA and urine studies if concerned about hepatorenal syndrome (HRS)
    - The UA is bland in HRS
    - A FENa < 1% and UNa < 10 mEq/L are typical urine study findings in HRS
- Additional studies if the underlying cause of cirrhosis is unknown
    - Ceruloplasmin and 24-h urinary copper
        - Evaluates for Wilson's disease
        - Ceruloplasmin will be decreased, as it is synthesized in the liver
        - 24-h urinary copper will be increased
    - Antimitochondrial antibody (AMA)
        - Evaluates for primary biliary cholangitis
    - Anti–smooth muscle antibody
        - Evaluates for autoimmune hepatitis

PROCEDURES

- Paracentesis studies
    - Almost always need to perform a paracentesis on hospitalized patients with cirrhosis if ascites is present
    - Perform paracentesis if new-onset ascites, worsening ascites, or spontaneous bacterial peritonitis is suspected
    - Need the SAAG (Fig. 24-4) and ascitic protein level to help evaluate the cause of cirrhosis
    - Peritoneal fluid studies to always order
        - Ascitic albumin
        - Ascitic protein
        - Cell count and culture
    - Other peritoneal fluid studies to order are based on the clinical presentation
        - For example, order cytology if concerned about cancer as a cause of ascites
        - Order adenosine deaminase (ADA) if concerned about tuberculosis
        - Order amylase if concerned about pancreatitis
    - The SAAG is used to help classify/diagnose the cause of ascites
        - Ascites is due to cirrhosis causing portal hypertension > 95% of the time, but it should be confirmed the first time ascites occurs to rule out other causes
        - Figure 24-4 describes the SAAG and ascitic protein levels that narrow your differential
- Liver biopsy may be performed to
    - Assess the severity of fibrosis
    - Help determine the underlying etiology of the cirrhosis

IMAGING

- Abdominal ultrasound with Doppler study (of kidneys, too, if increased SCr)
    - Evaluates for
        - Hepatic steatosis

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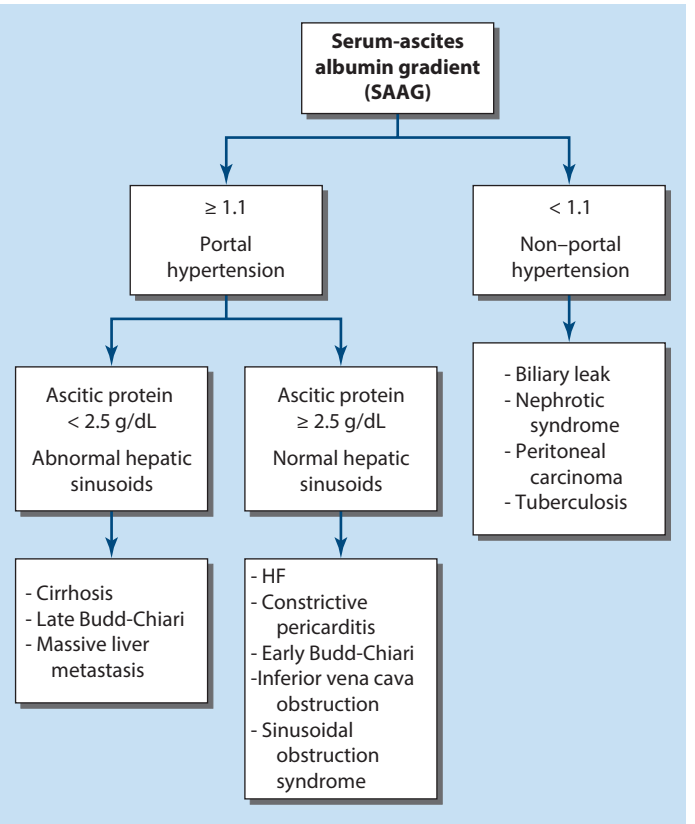

FIGURE 24-4 Serum-ascites albumin gradient interpretation in the workup of ascites. IVC, inferior vena cava. (*Source:* Original.)

    - Size of liver (e.g., a small nodular liver is seen in later stage cirrhosis)
    - Biliary tree anatomy
    - Presence of ascites
    - Portal vein thrombosis
- CXR
    - Evaluates for potential other causes of decompensation, such as
        - Pneumonia
        - Cardiomegaly and pulmonary edema
        - Pleural effusions
- Triple-phase abdominal CT scan if assessing for hepatocellular carcinoma
- Echocardiogram (possibly with agitated saline) if assessing for hepatopulmonary syndrome or portopulmonary syndrome

MANAGEMENT

This section focuses on complications of cirrhosis that require hospitalization. The treatment of specific etiologies of cirrhosis (see Etiology section) is not discussed in this chapter.

GENERAL MANAGEMENT OF CIRRHOSIS

- Sodium restricted diet (< 2 g/d), spironolactone, 50 mg PO daily (if ascites is present), and furosemide, 20 mg PO daily (if peripheral edema is present in addition to ascites); can uptitrate dose of spironolactone and furosemide
    - Generally, use a ratio of 5:2 for dose of spironolactone:furosemide to balance the serum potassium level
- Multivitamin
- Avoid opioids and anxiolytics

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- Lactulose and rifaximin if hepatic encephalopathy is present
- IV proton pump inhibitor, octreotide infusion, and ceftriaxone 2 g/day if bleeding esophageal varices present
- Treat the underlying cause of the decompensation
  - GI bleeding
  - Infections
  - Alcohol use disorder and withdrawal
  - Illicit drug use
  - Electrolyte abnormalities
  - Ascites and peripheral edema
  - Medication nonadherence
  - Overdiuresis
  - Poor oral intake and malnutrition causing hypovolemia
- In addition, always manage the underlying cause of cirrhosis

PORTAL HYPERTENSION

- Portal hypertension is defined as an increased hepatic venous pressure gradient > 5 mm Hg caused by
  - Increased resistance of blood flow through the liver due to cirrhosis and regenerative nodules
  - Increased splanchnic blood flow secondary to vasodilation within the splanchnic vascular bed
- Portal hypertension directly causes
  - Gastroesophageal varices with hemorrhage
  - Ascites with edema
  - Hypersplenism with thrombocytopenia and leukopenia
- Manage the underlying cause of portal hypertension (most below result from long-standing portal hypertension) and the complications from portal hypertension
  - Prehepatic causes (those affecting the portal venous system before it enters the liver)
    - Portal vein thrombosis
    - Splenic vein thrombosis
    - Massive splenomegaly (Banti's syndrome)
  - Hepatic causes (> 95% of cases)
    - Cirrhosis (most common cause)
    - Schistosomiasis
    - Congenital hepatic fibrosis
    - Alcohol-associated hepatitis
    - Sinusoidal obstruction syndrome
  - Posthepatic causes (those affecting the hepatic veins and venous drainage to the heart)
    - Budd-Chiari syndrome
    - Inferior vena cava webs
    - Cardiac causes (restrictive cardiomyopathy, constrictive pericarditis, severe right HF)
    - Metabolic dysfunction–associated steatohepatitis (MASH)
    - Autoimmune hepatitis (primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis)

VARICEAL HEMORRHAGE

- Blood backs up from portal hypertension into the gastric veins, causing esophageal veins to dilate, which can lead to tear and rupture (see **Fig. 23-3**)
- Has a 20–30% mortality rate associated with each bleeding episode (life-threatening)
- Varices will develop in most patients with cirrhosis over their lifetime
- The risk of bleeding from the varix depends on
  - The severity of cirrhosis (Model for End-Stage Liver Disease [MELD] score, Child-Pugh class)
  - Hepatic vein pressure (higher risk when > 12 mm Hg)
  - Size and location of varix
  - Presence of tense ascites
  - Certain endoscopic stigmata
    - Red wale signs
    - Hematocystic spots
    - Diffuse erythema
    - Bluish color
    - Cherry red spots
    - White-nipple spots

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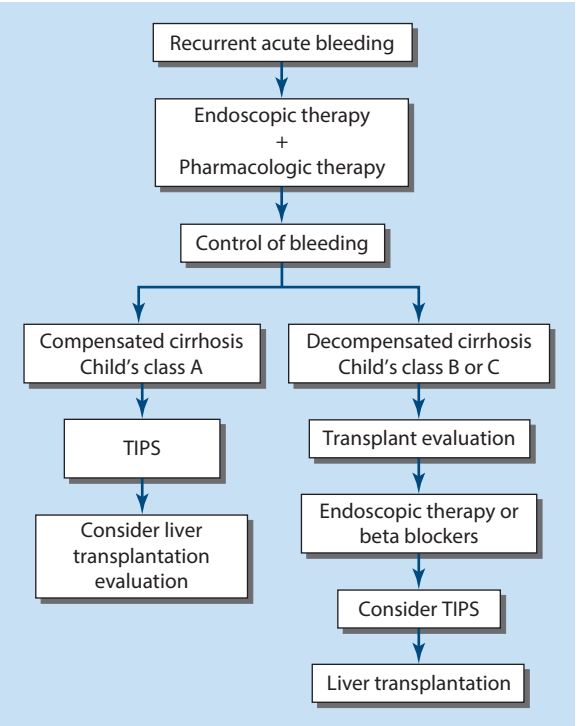

FIGURE 24-5 Management of recurrent variceal hemorrhage. This algorithm describes an approach to management of patients who have recurrent bleeding from esophageal varices. Initial therapy is generally with endoscopic therapy often supplemented by pharmacologic therapy. With control of bleeding, a decision needs to be made as to whether patients should go on to transjugular intrahepatic portosystemic shunt (TIPS; if they are Child-Pugh class A) or if they should have TIPS and be considered for transplant (if they are Child-Pugh class B or C). (Reproduced with permission from Befeler AS, Bacon BR. Cirrhosis and its complications, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Management of bleeding esophageal varices
  - IV fluid resuscitation (and two large-bore IVs)
  - NPO
  - Transfuse PRBCs for hemoglobin < 7 g/dL or sooner if ongoing active hemorrhage and unstable hemodynamics (avoid excessive transfusion as this can increase variceal pressure and worsen the bleed)
  - Correct an elevated INR with fresh frozen plasma only if there is evidence of coagulopathy (i.e., bleeding at other sites such as IV lines)
  - Hold patients' nonselective β-blocker if they are taking one at home
  - IV proton pump inhibitor bid in case the bleeding is not from varices but a gastric ulcer
  - IV antibiotics (ceftriaxone, 2 g/d for 5–7 days)
    - Among patients with cirrhosis and a GI bleed, ceftriaxone reduces the rate of bacterial infection by 67% but does not confer an increased survival benefit compared with norfloxacin [1]
  - Vasoactive medications (octreotide, 50 μg IV × 1, then 50 μg/h IV infusion × 2–5 days)
    - Octreotide is a splanchnic vasoconstrictor acting to shunt blood away from esophageal varices, reducing variceal pressure
    - Improves control of bleeding in the 12 h after presentation [2]
  - Consult gastroenterologist for endoscopic evaluation intervention
  - Balloon tamponade (Sengstaken-Blakemore tube or Minnesota tube) or placement of self-expandable metal stents
    - Used in patients who need stabilization prior to endoscopic therapy or as a bridge to transjugular intrahepatic portosystemic shunt (TIPS) after endoscopic failure
  - The combination of endoscopic and medical therapy is superior to either therapy alone in decreasing rebleeding
    - Gastroenterologist can perform endoscopic ligation and banding of varices

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- Nonselective β-blockers on day 5 after the initial bleeding episode if hemostasis has been achieved
  - For example: carvedilol 3.125 mg bid; nadolol 20 mg daily; propranolol 20 mg bid
  - Nonselective β-blockers have been shown to lower the risk of variceal hemorrhage over a 1- to 2-year follow-up, as well as decrease mortality related to variceal hemorrhage
  - Titrate to a resting heart rate of 55–60 beats/min, or to a hepatic venous pressure gradient < 12 mm Hg
    - Reduction of hepatic venous pressure gradient from β-blockers has been shown to decrease the risk of esophageal varices if they respond, but this would necessitate repeat measurement serially, which can be hard to manage
  - Carvedilol is becoming the nonselective β-blocker of choice
    - Given its additional anti–α_1-adrenergic vasodilating properties, it more effectively lowers portal pressure, lacks the need for heart rate goals, and has emerging data that suggest it can prevent hepatic decompensation and improve survival

- TIPS is recommended in patients who have persistent or recurrent bleeding despite endoscopic and medical therapy **(Fig. 24-5)**
  - TIPS is also suggested for acute variceal bleeding in patients with advanced liver disease (Child-Pugh class B with score 8–9 and active bleeding at endoscopy, Child-Pugh class C with score 10–13)
  - In patients with cirrhosis who are hospitalized for acute variceal bleeding and at high risk for treatment failure, the early use of TIPS was associated with significant reductions in treatment failure and in mortality
  - Patient selection for TIPS is critical with the following *absolute* contraindications
    - HF
    - Severe tricuspid regurgitation or pulmonary hypertension
    - Polycystic liver disease
    - Active systemic infection
  - *Relative* contraindications to TIPS include
    - Hepatic tumors
    - Hepatic vein obstruction
    - Hepatic encephalopathy
    - Significant thrombocytopenia
  - Hepatic encephalopathy occurs in as many as 20% of patients after TIPS and is particularly problematic in older patients and in patients with preexisting encephalopathy
- Liver transplantation may be indicated for patients with recurrent bleeding esophageal varices
- Screen for esophageal varices with endoscopy every 2 years in patients with cirrhosis

ASCITES

- Ascites is the accumulation of fluid in the peritoneal cavity
- The most common cause of ascites is portal hypertension from cirrhosis
- Symptoms
  - Increased abdominal girth
  - Peripheral edema
  - Insidious respiratory compromise causing dyspnea
  - Hepatic hydrothorax (if present, may contribute to respiratory symptoms)
  - Malnourishment with muscle wasting, excessive fatigue, and weakness
- Management
  - Perform a diagnostic paracentesis in patients with new ascites (see Procedures section)
    - Long-term prophylactic antibiotic therapy to prevent spontaneous bacterial peritonitis (SBP) in patients with ascites is indicated when
      - The ascitic fluid protein level is < 1.5 g/dL and is associated with one of the following
        - Impaired kidney function (SCr level > 1.2 mg/dL, BUN > 25 mg/dL)
        - Serum sodium level < 130 mEq/dL
        - Liver failure (Child-Pugh score > 9 and bilirubin level > 3 mg/dL)
      - A fluoroquinolone or trimethoprim-sulfamethoxazole is indicated if the above criteria are met
  - A low-sodium diet (< 2 g/d) can usually manage small amounts of ascites by itself
  - Avoid NSAIDs, ACE-Is, and aminoglycosides for increased risk of AKI when ascites is present
  - Diuretic therapy is recommended when moderate-sized ascites is present
    - Start spironolactone in patients with moderate ascites
    - If also have peripheral edema, add furosemide

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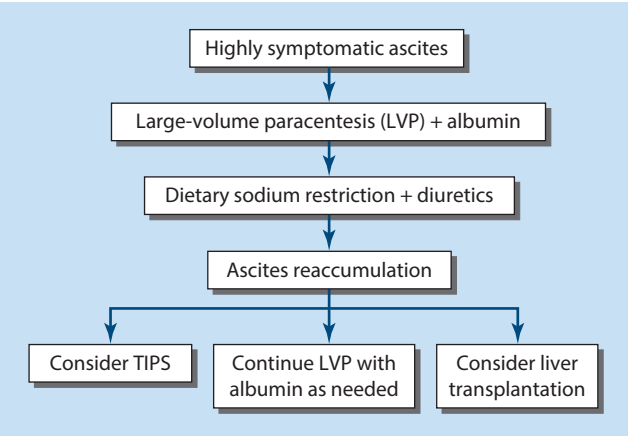

FIGURE 24-6 Treatment of refractory ascites. In patients who develop azotemia in the course of receiving diuretics in the management of their ascites, some will require repeated large-volume paracentesis (LVP), some may be considered for transjugular intrahepatic portosystemic shunt (TIPS), and some would be good candidates for liver transplantation. These decisions are all individualized. (Reproduced with permission from Befeler AS, Bacon BR. Cirrhosis and its complications, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Administer spironolactone:furosemide in a 5:2 ratio to maintain serum potassium balance
    - Failure of diuretics suggests nonadherence with a low-sodium diet
  - If patients still have ascites despite the above strategies, they are considered to have refractory ascites (Fig. 24-6)
    - Regular large-volume paracentesis, a transjugular intrahepatic portosystemic shunt (TIPS) procedure, and/or a liver transplant should be considered
    - If performing a large-volume paracentesis
      - Order 25% albumin, 6–8 g/L, if ≥ 5 L of peritoneal fluid is removed
        - For example, if 3 L are taken off, do not order albumin
        - If 6 L are taken off, administer 36–48 g of albumin
      - Albumin reduces morbidity and mortality among patients with tense ascites undergoing large-volume paracentesis compared with alternative treatments investigated thus far [3]
  - Patients with cirrhosis and ascites should be considered for liver transplantation

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- SBP is an infection of the ascitic fluid with a 25% in-hospital mortality rate
- It is usually caused by gut bacterial translocation into the intestinal wall and mesenteric lymph nodes, leading to bacteremia and seeding of the ascitic fluid
- Common symptoms (though some patients may present with none of these)
  - Fever
  - Altered mental status
  - Abdominal pain
  - Leukocytosis and AKI may be present
- *Escherichia coli* is the most common cause of SBP
- Other organisms include
  - *Streptococcus viridans*
  - *Staphylococcus aureus*
  - Enterococcal species
- Diagnosis
  - Made by paracentesis → an absolute neutrophil count > 250/μL confirms the diagnosis
  - Gram stain is usually negative
  - Culture is the most specific test, but need to start empirical antibiotics before the results of the culture are available
  - If ≥ 2 organisms are found on culture of the ascitic fluid, then consider perforated viscus and surgical consultation
- Management
  - Ceftriaxone, 2 g/d for 5 days

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- 25% albumin (1.5 g/kg body weight on day 1 and 1.0 g/kg on day 3)
  - Albumin reduces the risk of AKI and improves survival [4]
- If there is no improvement clinically, perform another paracentesis at 48 h to check if the neutrophil count has decreased
  - If it is not decreasing, then the infection is not under control
- Prophylactic antibiotics are indicated in patients who have had an episode of SBP and recovered to prevent recurrent SBP
  - Ciprofloxacin, 500 mg daily, or
  - Trimethoprim-sulfamethoxazole, one double-strength tablet daily

HEPATORENAL SYNDROME (HRS)

- HRS is a functional renal failure without renal pathology
- Splanchnic vasodilation occurs in cirrhosis from portal hypertension, causing arterial underfilling and increased vascular resistance (increase in local vasoconstrictors)
- Patients usually have large-volume ascites and a low mean arterial pressure when HRS is present
- HRS-AKI (previously HRS type I)
  - Rapid and more severe impairment, doubling of the creatinine in < 2 weeks
- HRS-CKD (previously HRS type II)
  - Less severe, with a more gradual increase in the creatinine, has better outcomes than HRS-AKI
- HRS-AKI requires exclusion of other causes of AKI, most notably volume depletion
  - HRS does *not* respond to fluid expansion
- Exclude other causes of AKI, including intrinsic (acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis) and obstructive kidney disease
  - FENa < 1% and UNa < 10 are typical urine study findings in HRS
- Stop diuretics when concerned about HRS
- Administer an albumin challenge (to see if the AKI improves with fluids, ruling out HRS)
  - Administer 25% albumin, 1 g/kg/d for 48 h
    - If kidney function improves after albumin, then the AKI was *not* from HRS
    - If kidney function does not improve, this further supports a diagnosis of HRS
- Management
  - Continue 25% albumin, 20–40 g daily (the optimal dose of albumin is unclear)
    - Use 40 g for most patients
    - Use 20 g if at risk for intravascular volume overload
  - Terlipressin, 0.85 mg q6h for 3 days; on day 4, adjust dose based on kidney function
    - Terlipressin plus albumin may prolong short-term survival in HRS-AKI
  - Low-dose norepinephrine
    - Administer if terlipressin is not available
  - Midodrine, 7.5–12.5 mg PO tid along with octreotide, 100–200 μg subcutaneously tid
    - A commonly used regimen but is considered third-line therapy
  - The best treatment for both HRS-AKI and HRS-CKD is liver transplantation
  - If treatment fails, renal replacement therapy can be initiated as a bridge to liver transplant

HEPATIC ENCEPHALOPATHY

- Changes in mental status and cognition in the setting of liver failure
- Gut-derived neurotoxins are not removed by the liver and travel to the brain, causing hepatic encephalopathy
- Ammonia levels are typically high, but the level does not correlate with the severity of liver disease, and most hepatologists do not rely on ammonia levels to make a diagnosis or follow clinical progress
- Less likely to develop brain edema and/or cerebral herniation compared to acute liver failure
- Symptoms range from comatose to a violent change in personality
- Occurs as a result of certain precipitants (hypokalemia, infection, electrolyte imbalances, GI bleeding, hypovolemia, or constipation)
  - These should be investigated and corrected in all patients with hepatic encephalopathy
- Asterixis: classic finding in hepatic encephalopathy
  - However, this is only found in grades 2 and 3 hepatic encephalopathy and does not occur in 0, 1, and 4
  - Therefore, one can have the worst stage of hepatic encephalopathy and not have asterixis
- Management
  - Correct electrolytes, fluids, and the precipitating event, and provide supportive therapy
  - If ascites is present, rule out spontaneous bacterial peritonitis (SBP) with a paracentesis and manage as appropriate

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- Lactulose, 30–45 mL PO tid or qid
  - Lactulose causes colonic acidification of $NH_3 \rightarrow NH_4^+$
  - This eliminates nitrogenous products in the feces
  - The goal of therapy is to correct altered mental status, *not* a certain number of bowel movements/day
  - Once mental status is improved, then titrate lactulose dose to a number of bowel movements per day to prevent encephalopathy
    - It varies per patient, but ~ 2–3 bowel movements/day meets most patients' needs
- Rifaximin, 550 mg bid (a poorly absorbed antibiotic)
  - Maintains remission of hepatic encephalopathy more effectively than placebo and decreases hospitalization rate with few side effects [5]
- Neomycin and metronidazole were previously used, but both have side effects
- Zinc supplementation is sometimes helpful and is relatively harmless
- A low-protein diet is no longer recommended
- In patients with recurrent symptoms despite treatment, closure of large portosystemic shunts can be helpful

- Often when patients have encephalopathy for the first time
  - The patient and/or their caregivers are unaware of what is transpiring
  - Once they have been through the experience, they can identify when this is developing in subsequent situations and can often self-medicate with lactulose to prevent the development or worsening of encephalopathy

ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

- ACLF is a recently recognized clinical syndrome that is characterized by acutely decompensating cirrhosis with associated failure of one or more organ systems, including
  - Liver
  - Kidneys
  - Brain
  - Lungs
  - Circulatory system
  - Coagulation
- ACLF mostly occurs in patients with chronic liver disease, almost always with cirrhosis, and portends a poor prognosis
  - 28-day mortality is 20–70%, increasing with the number of organ failures
- ACLF is precipitated by either
  - Direct injury to the liver
    - Most commonly from alcohol-associated hepatitis and less often from new or flaring viral hepatitis, autoimmune hepatitis, or drug-induced liver injury
  - Systemic effects
    - Most commonly bacterial or fungal infection and less often GI bleeding or the postoperative state
    - Results in a marked systemic inflammatory response followed by organ failure, which is analogous to sepsis syndrome
- Management
  - Search for and treat precipitating causes of ACLF, determine if ICU care is needed, and consider immediate referral for liver transplantation
  - Complications of cirrhosis should be treated as described in this chapter
  - Consider transition to palliative care if, after 3–7 days of ICU support, there continue to be ≥ 4 organ failures and liver transplantation is not an option

HEPATOPULMONARY SYNDROME

- Arterial hypoxemia in a patient with cirrhosis without significant lung disease
- The liver disease causes intrapulmonary vascular dilations, resulting in blood shunting past alveoli and significant ventilation–perfusion mismatch
- Common findings
  - Platypnea: dyspnea relieved with lying flat and worse with sitting upright
  - Orthodeoxia: worsening oxygen saturation while upright
- Diagnosed with echocardiogram with agitated saline administration revealing left-sided bubbles in 3–6 beats, which is fairly specific for this syndrome
- Management comprises oxygen supplementation and liver transplantation

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PORTOPULMONARY SYNDROME

- Pulmonary hypertension in a patient with portal hypertension
- Production of vasoconstrictor substances affects the pulmonary artery
- Fatigue and dyspnea develop in late-stage disease
- Diagnosis by
  - Identification of pulmonary hypertension on echocardiogram
  - Confirmation on right heart catheterization showing
    - Elevated mean pulmonary artery pressure
    - Elevated pulmonary vascular resistance
    - Normal pulmonary capillary wedge pressure
- Management is liver transplantation

HEPATIC HYDROTHORAX

- Pleural effusion caused by ascites; usually a right-sided effusion
- Management is similar to ascites
  - Sodium restriction
  - Diuretics
  - Large-volume paracentesis with albumin afterward, if indicated
  - If refractory despite medical management, a multidisciplinary team considers
    - Recurrent thoracentesis
    - Transjugular intrahepatic portosystemic shunt (TIPS)
    - Pleurodesis
    - Thoracoscopic repair, and/or
    - Liver transplantation

SPLENOMEGALY & HYPERSPLENISM

- Backup from portal hypertension and platelet sequestration
- Thrombocytopenia, leukopenia, left-sided and left upper quadrant pain
- Thrombocytopenia can be the first manifestation of portal hypertension
- Splenomegaly itself usually requires no specific treatment

COAGULATION DISORDERS

- All clotting factors except VIII are produced in the liver
- Typical clinical measures of coagulation (PT and INR) are not reliable measures of clotting ability in patients with cirrhosis
- Patients have both decreased synthesis of clotting factors and impaired clearance of anticoagulants—some balance is achieved
  - However, the coagulation cascade can easily tip toward thrombosis or bleeding
- Vitamin K absorption is frequently diminished (due to cholestasis), reducing vitamin K–dependent clotting factors II, VII, IX, and X
- IV or IM vitamin K can quickly correct this abnormality
  - Overall, the status of coagulation in a patient with cirrhosis needs to be judged clinically rather than relying on current lab tests
- May have similar lab abnormalities as in disseminated intravascular coagulation
  - Measure factor VIII, which will be elevated in liver coagulopathy to differentiate the two
- Management includes treatment of the underlying cirrhosis and control of bleeding or clotting if they occur

PANCYTOPENIA

- Hypersplenism, hemolysis, iron deficiency, and folate deficiency of cirrhosis contribute to pancytopenia
- Thrombocytopenia occurs from portal hypertension and hypersplenism
- Macrocytosis is common, and neutropenia may occur from hypersplenism
- Management includes treatment of the underlying cirrhosis, iron and folate supplementation, and transfusions prn

HEPATOCELLULAR CARCINOMA

- Occurs in 10–25% of patients with cirrhosis
- Screen with ultrasound every 6 months and α fetoprotein measurement
- If diagnosed, manage with guidance from oncology

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INDICATIONS FOR LIVER TRANSPLANT EVALUATION

- α_1-Antitrypsin deficiency
- Acute liver failure
- Alcohol-associated cirrhosis
- Autoimmune hepatitis
- Caroli's disease
- Chronic viral hepatitis with cirrhosis
- Cryptogenic cirrhosis
- Hemochromatosis-associated cirrhosis
- Hepatic venous outflow obstruction (Budd-Chiari syndrome)
- Hepatocellular carcinoma
- Metabolic dysfunction–associated steatohepatitis (MASH)
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Secondary biliary cirrhosis
- Severe alcohol-associated hepatitis
- Select cases for the following indications
    - Erythropoietic protoporphyria
    - Familial amyloidosis
    - Hepatic adenomas
    - Hepatic epithelioid hemangioendothelioma
    - Metastatic neuroendocrine tumors
    - Polycystic liver disease

PROGNOSIS

- Variceal hemorrhage is an immediate life-threatening problem with a 20–30% mortality rate associated with each episode of bleeding
- The prognosis for patients with cirrhosis with ascites is poor, and some studies have shown that < 50% of patients survive 2 years after the onset of ascites
- Spontaneous bacterial peritonitis has a 25% in-hospital mortality rate
- Acute-on-chronic liver failure's 28-day mortality is 20–70%, increasing with the number of organ failures

MELD 3.0 SCORE

- Stratifies patients on the liver transplant list to predict the 3-month survival rate
- To calculate the score, uses
    - Patient's sex
    - Serum creatinine
    - INR
    - Total bilirubin
    - Sodium
    - Albumin
    - The age the patient was added to the transplant list
    - Whether the patient receives dialysis
- High MELD scores (~ 15 or higher) should be referred for liver transplant
- Calculate the MELD score every day the patient is in the hospital and at every clinic visit

MODIFIED CHILD-PUGH SCORING SYSTEM

- A scoring system used
    - To predict 1-year survival
    - For transplant evaluation
- Takes into account
    - The level of ascites
    - Encephalopathy
    - Bilirubin
    - Albumin
    - PT or INR
- Gives each category a score from 1 to 3 to classify a patient into class
    - A (5–6 points, 1-year survival 100%)
    - B (7–9 points, 1-year survival, 80%)
    - C (10–15 points, 1-year survival, 45%)

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PATHOPHYSIOLOGY

- The development of cirrhosis from a specific etiology dictates its individual pathophysiology
- The general theme in the development of cirrhosis
  - Oxidative stress → Kupffer cell activation → cytokines are released and activate stellate cells → increased collagen and fibrosis cause shrinkage of the liver and regenerative nodule formation
- Portal hypertension
  - Caused by a combination of two simultaneously occurring hemodynamic processes
    - Increased hepatic resistance to the passage of blood flow through the liver due to cirrhosis, regenerative nodules, and microthrombi
    - Increased splanchnic blood flow secondary to vasodilation within the splanchnic vascular bed
  - In more advanced stages, there is also activation of neurohumoral responses and vasoconstrictive systems, resulting in
    - Sodium and water retention
    - Increased blood volume
    - A hyperdynamic circulatory system producing further portal hypertension
  - When clinically significant portal hypertension develops (defined as a hepatic venous pressure gradient ≥ 10 mm Hg), there is a substantial risk of decompensation with variceal bleeding, ascites, or hepatic encephalopathy
- Hepatorenal syndrome (HRS)
  - There are marked disturbances in the arterial renal circulation in patients with HRS
    - These include an increase in splanchnic vasodilation from portal hypertension leading to an increase in systemic vascular resistance, which releases systemic vasoconstrictors and reduces renal perfusion
  - In later stages of cirrhosis, the quantity of local vasodilators decreases, and in combination with increased vasoconstrictors, renal perfusion further decreases
  - The renin-angiotensin-aldosterone system (RAAS) becomes activated, causing further decreased perfusion to the kidneys from vasoconstriction of renal arterioles and pooling of fluid in the portal venous system
  - The reason for renal vasoconstriction is most likely multifactorial and is poorly understood
- Hepatic encephalopathy
  - Gut-derived neurotoxins that are not removed by the liver because of vascular shunting and decreased hepatic mass reach the brain and cause the symptoms known as hepatic encephalopathy
  - Ammonia levels are typically elevated, but the correlation between severity of liver disease and height of ammonia levels is often poor
  - Other compounds and metabolites that may contribute to the development of encephalopathy include certain false neurotransmitters and mercaptans
- Development of ascites (Fig. 24-7)

RISK FACTORS

- Long-term heavy alcohol use
- Chronic infections with hepatitis B and/or C
- Autoimmune disorders
- Tobacco use
- Metabolic syndrome
- Genetic conditions (hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency)
- Chronic right HF
- Hypervitaminosis A
- Older age (> 50)

ADMITTING ORDERS

- Admit: to floor; to ICU if gross confusion and/or hemodynamically unstable
- Diagnosis: decompensated cirrhosis with (name specific entity, such as hepatic encephalopathy, bleeding esophageal varices, etc.) secondary to (name the cause of decompensation, if known)
- Condition: guarded
- Vital signs: q4h until stable
- Nursing: daily weights, strict *I*s/*O*s, Clinical Institute Withdrawal Assessment protocol if indicated for alcohol withdrawal
- Diet: low sodium

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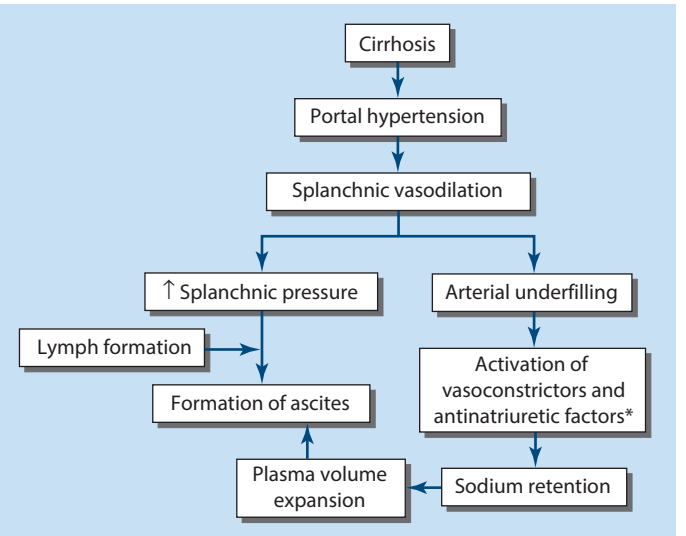

FIGURE 24-7 Development of ascites in cirrhosis. This flow diagram illustrates the importance of portal hypertension with splanchnic vasodilation in the development of ascites. *Antinatriuretic factors include the renin-angiotensin-aldosterone system and the sympathetic nervous system. (Reproduced with permission from Befeler AS, Bacon BR. Cirrhosis and its complications, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Fluids: provide fluids if the patient is hypovolemic
- Diagnostic tests
  - CBC
  - CMP
  - Coagulation studies
  - Iron studies
  - UA with culture
  - Blood cultures
  - Urine studies, if indicated for AKI
  - Hepatitis panels
  - CXR
  - Paracentesis for albumin, protein, cell count, differential, culture, and other studies if indicated (cytology, amylase, adenosine deaminase)
  - Abdominal ultrasound with Doppler of the portal system
- Medications
  - Spironolactone, 50 mg PO daily (unless hypovolemic or AKI is present)
  - Furosemide, 20 mg PO daily or IV (unless hypovolemic or AKI is present)
  - Multivitamin
  - Avoid opioids and anxiolytics
  - Lactulose and rifaximin if indicated
  - Octreotide infusion and ceftriaxone, 2 g/day if upper GI bleed is present
  - 25% albumin in the setting of concern for hepatorenal syndrome or diagnosed spontaneous bacterial peritonitis

DISCHARGE INFORMATION

- Education on diet and avoidance of toxins/alcohol
- Education on diuretics and lactulose/rifaximin therapies
- Follow up with primary care clinician and hepatology
- Vaccinations for hepatitis B/C, *Streptococcus*, and influenza
- Upper endoscopy screening for varices when indicated
- Ultrasound of liver to screen for hepatocellular carcinoma every 6 months

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CASE ANSWERS

1. This patient is presenting with signs and symptoms consistent with a clinical diagnosis of cirrhosis. She has several risk factors for developing cirrhosis, including injection drug use (hepatitis B and C), long-term heavy alcohol use, and a family history of liver disease (autoimmune hepatitis). Additionally, other etiologies, including metabolic dysfunction–associated steatohepatitis (MASH), primary biliary cholangitis, primary sclerosing cholangitis, cardiac cirrhosis, hemochromatosis, Wilson's disease, and α_1-antitrypsin deficiency should be considered.
2. This patient with findings of hepatic encephalopathy and ascites has decompensated cirrhosis.
3. Because infections are a common cause of decompensated cirrhosis, blood cultures, UA with culture, and a sputum culture with Gram stain should be obtained. Iron studies should be performed given the presence of anemia. A hepatitis panel will evaluate for chronic hepatitis infections. Since this is a new diagnosis of cirrhosis, serum ceruloplasmin and 24-h urinary copper, antimitochondrial antibody, and anti–smooth muscle antibody should be considered to evaluate for Wilson's disease, primary biliary cholangitis, and autoimmune hepatitis, respectively. An abdominal ultrasound with Doppler will evaluate the portal system for portal vein thrombosis (as a cause of ascites) and the kidneys for evaluation of the AKI. Because the patient has platypnea, an echocardiogram with agitated saline administration will evaluate for hepatopulmonary syndrome.
4. Given the presence of ascites, a diagnostic paracentesis should be performed to evaluate the cause of ascites and for the presence of spontaneous bacterial peritonitis. Peritoneal fluid studies to include are the ascitic albumin and protein, cell count with differential, and a culture with Gram stain.
5. While the underlying cause of her cirrhosis and decompensated state is being evaluated, lactulose and rifaximin can be administered to help with the patient's hepatic encephalopathy. Given the presence of AKI, 25% albumin, 1 g/kg/d for 48 h, can be administered as an "albumin challenge" to help rule out hepatorenal syndrome.

LANDMARK TRIALS

[1] Fernández J et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 131:1049. 2006. [PMID: 17030175]
- *Summary:* Among cirrhotic patients with GI bleed, ceftriaxone reduces the rate of bacterial infection by 67% but does not confer an increased survival benefit compared with norfloxacin.

[2] Corley DA et al. Octreotide for acute esophageal variceal bleeding: a meta-analysis. Gastroenterology 120:946, 2001. [PMID: 11231948]
- *Summary:* The results suggested that octreotide is more effective than vasopressin or terlipressin in the control of esophageal variceal bleeding, and that it is a safe and effective adjuvant therapy after variceal obliteration techniques.

[3] Bernardi M et al. Albumin infusion in patients undergoing large-volume paracentesis: A meta-analysis of randomized trials. Hepatology 55:1172, 2012. [PMID: 22095893]
- *Summary:* This meta-analysis provides evidence that albumin reduces morbidity and mortality among patients with tense ascites undergoing large-volume paracentesis, compared with alternative treatments investigated thus far.

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25 Acute Pancreatitis

KEY POINTS

1. Acute pancreatitis occurs when there is a sudden inflammatory event in the pancreas that is usually reversible. Mild interstitial pancreatitis is usually self-limited, while necrotizing pancreatitis can be life-threatening.
2. Severe, gnawing epigastric pain that radiates to the back and is worse after eating and when supine is characteristic of acute pancreatitis. Nausea and vomiting are common associated symptoms. Abnormal vital signs and epigastric pain with palpation are typical exam findings. Presence of xanthomas, jaundice, and Cullen's, Turner's, and Courvoisier's signs may provide clues to the underlying etiology or severity of the pancreatitis.
3. Acute pancreatitis is diagnosed when two of the following three criteria are present: (1) typical mid-epigastric abdominal pain radiating to the back; (2) ≥ 3× elevation in serum lipase and/or amylase; and (3) confirmatory findings of acute pancreatitis on CT imaging. Elevated BUN and hematocrit levels indicate severe disease.
4. IV fluid resuscitation using a moderate fluid resuscitation strategy, adequate pain control with IV opiates, and optimization of enteral nutrition are the cornerstones of acute pancreatitis management. Management of the underlying cause of the acute pancreatitis event (e.g., alcohol use, medications, gallstones, hypertriglyceridemia) also is imperative to treat the acute episode and prevent recurrent pancreatitis.
5. Necrotizing pancreatitis can lead to an infected pancreas, ARDS, shock, abdominal compartment syndrome, and multiorgan failure. Mild acute pancreatitis is usually self-limited with an excellent prognosis, while necrotizing pancreatitis has a mortality rate of ~17%.

EPIDEMIOLOGY & DEFINITIONS

Acute pancreatitis is one of the most common inpatient principal GI diagnoses in the United States. The annual incidence ranges from 15 to 45 per 100,000 persons, depending on the distribution of etiologies (i.e., alcohol use, gallstones) and country of study. Acute pancreatitis results in ~300,000 hospitalizations per year, with a median length of stay of 4 days and an estimated annual cost of ~$3 billion. The incidence of acute pancreatitis has been continually increasing since the late 1980s.

Acute pancreatitis is sudden inflammation of the pancreas and is usually reversible.

Interstitial pancreatitis is inflammation and edema of the pancreatic parenchyma and peripancreatic tissues without tissue necrosis; it is usually self-limited.

Necrotizing pancreatitis is acute pancreatitis with a disrupted blood supply to the pancreas leading to necrosis; this can be correlated with the severity of the inflammation and can lead to severe complications.

Chronic pancreatitis is a chronic inflammatory process of the pancreas characterized by irreversible morphologic changes.

CLINICAL VIGNETTE

A 65-year-old woman with pancreatic cancer presents to the ED for abdominal pain with nausea and vomiting. Two days ago, she underwent an endoscopic retrograde cholangiopancreatography (ERCP) with stent placement for biliary obstruction. The next day, she developed mid-epigastric gnawing abdominal pain with nausea and vomiting and has not been able to eat since. On physical exam she is afebrile, heart rate is 102 beats/min, respiratory rate is 16 breaths/min, BP is 124/82 mm Hg, and SpO_2 is 96% on room air. She appears anxious and jaundiced. Mild tenderness to palpation is present in the epigastric region. There is a palpable gallbladder on exam. There is decreased skin turgor. Lab data reveal lipase 1028 U/L, BUN 18 mg/dL, hematocrit 42%, and total bilirubin 4.8 mg/dL. An abdominal ultrasound reveals inflammation of the pancreas, an appropriately placed biliary stent, and the absence of cholelithiasis.

GUIDING QUESTIONS

1. What type of fluids, and what strategy of fluid resuscitation and monitoring, would you order for this patient?
2. How would you treat her pain?
3. When would you start oral nutrition?
4. What strategies can be used to prevent pancreatitis after endoscopic retrograde cholangiopancreatography?

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HISTORY

A thorough history helps identify the underlying cause of pancreatitis. While there are many etiologies of pancreatitis, gallstones and alcohol use account for 80–90% of identified cases in the United States. The severity of the pain also needs to be determined (can range from very mild discomfort to severe, constant, and incapacitating distress), as this can help determine the extent of inflammation and severity of disease. A history of recurrent alcohol-associated pancreatitis is preventable and needs to be addressed during admission.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Gnawing/steady epigastric/periumbilical pain that radiates to the back, chest, or flanks
  - The pain is typically worse with leaning back, partially relieved with leaning forward, and associated with nausea and vomiting
- Abdominal pain severity and location
  - Usually, there is severe pain in the epigastrium that radiates to the back
- Character of pain?
  - A steady or gnawing pain
- Radiation of pain?
  - Primarily radiates to the back
  - Can radiate to periumbilical region and lower abdomen
- Nausea and vomiting?
  - Common associated symptoms
  - May lead to worsened hypovolemia
- Recent illness
  - Coxsackie, mumps, Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis A or B, and tuberculosis can cause pancreatitis
- Recent endoscopic retrograde cholangiopancreatography (ERCP)?
  - Pancreatitis occurs in 5–10% of post-ERCP patients
- Abdominal blunt trauma?
  - Can damage the pancreas, causing pancreatitis
- Scorpion stings?
  - Rare but potential cause of pancreatitis
- Any new or recent medication changes (see Medications below)?

PAST MEDICAL HISTORY

- History of previous pancreatitis?
  - What was done for it?
  - How is this similar?
  - How is this different?
- History of gallstones?
  - How were they or are they being managed?
- History of hypertriglyceridemia?
  - Risk factor for pancreatitis
  - How high are your values normally (> 1000 mg/dL can cause pancreatitis)?
  - Are you being treated for it?
- History of cystic fibrosis?
  - Can cause pancreatitis by obstructing the pancreas exocrine glands
- History of cancer (especially pancreatic cancer)?
  - Biliary obstruction from pancreatic cancer can cause pancreatitis
- History of connective tissue disorders?
  - Some connective tissue disorders make patients more prone to pancreatitis (e.g., SLE or polyarteritis nodosa)

SURGICAL HISTORY

- ERCP recently?
  - Pancreatitis occurs in ~5–10% of post-ERCP patients
- Any recent surgeries?
  - Postop pancreatitis can occur

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SOCIAL HISTORY

- Alcohol use or recent heavy drinking episode?
  - The incidence of pancreatitis in persons with alcohol use disorder is surprisingly low (5 in 100,000), indicating that in addition to the amount of alcohol ingested, other factors affect a person's susceptibility to pancreatic injury (such as smoking and genetic predisposition)
- Smoking: risk factor for pancreatitis
- Recreational drugs
- Occupation
- Living situation
- Sexual history

MEDICATIONS

- Reported common medications that have caused pancreatitis
  - Furosemide
  - Thiazides
  - Dipeptidyl peptidase 4 (DPP-4) inhibitors
  - Sulfonamides
  - Sitagliptin
  - Estrogen (oral contraceptives)
  - 6-Mercaptopurine
  - Azathioprine, ACE-Is
  - Dapsone
  - 5-Aminosalicylic acid (ASA)
  - Didanosine
  - Pentamidine
  - Trimethoprim-sulfamethoxazole
  - Protease inhibitors
  - Valproate
- There are many other medications that have been reported to cause pancreatitis

PHYSICAL EXAM

The amount of distress the patient is in can help determine the severity of the pancreatitis. Patients may present with vital signs consistent with systemic inflammatory response syndrome (SIRS—e.g., fever, tachycardia, hypotension, hypoxemia). Hemorrhagic pancreatitis can manifest with specific physical exam findings to help with your diagnosis. It is also important to search for peritoneal signs in case urgent surgery is needed in the event of a complication, such as a perforated viscus.

- General appearance
  - May appear distressed and anxious, especially in severe pancreatitis
- Vital signs
  - Can have a low-grade fever, tachycardia, hypotension, or shock
  - 5–10% of patients have hypoxemia, which may herald the onset of ARDS
- Abdominal
  - Abdominal tenderness and muscle rigidity on exam are present to a variable degree, but compared with the intense pain, these may be less impressive
  - Diminished or absent bowel sounds from pancreatic inflammation, and possibly a distended abdomen
    - Ileus is a common complication
  - A palpable mass in the epigastric region may be an
    - Acute fluid collection
    - Walled-off necrosis
    - Pseudocyst (occurs 4–6 weeks later in the disease course)
  - Cullen's sign
    - Faint bluish discoloration around the umbilicus as a result of hemoperitoneum
    - A rare finding but if present indicates severe disease
  - Turner's sign
    - A blue-red-purple or green-brown discoloration of the flanks as a result of the breakdown of hemoglobin from severe necrotizing pancreatitis with hemorrhage
    - A rare finding but if present indicates severe disease

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- Courvoisier's sign
  - A palpable gallbladder in the right upper quadrant
  - May be a sign of a pancreatic head mass
- Hepatomegaly
  - May be a sign of a pancreatic head mass

- Pulmonary
  - 10–20% of patients have abnormal pulmonary findings
  - Basilar crackles, atelectasis, and pleural effusions (frequently left-sided) may be present
    - If severe enough, pancreatitis can lead to ARDS
- Skin
  - Jaundice
    - Is rare in pancreatitis, but if present, it may be a consequence of extrinsic compression of the biliary system due to
      - Peripancreatic edema
      - A pancreatic head mass
      - Intraductal obstruction from a common bile duct stone or sludge
  - Scleral icterus
    - Jaundice from bilirubin accumulation
  - Xanthomas
    - Sign of hypertriglyceridemia
  - Erythematous skin nodules ("pancreatic panniculitis") due to subcutaneous fat necrosis are possible but rare
- Extremities
  - Severe pancreatitis with shock may cause cool extremities

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL

- Acute cholecystitis and biliary colic
  - Pain occurring after meals (especially high-fat meals) in the right upper quadrant that can radiate to the right scapula
  - Fever in cholecystitis
  - Gallstones visualized on ultrasound with or without pericholecystic inflammation
- Perforated viscus (e.g., peptic ulcer disease)
  - Severe abdominal pain not necessarily in the epigastrium and rebound tenderness
  - Free air under the diaphragm on upright x-ray
- Renal colic
  - Severe flank pain that radiates to the inguinal area
  - The patient is writhing on the exam table from the pain
- Acute small or large bowel obstruction
  - Abdominal pain with peritoneal signs, rebound tenderness, crescendo-decrescendo pattern of pain, high-pitched and hyperactive bowel sounds
  - Abdominal x-ray reveals dilated loops of bowel with air fluid levels
- Mesenteric vascular occlusion
  - Severe abdominal pain that is out of proportion to findings on exam, nausea, bloody stools, in a debilitated older patient
  - Very high leukocytosis and lactic acidosis
  - Confirmed on CT or magnetic resonance angiography
- Diabetic ketoacidosis (DKA)
  - Diffuse abdominal pain with nausea, vomiting, and/or diarrhea and a history of diabetes
  - Amylase is elevated (likely due to acidemia from DKA)
  - Lipase is usually normal, and abdominal imaging shows a normal pancreas
- Dissecting aortic aneurysm
  - Older smoker with hypertension who now has severe abdominal pain and a pulsating palpable mass in the abdomen
- Connective tissue disorders with vasculitis (aortitis)
  - Systemic symptoms similar to pancreatitis, and would have other findings more specific to the vasculitis (e.g., SLE or polyarteritis nodosa)
- Inferior wall MI
  - May present with epigastric pain and nausea, does not radiate to the back

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- ECG shows ischemia and the troponin is elevated
- Pancreatitis can also show ST-segment and T-wave abnormalities mimicking MI in the acute setting

- Pneumonia
  - May have lower chest pain that is perceived as epigastric pain
  - Has associated fever/chills, productive cough, and lobar consolidation on CXR
- IgG_4-related disease
  - If affecting the pancreas and biliary tree, may present with abdominal pain mimicking pancreatitis and/or pancreatic cancer with elevated lipase levels
  - Patients classically have allergy features of atopy, eczema, nasal polyps, and sinusitis

ETIOLOGY

- Gallstones (35–60% of cases): most common cause in most reports
  - Risk is fourfold higher with smaller gallstones (< 5 mm) than with larger gallstones
  - Elevation of the ALT > 3× the upper limit of normal is strongly associated with a gallstone etiology of pancreatitis
- Alcohol (15–30%)
  - The incidence of pancreatitis in persons with alcohol use disorder is low (5 in 100,000), indicating that in addition to the amount of alcohol ingested, other factors affect a person's susceptibility to pancreatic injury (such as smoking and genetic predisposition)
- Post–endoscopic retrograde cholangiopancreatography (ERCP) (5–10% of post-ERCP patients)
  - Risk factors for post-ERCP pancreatitis include
    - Performing a minor papilla sphincterotomy during ERCP
    - Suspected functional sphincter syndrome (previously "sphincter of Oddi dysfunction")
    - Age < 60
    - > 2 contrast injections into the pancreatic duct during ERCP
    - Prior history of post-ERCP pancreatitis
    - Endoscopist inexperience
- Hypertriglyceridemia (1–4% of cases)
  - Triglyceride levels are usually > 1000 mg/dL
  - These patients are prone to recurrence of pancreatitis and higher severity of pancreatitis
  - Most patients have undiagnosed or uncontrolled diabetes
  - Any factor (e.g., alcohol use or medications, such as oral contraceptives) that causes an abrupt rise in serum triglyceride levels can precipitate an acute attack
- Medications (< 2% of cases)
  - See Medications in the History section for common medication causes of pancreatitis (many medications have been implicated in pancreatitis)
- Trauma: blunt abdominal trauma can cause pancreatitis
- Postop pancreatitis
- If the patient has recurrent pancreatitis, consider the following
  - Occult disease of the biliary tree or pancreatic ducts, especially microlithiasis/biliary sludge
  - Alcohol use disorder
  - Metabolic: hypertriglyceridemia, hypercalcemia
  - Anatomic: pancreatic divisum
  - Pancreatic cancer
  - Intraductal papillary mucinous neoplasm (IPMN)
  - Hereditary pancreatitis
  - Cystic fibrosis
  - Idiopathic
- Uncommon causes of pancreatitis
  - Vasculitis
  - Connective tissue disorders
  - Apolipoprotein CII deficiency
  - Thrombotic thrombocytopenic purpura
  - Pancreatic cancer
  - Hypercalcemia
  - Periampullary diverticulum
  - Hereditary pancreatitis
  - Cystic fibrosis
  - Infections (mumps, coxsackievirus, Epstein-Barr virus, cytomegalovirus, echovirus, tuberculosis, parasites)

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- Autoimmune pancreatitis (type 1 and 2)
- Scorpion sting
- Familial pancreatitis (pathologic variants in the *PRSS1*, *CFTR*, *SPINK1*, *CTRC*, *CASRv* and *CLDN2* genes)

DIAGNOSTIC TESTS

LABS

- CBC
  - Leukocytosis and anemia from severe inflammation may be present
  - A hematocrit > 44% is an important finding
    - Hemoconcentration from severe volume depletion increases the hematocrit, indicating severe pancreatitis; trending the hematocrit initially is a common strategy to guide fluid management
- BMP
  - Evaluate for electrolyte abnormalities and hyperglycemia that need to be treated
  - BUN/SCr ratio > 20:1 commonly indicates a prerenal azotemia
  - BUN can especially be important, with a value of > 22 mg/dL showing severe hypovolemia; trend initially
    - Azotemia is a significant risk factor for mortality in pancreatitis
  - Hyperglycemia is common and due to multiple factors
    - Decreased insulin release
    - Increased glucagon release
    - Increased output of adrenal glucocorticoids and catecholamines
- Lipase (preferred test) and amylase
  - Values > 3× or more above normal virtually clinch the diagnosis if gut perforation, ischemia, and infarction have been ruled out
  - Serum lipase is the preferred test due to its higher specificity for pancreatitis than amylase
  - There is no correlation between the severity of pancreatitis and the lipase level
    - Lipase levels should *not* be trended, as levels can remain elevated for 7–14 days
  - After 3–7 days, the amylase typically returns to normal even with continuing clinical evidence of pancreatitis
    - Lowering of amylase levels does not correlate with an improving clinical course
  - Amylase can be spuriously low in severe hypertriglyceridemia, causing pancreatitis
- Calcium
  - Hypocalcemia occurs in ~25% of patients due to saponification
- LDH
  - Elevations can be a marker of increased severity of pancreatitis
- Liver function tests
  - Hyperbilirubinemia (> 4 mg/dL) occurs in ~10% of patients but is usually transient (returns to normal in 4–7 days)
  - Alkaline phosphatase and transaminase levels also may be transiently elevated in parallel with bilirubin levels
  - Elevation of ALT > 3× the upper limit of normal is strongly associated with a gallstone etiology of pancreatitis
- Triglycerides
  - Triglycerides > 1000 mg/dL are a risk factor and potential cause of pancreatitis
- Lactic acid and CRP
  - Elevated levels during hospitalization can be used as a marker of severity
- PT/PTT/INR
  - Coagulopathy may be present in severe disease

IMAGING

- Abdominal ultrasound
  - Initial test and is recommended to be performed in the ED
  - Assesses for gallstone disease, biliary sludging, and pancreatic head anatomy
- Abdominal CT with IV contrast (Fig. 25-1)
  - Test of choice
  - A CT is not necessary to diagnose pancreatitis, but can consider ordering if not improving after 48–72 h or if the diagnosis of pancreatitis is not definitive in the ED
  - An initial CT scan on presentation can miss necrosis as this does not appear until ~72 h later
    - This is why CTs are not recommended to be performed in the ED

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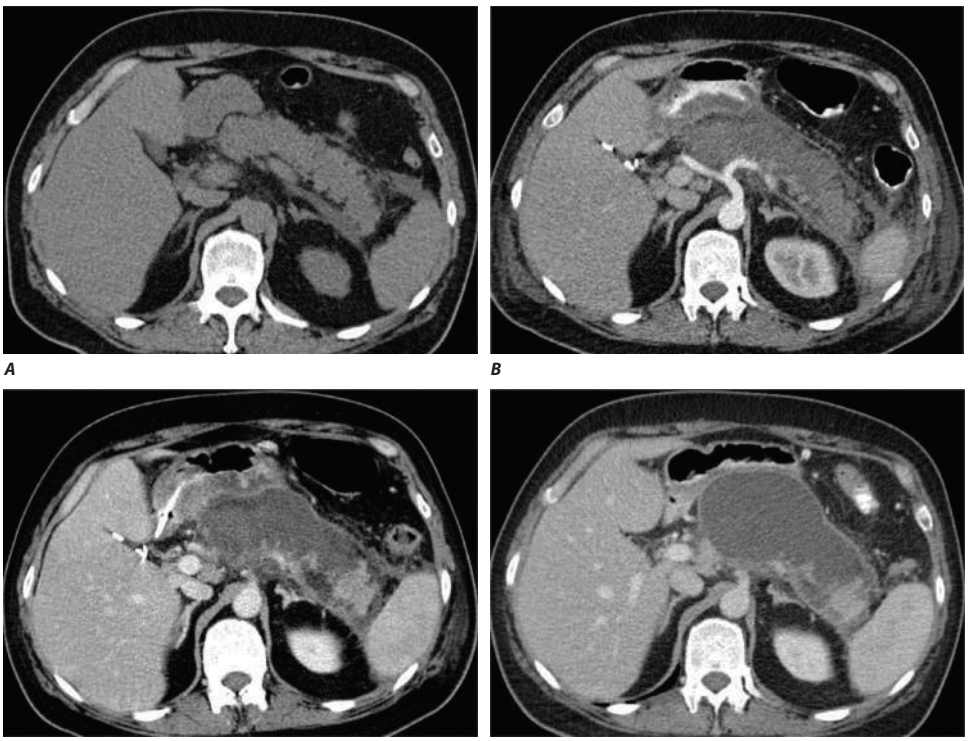

FIGURE 25-1 Evolution of changes of acute necrotizing pancreatitis on CT. ***A.*** CT scan of the abdomen without IV contrast performed on admission for a patient with acute gallstone pancreatitis, showing mild peripancreatic stranding. ***B.*** Contrast-enhanced CT scan of the abdomen performed on the same patient 1 week after admission shows extensive intrapancreatic necrosis, evidenced by the lack of contrast enhancement in the pancreatic body with minimal enhancement noted at the distal most aspect of the pancreatic tail. ***C.*** Contrast-enhanced CT scan of the abdomen performed on the same patient 2 weeks after admission demonstrates a semiorganized, heterogeneous fluid collection, referred to as an acute necrotic collection. On this image, a small area of viable pancreatic parenchyma is seen at the tail of the pancreas. ***D.*** Contrast-enhanced CT scan of the abdomen performed on the same patient 5 weeks after admission demonstrates a well-encapsulated fluid collection, essentially replacing the pancreas, referred to as walled-off necrosis. (Used with permission from Hart PA et al. Acute and chronic pancreatitis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Abdominal x-ray
  - A sentinel loop and/or air in the small bowel in the left upper quadrant may be present
- CXR
  - Atelectasis and/or pleural effusions may be present
  - In severe pancreatitis, ARDS may develop
- Endoscopic ultrasound/magnetic resonance cholangiopancreatography (MRCP)
  - Replacing endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes
  - An MRCP is useful if gallstone pancreatitis is the likely etiology
  - If choledocholithiasis is still present with MRCP imaging, an ERCP may be warranted
- ECG
  - May reveal ST-segment and T-wave abnormalities simulating myocardial ischemia in the acute setting

DIAGNOSTIC CRITERIA OF ACUTE PANCREATITIS

- Two of the following three findings are needed to diagnose acute pancreatitis
  - Typical mid-epigastric abdominal pain radiating to the back
  - 3× or greater elevation in serum lipase and/or amylase
  - Confirmatory findings of acute pancreatitis on imaging

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- Typical CT findings of acute pancreatitis include
  - Interstitial pancreatitis
  - Necrotizing pancreatitis
  - Acute pancreatic fluid collection
  - Pancreatic pseudocyst
  - Acute necrotic collection
  - Walled-off necrosis

SEVERITY OF ACUTE PANCREATITIS

- 85–90% of pancreatitis cases are self-limited and subside spontaneously in 3–5 days after initiation of treatment
- Table 25-1 describes various factors and scoring systems to assess the severity of acute pancreatitis
  - Ranson's criteria also can be used, but other scoring systems are often favored due to their ease of use and potentially greater accuracy in predicting outcomes
- Classification of acute pancreatitis severity
  - Mild pancreatitis
    - Self-limited without local complications or organ failure
    - Subsides spontaneously within 3–7 days after treatment is initiated
  - Moderately severe pancreatitis
    - Transient organ failure (resolves within 48 h) or
    - Local systemic complications in the absence of persistent organ failure

TABLE 25-1 Severity Assessment of Acute Pancreatitis

Risk Factors for Increased Severity
• Age > 60 years
• Obesity, BMI > 30
• Comorbid disease (based on Charlson comorbidity index)
Markers of Severity at Admission or Within 24 h
• SIRS—defined by presence of ≥ 2 criteria
– Core temperature < 36° or > 38°C
– Heart rate > 90 beats/min
– Respirations > 20/min or PCO_2 < 32 mm Hg
– WBC count > 12,000/μL, < 4000/μL, or 10% bands
• APACHE II (≥ 8 at 24 h)
• Hemoconcentration (hematocrit > 44%)
• Admission BUN (> 22 mg/dL)
• BISAP score (≥ 3 present)
– (B) BUN > 25 mg/dL
– (I) Impaired mental status
– (S) SIRS: ≥ 2 of 4 present
– (A) Age > 60 years
– (P) Pleural effusion
• Organ failure (Modified Marshall score) (≥ 1 present):
– Cardiovascular: systolic BP < 90 mm Hg, heart rate > 130 beats/min
– Pulmonary: Pao_2 < 60 mm Hg
– Renal: serum creatinine > 2.0 mg/dL
Markers of Severity during Hospitalization
• Elevated CRP (variable thresholds > 100 mg/L reported)
• Persistent organ failure (≥ 48 h)
• Pancreatic or extrapancreatic necrosis

APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, Bedside Index of Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome.
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- Severe pancreatitis
  - Persistent (> 48 h) single or multiorgan failure
  - A CT or MRI should be performed 3–5 days into hospitalization to assess for necrotizing pancreatitis when patients are not responding to supportive care
- Acute Physiology and Chronic Health Evaluation II (APACHE II) Score
  - The APACHE II score is the best scoring system for predicting the prognosis of acute pancreatitis
  - The score is based on points assigned to physical exam findings (i.e., the Acute Physiology Score [including rectal temperature, mean BP, respiratory rate, oxygenation, etc.]) as well as the Glasgow Coma Scale
  - The points are then calculated by age and chronicity of disease
  - A severe score is ≥ 8
  - You can use this both on admission and daily to assess the patient's prognosis and response to treatment
- Moderately severe and severe pancreatitis are associated with a long length of hospital stay (usually > 1 week)

MANAGEMENT

- The management of acute pancreatitis begins in the ED
  - After diagnosis, early fluid resuscitation is critical
  - IV analgesics are administered
  - Severity is assessed
  - A search for etiologies is initiated

INITIAL TRIAGE OF THE PATIENT WITH ACUTE PANCREATITIS

- Where to admit the patient
  - Hospital floor
    - Low BISAP scores (< 3)
    - Hematocrit < 44% on admission
    - BUN < 22 mg/dL on admission
    - No SIRS criteria are present at 24 h
    - Consider transfer to a step-down unit if
      - SIRS criteria become present/persistent at 24 h, and
      - The patient has underlying comorbidities (such as COPD or HF)
  - ICU
    - APACHE II scores ≥ 8 at presentation or at 24 h
    - BISAP score ≥ 3
    - Modified Marshal score of ≥ 1
    - Severely elevated hematocrit or BUN requiring intensive fluid resuscitation

FLUID RESUSCITATION & MONITORING OF RESPONSE

- *The most important treatment intervention is early IV fluid resuscitation* to prevent systemic complications from the secondary systemic inflammatory response
- Most clinicians use LR for resuscitation, but NS can be used as well
  - Patients with acute pancreatitis who were resuscitated with LR had reduced systemic inflammation (reduced CRP levels from admission) compared with those who received NS [1]

GOAL-DIRECTED HYDRATION STRATEGIES

- Serial bedside evaluations q6–8h to assess vital signs, oxygen saturation, and changes in physical exam to optimize fluid resuscitation are recommended
  - ARDS and acute abdominal compartment syndrome are known complications of excessive IV fluids
- Two strategies of fluid resuscitation can be used in isolation or as a combination
  - *Moderate fluid resuscitation strategy*
    - Provide a 10-mL/kg bolus in patients with signs of hypovolemia (e.g., hypotension, tachycardia, decreased skin turgor)
    - Follow this by 1.5 mL/kg/h for 20 h if tolerating oral intake for > 8 h
    - Further 10-mL/kg boluses if urine output < 0.5 mL/kg/h or systolic BP < 90 mm Hg during assessments at 12–72 h
    - This moderate fluid resuscitation strategy was compared with aggressive fluid management and was found to have no significant difference in outcomes and less fluid overload [2]
  - *A targeted resuscitation strategy*
    - Administer fluids as in the moderate fluid resuscitation strategy
    - Serially measure the hematocrit and BUN q8–12h to ensure adequate fluid resuscitation and monitoring the response to therapy

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- A rising hematocrit and BUN indicate inadequate fluid resuscitation
- In this scenario, IV fluid boluses should be administered to decrease the hematocrit and BUN levels
- A rising BUN during hospitalization is associated with higher in-hospital mortality

- A decrease in hematocrit and BUN during the first 12–24 h provides strong evidence that an adequate volume of fluids is being administered
- Adjustments in fluid resuscitation may be required in patients with cardiac, pulmonary, or renal disease

PAIN CONTROL

- IV opiates are usually necessary to control acute pancreatitis pain
- The choice of scheduling or having prn opiates available depends on the severity of pain and frequent reassessment
- Common opiate choices
  - Morphine (if normal kidney function)
  - Hydromorphone
  - Fentanyl
- A patient-controlled analgesia (PCA) pump may be required if pain is not controlled with scheduled and prn IV opiates, but is associated with longer lengths of stay and higher rates of opiate prescriptions on discharge
- Transition to PO opiates is reasonable when the patient is eating and pain is improving

NUTRITION

- If mild pancreatitis, initiate oral nutrition when pain/nausea allows with a low-fat solid diet
  - The American Gastroenterological Association guidelines recommend trying enteral feeding in the first 24 h if possible
- Severe pancreatitis with nausea and vomiting may require the patient to be NPO at first
  - If the patient cannot tolerate a PO diet by day 2–3, start enteral feeding (via nasogastric or nasojejunal tube)
- Avoid total parenteral nutrition (TPN) and partial parenteral nutrition (PPN) if possible
  - Enteral feeding maintains gut integrity, limits bacterial translocation, is less expensive, and has fewer complications than TPN/PPN

ALCOHOL-INDUCED PANCREATITIS

- Manage alcohol withdrawal, if present, with
  - Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) scale monitoring
  - Benzodiazepines (e.g., lorazepam) and/or barbiturates (e.g., phenobarbital)
  - Thiamine and a multivitamin administration
  - See Chap. 54 for further details of alcohol withdrawal monitoring and management
- Counseling about alcohol cessation is critical prior to discharge to prevent recurrence
- Referral to an addiction treatment team with close outpatient follow-up

GALLSTONE PANCREATITIS MANAGEMENT

- Endoscopic retrograde cholangiopancreatography (ERCP) should be performed within 24–48 h of admission if there is evidence of ascending cholangitis
- An ERCP in choledocholithiasis without ascending cholangitis should be performed to remove the gallstone
  - However, there is evidence that early ERCP does not decrease the risk of complications
  - Placement of a pancreatic duct stent and administration of rectal indomethacin help prevent post-ERCP pancreatitis
- Surgery consult for cholecystectomy evaluation prior to discharge is indicated in patients with mild acute gallstone pancreatitis
  - Compared with interval cholecystectomy, same-admission cholecystectomy reduced the rate of recurrent gallstone-related complications in patients with mild gallstone pancreatitis, with a very low risk of cholecystectomy-related complications [3]
  - If cholecystectomy is not performed prior to discharge, it should be scheduled within 4–6 weeks after discharge
- Endoscopic biliary sphincterotomy prior to discharge is an alternative for patients who are not surgical candidates

HYPERTRIGLYCERIDEMIA-INDUCED PANCREATITIS MANAGEMENT

- Start an insulin infusion and NPO status for the initial 24-36 h to promote resolution of severe hypertriglyceridemia
- Adjunct therapies include heparin or plasmapheresis (no specific evidence that these improve outcomes)
- Control diabetes if present

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- Administer lipid-lowering therapies
- Advise weight loss
- Avoid alcohol and medications that can elevate triglyceride levels

ADJUNCT THERAPIES

- Supplemental oxygen if oxygen saturation < 92%
- Frequent monitoring of electrolytes and repletion as needed
- Scheduled or prn antiemetics with IV ondansetron 4 mg q4–6h (first line) or IV metoclopramide 10 mg q4–6h
- While rare, hypercalcemia can cause pancreatitis
- Stop any precipitating factors (e.g., medications)
- Antibiotics
  - Antibiotic prophylaxis is *not* recommended
  - If necrosis is suspected, a multidisciplinary team is necessary for management decisions
    - Percutaneous aspiration of necrosis with Gram stain and culture should be considered if there are ongoing signs of possible pancreatic infection including a sustained leukocytosis, fever, or organ failure
      - This is institution-dependent on how comfortably a percutaneous fine-needle aspiration can be performed
    - It is reasonable to start broad-spectrum antibiotics (with a carbapenem) while awaiting the Gram stain and culture results and/or if the patient is clinically decompensating
    - Empirical antibiotics do not lead to improved survival and may promote the development of opportunistic fungal infections
    - If infected necrosis is established and an organism is identified
      - Targeted antibiotics should be administered
      - Pancreatic drainage and/or debridement (necrostomy) should be considered for definitive management

COMPLICATIONS

LOCAL COMPLICATIONS

- Pancreatic/peripancreatic fluid collections
  - Acute necrotic collection (sterile or infected)
  - Walled-off necrosis (sterile or infected)
  - Pancreatic pseudocyst
    - Fluid collection that is encapsulated and persists for 4–6 weeks
    - May feel an epigastric mass on exam
    - Most resolve spontaneously
      - If > 6 cm or lasts > 6 weeks, drain with biopsy to rule out cancer
- Disruption of the main pancreatic duct or secondary branches
  - May present as increasing abdominal pain or shortness of breath in the setting of an enlarging fluid collection resulting in pancreatic ascites (high ascitic amylase level)
  - Diagnosis established via magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP)
  - A bridging pancreatic stent for at least 6 weeks is > 90% effective at resolving the leak with or without parenteral nutrition and octreotide
- Pancreatic ascites
- Chylous ascites
- Involvement of contiguous organs in necrotizing pancreatitis (e.g., colon perforation)
- Splanchnic thromboses (splenic vein, superior mesenteric vein, and/or portal vein)
- Gastric outlet obstruction
- Biliary obstruction

SYSTEMIC COMPLICATIONS

- Shock
- Pulmonary
  - Pleural effusions
  - Atelectasis
  - Mediastinal fluid accumulation

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    - Pneumonitis
    - ARDS
- Cardiovascular
    - Hypotension
    - Hypovolemia
    - Nonspecific ST-T changes on ECG mimicking MI
    - Pericardial effusion
- Hematologic: disseminated intravascular coagulation
- Gastrointestinal
    - Peptic ulcer disease
    - Erosive gastritis
    - Hemorrhagic pancreatic necrosis with erosion into major blood vessels (hemosuccus pancreaticus)
    - Variceal hemorrhage secondary to splanchnic thrombosis
    - Acute abdominal compartment syndrome
- Renal
    - Oliguria
    - Azotemia
    - Renal artery and/or renal vein thrombosis
    - Acute tubular necrosis
- Metabolic
    - Hyperglycemia
    - Hypertriglyceridemia
    - Hypocalcemia (poor prognosis if present)
    - Encephalopathy
    - Sudden blindness (Purtscher's retinopathy)
- CNS
    - Psychosis
    - Fat embolism
- Fat necrosis of
    - Subcutaneous tissues (erythematous nodules)
    - Bone
    - Miscellaneous structures (mediastinum, pleura, nervous system)
- Hospital-acquired infections
    - Occur in up to 20% of patients admitted with pancreatitis
    - Continuously monitor for the development of pneumonia, urinary tract infections, and line infections

CHRONIC PANCREATITIS COMPLICATIONS

- After initial or recurrent pancreatitis, patients can develop chronic pancreatitis, which has its own complications (Table 25-2)

TABLE 25-2 Complications of Chronic Pancreatitis

Chronic abdominal pain
Exocrine pancreatic insufficiency
Diabetes mellitus
Splanchnic venous thrombosis
Metabolic bone disease (osteoporosis)
Biliary stricture and/or biliary cirrhosis
Pancreatic duct stricture
Pseudocyst
Pancreatic cancer
Malnutrition, micronutrient deficiencies

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PROGNOSIS

- The overall mortality in acute pancreatitis is < 5%, with a lower mortality in patients with interstitial pancreatitis compared with those with necrotizing pancreatitis (3% vs 17%)
- In most patients with acute pancreatitis, the disease is mild in severity, and patients recover in 3–5 days without complications or organ failure
- However, ~20% of patients have moderately severe or severe acute pancreatitis with local or systemic complications or organ failure
    - Hospitalizations for moderately severe and severe acute pancreatitis can be prolonged and last weeks to months and often involve periods of intensive care unit admission and outpatient rehabilitation or subacute nursing care
- The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is the best scoring system to gauge prognosis

PATHOPHYSIOLOGY

- The pancreas secretes 1500–3000 mL of isosmotic alkaline (pH > 8) fluid per day containing ~20 enzymes
- Pancreatic secretions provide the enzymes and bicarbonate needed to perform the major digestive activity of the GI tract and produce an optimal pH for the function of these enzymes
- There is a vast interplay of hormones and enzymes that regulate secretion of these enzymes, which include
    - Gastric acid
    - CCK
    - Long-chain fatty acids
    - Amino acids
    - The parasympathetic nervous system
    - VIP
    - Somatostatin
- The pancreas protects itself from autodigestion by several mechanisms, including
    - The packaging of pancreatic proteases in precursor form
    - Intracellular calcium homeostasis
    - Acid-base balance
    - Synthesis of protective protease inhibitors (PSTI or SPINK)
- Loss of any of the above four mechanisms can lead to premature activation of enzymes and autodigestion of the pancreas
- *Initial phase* of pancreatitis
    - Intrapancreatic digestive enzyme activation and acinar injury from trypsin activation, causing acinar injury
    - Trypsin activation appears to be mediated by lysosomal hydrolases such as cathepsin B that become colocalized with digestive enzymes in intracellular organelles
    - It is currently believed that acinar cell injury is the consequence of trypsin activation
- *Second phase* of pancreatitis
    - Activation, chemoattraction, and sequestration of leukocytes and macrophages in the pancreas
    - This results in an enhanced intrapancreatic inflammatory reaction
        - Neutrophil depletion induced by prior administration of an antineutrophil serum has been shown to reduce the severity of experimentally induced pancreatitis
    - There is also evidence to support the concept that neutrophils can activate trypsinogen
        - Thus, intrapancreatic acinar cell activation of trypsinogen could be a two-step process
            - An early neutrophil-independent phase
            - A later neutrophil-dependent phase
- *Third phase* of pancreatitis
    - The effects of activated proteolytic enzymes and cytokines released by the inflamed pancreas on distant organs
    - Activated proteolytic enzymes, especially trypsin, not only digest pancreatic and peripancreatic tissues but also activate other enzymes such as elastase and phospholipase A_2
    - These active enzymes and cytokines digest cell membranes, causing
        - Proteolysis
        - Edema
        - Interstitial hemorrhage
        - Vascular damage
        - Coagulation and fat necrosis
        - Parenchymal cell necrosis

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    - Cellular injury and death result in the liberation of
        - Bradykinin peptides
        - Vasoactive substances
        - Histamine
        - These substances produce vasodilation, increased vascular permeability, and edema, with profound effects on other organs
    - The systemic inflammatory response syndrome (SIRS), ARDS, and multiorgan failure may occur because of this cascade, producing local and distant effects
- Several factors (e.g., endotoxins, exotoxins, viral infections, ischemia, oxidative stress, lysosomal calcium, direct trauma) are believed to facilitate premature activation of trypsin, which can activate other enzymes
    - Spontaneous activation of trypsin also can occur, resulting in autodigestion
- Genetic factors can increase the susceptibility and/or modify the severity of pancreatic injury, recurrent pancreatitis, and chronic pancreatitis
    - The major genetic susceptibility factors center on the control of trypsin activity within the pancreatic acinar cell
    - Six genetic variants have been identified as being associated with susceptibility to pancreatitis
        - Cationic trypsinogen gene (*PRSS1*)
        - Serine peptidase inhibitor Kazal type 1 gene (*SPINK1)*
        - Cystic fibrosis transmembrane conductance regulator gene (*CFTR*)
        - Chymotrypsin C gene (*CTRC*)
        - Calcium-sensing receptor (*CASR*)
        - Claudin-2 (*CLDN2*)
    - Only *PRSS1* pathogenic variants are sufficient to precipitate acute pancreatitis in the absence of other risk factors; the others are disease modifiers
- Shock is not unusual and may result from
    - Hypovolemia secondary to exudation of blood and plasma proteins into the retroperitoneal space
    - Increased formation and release of kinin peptides, which cause vasodilation and increased vascular permeability
    - Systemic effects of proteolytic and lipolytic enzymes released into the circulation

RISK FACTORS

- Certain medications (see History section)
- Alcohol
- Smoking
- Gallstones and metabolic syndrome
- Abnormalities in lipid metabolism
- Patients with ESRD on dialysis
- Genetic predispositions (see Differential Diagnosis & Etiology and Pathophysiology)
- HIV/AIDS
    - Increased susceptibility to pancreatitis for a higher incidence of infections of the pancreas with cytomegalovirus, *Cryptosporidium*, and *Mycobacterium avium* complex, as well as the frequent use of medications that can cause pancreatitis in AIDS patients, including didanosine, pentamidine, trimethoprim-sulfamethoxazole, and protease inhibitors

ADMITTING ORDERS

- Admit to floor if mild, ICU if severe (use severity scores)
- Diagnosis: acute pancreatitis
- Condition: guarded
- Vital signs: every 4 h until stable
- Nursing: accurate *I*s/*O*s, daily weights, assess and treat pain every 2–4 h, call for systolic BP < 100 mm Hg, heart rate > 110 beats/min, temperature > 38.5°C (101.3°F), hypoxemia, or urine output < 30 mL/h averaged over 4 h, Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) monitoring if indicated
- Diet: NPO or initiate oral nutrition when pain/nausea allows with a low-fat solid diet
- Fluids
    - Provide a 10-mL/kg bolus if signs of hypovolemia are present
    - Follow this by 1.5 mL/kg/h for 20 h if tolerating oral intake for > 8 h
    - Further 10-mL/kg boluses if urine output < 0.5 mL/kg/h or systolic BP < 90 mm Hg during assessments at 12–72 h

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- Diagnostic tests
  - CBC
  - Amylase
  - Lipase
  - CMP
  - Calcium
  - Triglycerides
  - LDH
  - Lactic acid and CRP
  - PT/PTT/INR
  - Abdominal ultrasound
  - CT abdomen/pelvis with IV contrast (consider at the 48–72 h mark if patient is not improving)
- Medications
  - IV opiates (morphine, hydromorphone, or fentanyl) are usually needed
  - IV ondansetron 4 mg q4–6h
  - Benzodiazepines and/or barbiturates if alcohol withdrawal is present

DISCHARGE INFORMATION

- If mild pancreatitis → discharge when can tolerate oral diet and oral pain meds
- If severe → often stay in hospital for weeks if complications; educate on discharge about late-stream complications that can occur
- If gallstones are the cause → surgical evaluation for cholecystectomy before discharge
- If alcohol is the cause → educate about high recurrence, counsel about cessation with medication supplementation if interested, and refer for longitudinal alcohol cessation programs
- If the patient uses tobacco products → counsel on the importance of smoking cessation
- Should evaluate for development of diabetes, exocrine insufficiency, recurrent cholangitis, and development of fluid collections in the outpatient setting
- Follow up with primary care within 2 weeks

CASE ANSWERS

1. Early IV fluid administration with LR (preferred) or NS is one of the cornerstones of acute pancreatitis management. A moderate fluid resuscitation strategy (an initial 10-mL/kg bolus [in patients with signs of hypovolemia], followed by 1.5 mL/kg/h for 20 h and further 10-mL/kg boluses for oliguria or hypotension) has been shown to have no significant difference in outcomes and less fluid overload when compared with an aggressive fluid management strategy. Serial measurements of hematocrit and BUN at 8- to 12-h intervals can help determine the response to fluid management.
2. Adequate pain management is another cornerstone of acute pancreatitis treatment. IV opiates are usually necessary, either scheduled or prn. Morphine, hydromorphone, and fentanyl are common opiate choices. If the pain is uncontrolled, a PCA pump may be necessary.
3. Early PO enteral nutrition is recommended within the first 24 h if the patient is able to tolerate a low-fat solid diet. In severe pancreatitis where the patient cannot tolerate oral feeding, enteral nutrition via nasogastric or nasojejunal tube is recommended at day 2–3 of admission. TPN and PPN should be avoided, if possible.
4. Post-ERCP pancreatitis is sometimes prevented with the placement of pancreatic duct stent and administration of rectal indomethacin.

LANDMARK TRIALS

[1] Wu BU et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 9:710, 2011. [PMID: 21645639]
  - *Summary:* Patients with acute pancreatitis who were resuscitated with lactated Ringer's solution had reduced systemic inflammation compared with those who received saline.

[2] de-Madaria E et al. Aggressive or moderate fluid resuscitation in acute pancreatitis. N Engl J Med 387:989, 2022. [PMID: 36103415]
  - *Summary:* The WATERFALL trial compared aggressive fluid resuscitation strategy to moderate fluid resuscitation and found that moderate fluid resuscitation had similar outcomes and less fluid overload in patients with acute pancreatitis.

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[3] da Costa DW et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): A multicentre randomised controlled trial. Lancet 386:1261, 2015. [PMID: 26460661]
    - *Summary:* The PONCHO trial showed that compared with interval cholecystectomy, same-admission cholecystectomy reduced the rate of recurrent gallstone-related complications in patients with mild gallstone pancreatitis, with a very low risk of cholecystectomy-related complications.

FURTHER READING

- Hart PA et al. Acute and chronic pancreatitis, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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26 Acute Kidney Injury

KEY POINTS

1. Acute kidney injury (AKI) occurs when impairment of kidney filtration and excretory function over days to weeks results in the retention of nitrogenous and other waste products normally cleared by the kidney. AKI complicates 5–7% of acute-care hospital admissions and up to 30% of admissions to the ICU.
2. Many patients with AKI present with symptoms related to the underlying cause, rather than the kidney injury itself. In severe cases, peripheral and pulmonary edema may be present causing dyspnea and/or hypoxemia. AKI can be complicated by the uremia syndrome, including encephalopathy, nausea, vomiting, anorexia, pericarditis, muscle cramps, bleeding, asterixis, and peripheral neuropathies.
3. AKI is defined as an abrupt (< 48 h) increase in the SCr ≥ 0.3 mg/dL, or an increase in SCr ≥ 1.5 times from baseline within 1 week, or urinary output < 0.5 mL/kg/h for ≥ 6 h. Additional useful lab tests to help establish an etiology of the AKI include a UA and urine sediment, serum sodium, urine creatinine, and urine sodium. A renal ultrasound and postvoid residual are helpful imaging tests to visualize kidney and bladder anatomy.
4. AKIs are commonly categorized into prerenal, intrinsic, and postrenal groups. This categorization helps narrow the etiologies of the underlying condition causing the AKI. Management strategies highly depend on the underlying cause of AKI. In all cases of AKI, optimization of hemodynamics, fluid status, and nutrition; correction of electrolytes and acid-base abnormalities; and either discontinuing or avoiding nephrotoxin agents are important strategies.
5. If the kidney function is not improved over time, complications of hypervolemia (including pulmonary edema), uremia, electrolyte abnormalities (e.g., hyperkalemia and hyponatremia), metabolic acidosis, pericarditis, and dysrhythmias can occur. AKIs are associated with an increased risk of in-hospital and long-term mortality. The morbidity of AKI in patients admitted to the ICU exceeds 50%.

EPIDEMIOLOGY & DEFINITIONS

AKI occurs when impairment of kidney filtration and excretory function over days to weeks results in the retention of nitrogenous and other waste products normally cleared by the kidney. AKI is not a single disease but rather a designation for a heterogeneous group of conditions that share common diagnostic features (an increase in filtration markers [SCr or cystatin C]) often associated with a reduction in urine volume. AKI is a clinical diagnosis, not a structural one.

AKI complicates 5–7% of acute-care hospital admissions and up to 30% of admissions to the ICU. The incidence of AKI has grown more than fourfold in the United States since 1998 and is estimated to have a yearly incidence of 500 per 100,000 population, higher than the yearly incidence of stroke. Determining the difference between an AKI and CKD is difficult, as no set of tests can rule out AKI superimposed on CKD. The electronic medical record is being utilized for automated alerts to identify AKI and artificial intelligence approaches for AKI prediction (areas under active investigation).

Acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO]) definition: an abrupt (< 48 h) increase in the SCr ≥ 0.3 mg/dL, or increase in SCr ≥ 1.5 times from baseline within 1 week, or urinary output < 0.5 mL/kg/h for ≥ 6 h.

CLINICAL VIGNETTE

A 36-year-old man presents to the ED with progressively worsening pain, weakness, and swelling in his arms, chest, and legs over the past 2 days. He states these symptoms began the day after he started a workout plan that included weightlifting and running on a treadmill. The last time he exercised was 10 years ago. He also has dark-colored urine and has urinated less in the last day. On physical exam, he is afebrile, heart rate is 100 beats/min, respiratory rate is 16 breaths/min, BP is 140/82 mm Hg, and oxygen saturation is 96% on room air. His biceps, triceps, pectoralis majors, and quadriceps are taut on exam without blistering and are mildly tender to palpation. The pulses in his distal arms and legs are strong, and he has intact sensation of the hands and feet. A urine sample, taken at the bedside, reveals red-brown urine. Initial lab workup reveals a SCr of 3.4 mg/dL, BUN of 38 mg/dL, and creatine kinase of 25,288 U/L. The ED administers 1 liter of LR.

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GUIDING QUESTIONS

1. What is the underlying etiology of this patient's AKI?
2. What would you expect to find on UA and urinary sediment?
3. How would you manage this patient?

HISTORY

As a provider, you will usually see a high BUN or SCr on lab data, prompting an investigation of the cause of the abnormalities. AKI can range from asymptomatic to severe. It is helpful to know the causes of prerenal, intrinsic, and postrenal AKI to help you narrow your history, as the differential of AKI is vast. Assessing prior SCr levels as a baseline is important.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated Signs/symptoms—or use your preferred mnemonic)
  - The presentation in patients with AKI is variable, given its many etiologies
- Dehydration? Vomiting? Diarrhea? Thirst?
  - Prerenal causes of AKI from volume depletion
- Polyuria?
  - Can occur from relief of postrenal obstruction, prerenal from HF, or in the setting of glycosuria from uncontrolled diabetes
- Reduced urine output (oliguria) or lack of urine output (anuria)?
  - Markers of potential severity of AKI
  - Complete anuria is uncommon early in the course of AKI except in
    - Complete urinary tract obstruction
    - Renal artery occlusion
    - Overwhelming septic shock
    - Severe ischemic AKI
    - Severe proliferative glomerulonephritis or vasculitis
- What color is the urine?
  - Red or brown urine may be seen with and without hematuria
  - If the color persists in the supernatant after centrifugation, then pigment nephropathy from rhabdomyolysis or hemolysis should be suspected
- Hematuria?
  - Can be a sign of intrinsic or postrenal AKI
- Recent procedures?
  - Where? On the genitourinary system?
- Trouble urinating? Straining when urinating?
  - Signs of a postrenal AKI and potentially needing a Foley catheter
- If they have a chronic Foley catheter, has it been draining normally?
  - Inquire about the cause of the chronic Foley; if it is obstructed this can change management
- Recent illness?
  - Can be a sign of dehydration, or some infections can cause prerenal or intrinsic AKI
- Fever?
  - Can lead to insensible losses leading to prerenal AKI
- Recent excessive exercise and muscle pain?
  - Rhabdomyolysis can cause intrinsic AKI when severe
- Purpura?
  - Can be a sign of systemic vasculitis with glomerulonephritis (e.g., IgA vasculitis [also called Henoch-Schönlein purpura])
- Colicky flank pain radiating to the groin?
  - Kidney stones can cause obstruction and postrenal AKI
- Suprapubic pain/distension?
  - Bladder obstruction causing postrenal AKI needs to be ruled out
- Hearing loss?
  - AKI/CKD in Alport's syndrome causes hearing loss
- Hemoptysis?
  - Could be a sign of systemic vasculitis with glomerulonephritis (e.g., anti–glomerular basement membrane disease)

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- Pregnancy?
  - Preeclampsia can cause AKI
- Arthralgias and rash?
  - Potential signs of allergic interstitial nephritis or vasculitis

PAST MEDICAL HISTORY

- History of kidney disease?
  - When was it diagnosed?
  - How severe (CKD stage)?
  - What is the baseline SCr?
- History of HF, liver disease, or nephrotic syndrome?
  - All can be associated with reductions in renal blood flow and/or alterations to hemodynamics, resulting in a reduction of the GFR
- History of benign prostatic hyperplasia?
  - How severe is it?
  - How is it being treated?
- Chronic indwelling Foley catheter?
  - Why do you have a Foley catheter?
- History of chronic neurologic disorder?
  - Risk factor for postrenal AKI
- History of kidney stones?
  - Potential cause of postrenal AKI
- History of vascular disease?
  - Risk factor for renal artery disease
- History of autoimmune disease?
  - AKI can be from a worsening of the underlying autoimmune disease (e.g., SLE)

SURGICAL HISTORY

- Any recent procedures?
- Genitourinary procedures?

SOCIAL HISTORY

- Use of alcohol or recreational drugs, smoking
- Occupation
- Living situation
- Sexual history

MEDICATIONS

- A careful medication review, including dosages, is necessary
- Many medications can cause AKI, including, but not limited to
  - Antibiotics
    - Aminoglycosides
    - Vancomycin
    - Cephalosporins
    - β-Lactams
    - Amphotericin
    - Sulfonamides
    - Amphotericin
  - Antineoplastics
    - Cisplatin
    - Methotrexate
  - Hydroxyethyl starch solution
  - Metformin
  - NSAIDs
  - Proton pump inhibitors

PHYSICAL EXAM

Assessment of the volume status in patients with AKI is important. Suprapubic examination is necessary in all patients in case there is bladder distention from obstruction. A thorough skin and joint exam may help identify systemic causes of the AKI.

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- Vital signs
  - Orthostatic BP
  - Fever can be a potentially important clue to the etiology of AKI
  - Can be tachycardic in any type of AKI (e.g., sepsis causing prerenal or intrinsic, intense pain from bladder obstruction in postrenal)
- Volume status
  - Assess the JVP, skin turgor, mucous membranes, lower extremities for edema, and capillary refill time
  - Volume status can help determine if decreased effective arterial blood flow is present (decreasing perfusion to kidneys)
- Cardiovascular
  - JVP exam
  - Assess for uremic pericarditis with the presence of a pericardial friction rub
- Respiratory
  - Pulmonary edema can occur with severe AKI when fluid accumulates rapidly
  - Clues to the etiology of AKI may be observed (e.g., bilateral pleural effusions in HF)
- GI
  - Perform a full abdominal exam
  - Assess the bladder for tenderness and distention
  - A tense abdomen can be a sign of abdominal compartment syndrome from bladder distention
- Genitourinary
  - If suspecting benign prostatic hyperplasia, perform digital rectal exam
- Neurologic
  - Assess for asterixis (sign of symptomatic uremia)
- Skin
  - Evaluate for purpura or livedo reticularis
  - Evaluate for findings of systemic vasculitis with glomerulonephritis or atheroembolic disease
- HEENT
  - Assess hearing for Alport's syndrome

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

There are several schemas to help determine the cause of an AKI. The three major classifications of AKI are generally separated into prerenal, intrinsic, and postrenal causes (Fig. 26-1). Prerenal AKIs are the most common form of AKI.

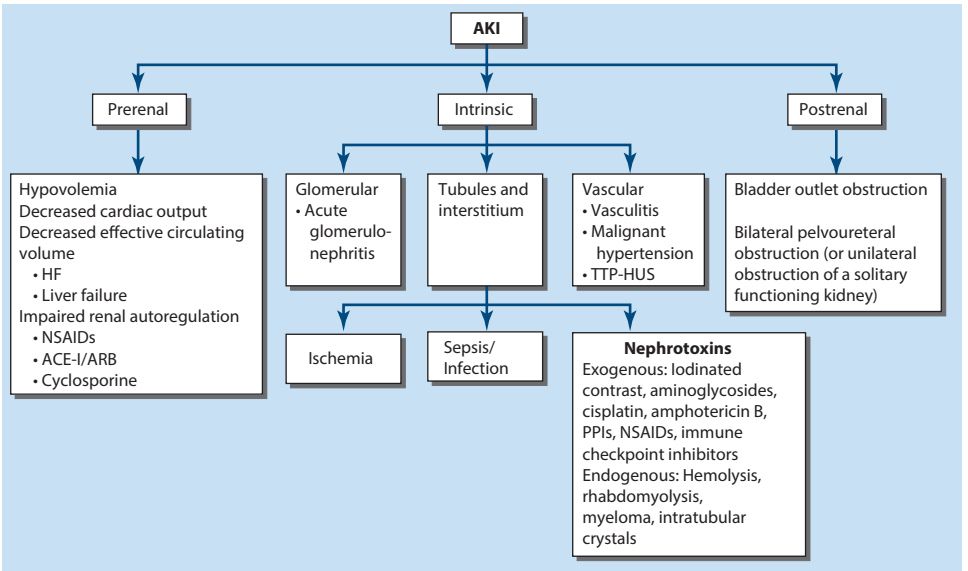

FIGURE 26-1 Classification of the major causes of AKI. PPIs, proton pump inhibitors; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome. (Reproduced with permission from Waikar SS, Bonventre JV. Acute kidney injury, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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After determining if the AKI is prerenal, intrinsic, or postrenal, the history, physical exam, lab results (see Diagnostic Tests section for more details), and corresponding urine study findings can help identify more specific causes (Table 26-1).

Intrinsic AKI can be categorized based on the anatomic and physiologic location of the injury (Fig. 26-2).

TABLE 26-1 Major Causes, Clinical Features, and Diagnostic Studies for Prerenal and Intrinsic AKI

ETIOLOGY	CLINICAL FEATURES	LAB FEATURES AND COMMENTS
Prerenal AKI	History of poor fluid intake or fluid loss (hemorrhage, diarrhea, vomiting, sequestration into extravascular space); NSAID/ACE-I/ARB; HF; evidence of volume depletion (tachycardia, absolute or postural hypotension, low JVP, dry mucous membranes), decreased effective circulatory volume (cirrhosis, HF)	BUN/SCr ratio > 20, FeNa < 1%, hyaline casts in urine sediment, urine specific gravity > 1.018, urine osmolality > 500 mOsm/kg Low FeNa, high specific gravity and osmolality may not be seen in the setting of CKD, diuretic use. Response to restoration of hemodynamics is most diagnostic
Sepsis-associated AKI	Sepsis, sepsis syndrome, or septic shock; overt hypotension not always seen in mild to moderate AKI	Positive culture from normally sterile body fluid or other test confirming infection; urine sediment often contains granular casts, renal tubular epithelial cell casts FeNa may be low (< 1%), particularly early in the course, but is usually > 1% with osmolality < 500 mOsm/kg
Ischemia-associated AKI	Systemic hypotension, often superimposed upon sepsis and/or reasons for limited renal reserve such as older age, CKD	Urine sediment often contains granular casts, renal tubular epithelial cell casts; FeNa typically > 1%
Nephrotoxin-Associated AKI: Endogenous		
Rhabdomyolysis	Traumatic crush injuries, seizures, immobilization, excessive exercise	Elevated myoglobin, creatine kinase; urine heme positive with few RBCs FeNa may be low (< 1%)
Hemolysis	Recent blood transfusion with transfusion reaction	Anemia, elevated LDH, low haptoglobin FeNa may be low (< 1%)
Tumor lysis	Recent chemotherapy	Hyperphosphatemia, hypocalcemia, hyperuricemia
Multiple myeloma	Age > 60 years, constitutional symptoms, bone pain	Monoclonal spike in urine or serum electrophoresis; elevated serum free light chains, low anion gap; anemia Bone marrow or renal biopsy can be diagnostic
Nephrotoxin-Associated AKI: Exogenous		
Contrast nephropathy	Exposure to iodinated contrast	Characteristic course is rise in SCr within 1–2 d, peak within 3–5 d, recovery within 7 d FeNa may be low (< 1%)
Tubular injury	Aminoglycoside antibiotics, cisplatin, tenofovir, vancomycin, zoledronate, ethylene glycol, aristolochic acid, and melamine (to name a few)	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically > 1% Can be oliguric or nonoliguric
Other Causes of Intrinsic AKI		
Glomerulonephritis/ vasculitis	Variable features include skin rash, arthralgias, sinusitis (AGBM disease), lung hemorrhage (AGBM, ANCA, lupus), recent skin infection or pharyngitis (poststreptococcal), thrombotic microangiopathies including those related to drugs, such as cocaine, anti-VEGF agents, genetic abnormalities of the complement pathways	ANA, ANCA, Anti-GBM antibody, hepatitis serologies, cryoglobulins, blood culture, complement abnormalities, ASO titer (abnormalities of these tests depending on etiology) Kidney biopsy may be necessary

(*Continued*)

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TABLE 26-1 Major Causes, Clinical Features, and Diagnostic Studies for Prerenal and Intrinsic AKI (*Continued*)

ETIOLOGY	CLINICAL FEATURES	LAB FEATURES AND COMMENTS
Tubulointerstitial nephritis	Drugs are responsible for ~75% of the biopsy-proven acute interstitial nephritis, which involves tubules in most cases. Examples of causes include antibiotics, PPIs, immune checkpoint inhibitors. Non-drug-related causes include tubulointerstitial nephritis-uveitis (TINU) syndrome, lupus, viral infection (e.g., COVID, HIV, and hantavirus), and *Legionella* infection	Eosinophilia, sterile pyuria; often nonoliguric Urine eosinophils have limited diagnostic accuracy; kidney biopsy may be necessary
TTP/HUS	Neurologic abnormalities and/or AKI; recent diarrheal illness; use of calcineurin inhibitors; pregnancy or postpartum; spontaneous	Schistocytes on peripheral blood smear, elevated LDH, anemia, thrombocytopenia "Typical HUS" refers to AKI with a diarrheal prodrome, often due to Shiga toxin released from *Escherichia coli* or other bacteria; "atypical HUS" is due to inherited or acquired complement dysregulation. Diagnosis may involve screening for ADAMTS13 activity, Shiga toxin–producing *E. coli*, genetic evaluation of complement regulatory proteins, and kidney biopsy
Atheroembolic disease	Recent manipulation of the aorta or other large vessels; may occur spontaneously or after anticoagulation; retinal plaques, palpable purpura, livedo reticularis, GI bleed	Hypocomplementemia, eosinophiluria (variable), variable amounts of proteinuria Skin or kidney biopsy can be diagnostic
Postrenal AKI	History of kidney stones, prostate disease, obstructed bladder catheter, retroperitoneal or pelvic neoplasm	No specific findings other than AKI; may have pyuria or hematuria Imaging with CT or ultrasound

AGBM, anti–glomerular basement membrane; ANCA, antineutrophilic cytoplasmic antibody; ASO, antistreptolysin O; FeNa, fractional excretion of sodium; ; PPIs, proton pump inhibitors; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome; VEGF, vascular endothelial growth factor.
Reproduced with permission from Waikar SS, Bonventre JV. Acute kidney injury, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

DIAGNOSTIC TESTS

LABS

- BMP
  - Certain patterns of the rise and fall of the SCr can help aid diagnosis
    - Prerenal AKI typically leads to modest rises in SCr that return to baseline with improvement in hemodynamic status
    - Atheroembolic disease usually manifests with more subacute rises in SCr
      - Severe AKI with rapid increases in SCr can occur in this setting, however
    - Epithelial cell toxins (e.g., aminoglycosides, cisplatin, contrast) have a characteristically delayed rise in SCr delayed for 3–5 days to 2 weeks after initial exposure
  - Elevated BUN:SCr ratio > 20:1 suggests a prerenal cause of AKI
  - Assess for electrolyte abnormalities as complications of AKI
    - Hyperkalemia
    - Hyperphosphatemia
    - Hypocalcemia
  - Evaluate for hyperglycemia (is diabetic ketoacidosis possible?)
  - An elevated anion gap may be increased with any cause of uremia
    - The co-occurrence of an increased anion gap and an osmolal gap may suggest ethylene glycol poisoning
  - Low anion gap may be a clue to multiple myeloma causing AKI
- Cystatin C
  - Increasingly used to estimate eGFR and may have a role in AKI diagnosis
    - Both SCr and cystatin C have distinct non-eGFR determinants that can influence their sensitivity and specificity

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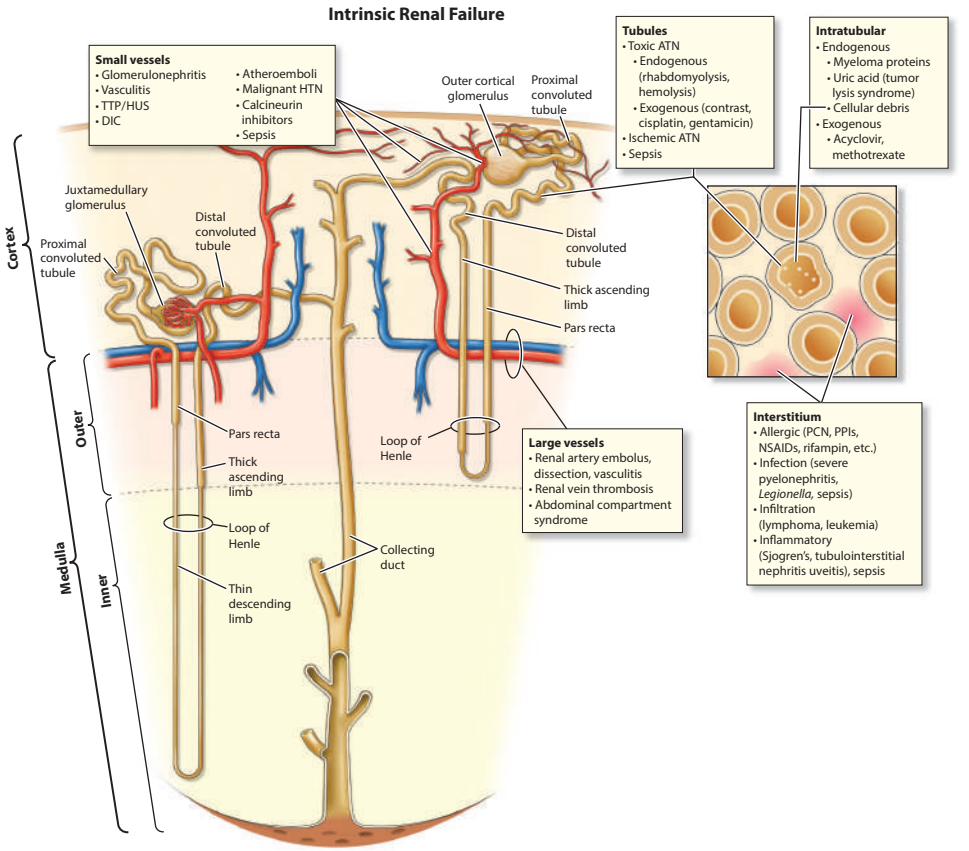

FIGURE 26-2 Major causes of intrinsic AKI. ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertension; PCN, penicillin; PPIs, proton pump inhibitors; TINU, tubulointerstitial nephritis-uveitis; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. (Reproduced with permission from Waikar SS, Bonventre JV. Acute kidney injury, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- UA and, if indicated to evaluate for a UTI, urine culture
  - Nitrates/leukocyte esterase → infection
  - Proteinuria → sign of kidney damage
    - Patients with AKI and proteinuria on UA need to have the quantity of proteinuria measured
    - Figure 26-3 describes an approach to the etiology of proteinuria after its amount is quantified
  - RBCs → hematuria
    - Patients with hematuria can be evaluated using the schematic in Fig. 26-4
  - No RBCs but "positive blood" → rhabdomyolysis
    - Evaluate the urine myoglobin
      - The finding of myoglobinuria strongly suggests rhabdomyolysis, but its absence does not exclude rhabdomyolysis
  - Eosinophils → acute interstitial nephritis
    - Limited role in diagnosis, as urine eosinophils are found in many other etiologies
- Urinary sediment
  - Basics of casts and potential causes of AKI (see Fig. 26-5 for further details)
    - RBC casts → glomerulonephritis
    - WBC casts → pyelonephritis
    - Muddy brown granular casts → acute tubular necrosis (Fig. 26-6)
    - Waxy casts → CKD
    - Hyaline casts → not a specific finding

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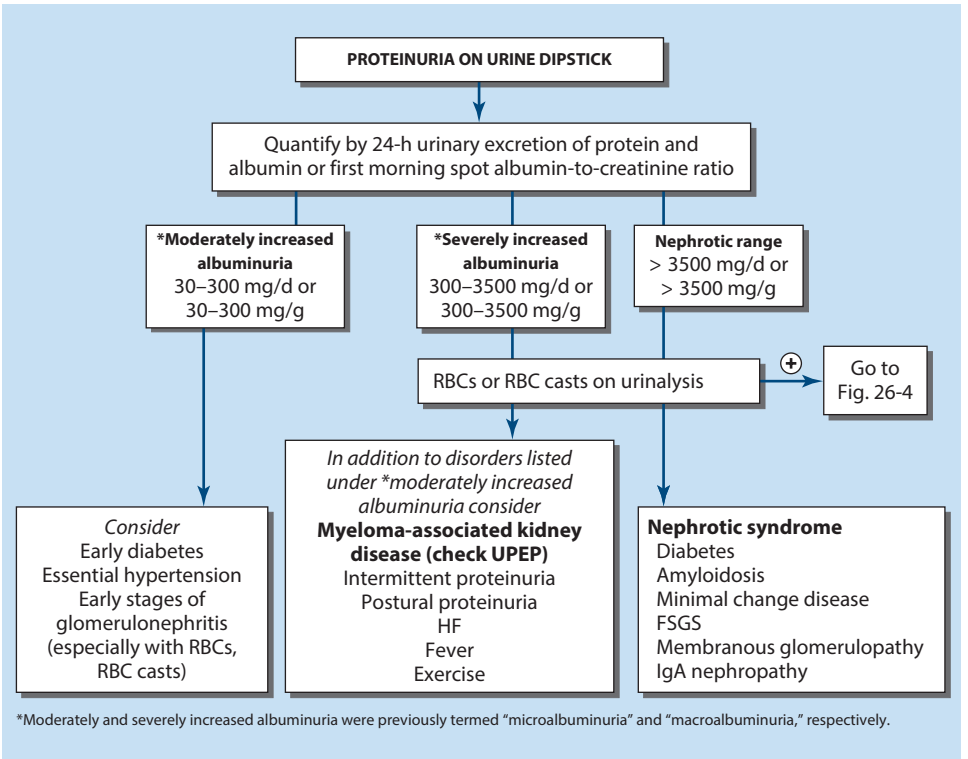

FIGURE 26-3 Approach to the patient with proteinuria. Investigation of proteinuria is often initiated by a positive dipstick on routine urinalysis. Conventional dipsticks detect predominantly albumin and provide a semiquantitative assessment (trace, 1+, 2+, or 3+), which is influenced by urinary concentration as reflected by urine specific gravity (minimum, < 1.005; maximum, 1.030). However, more exact determination of proteinuria should employ a spot morning protein/creatinine ratio (mg/g) or a 24-h urine collection (mg/24 h). FSGS, focal segmental glomerulosclerosis; UPEP, urine protein electrophoresis. (Reproduced with permission from Mount DB. Azotemia and urinary abnormalities, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Several lab and urine markers can help differentiate a prerenal versus an intrinsic renal AKI (Table 26-2)
- FeNa
  - Fraction of filtered sodium not reabsorbed by tubules
  - Calculated by measuring the
    - SCr
    - Serum sodium
    - Urine creatinine
    - Urine sodium
  - Reflects the kidney's sodium reabsorptive ability and factors affecting tubular function
    - Determinants of FeNa include sodium intake, intravascular volume status, GFR, diuretic use, and tubular integrity
    - Best utility is in oliguric patients without CKD not on diuretics
    - < 1% in prerenal AKI from avid sodium reabsorption
      - Diuretics can cause the FeNa to be > 1% despite hypovolemia
      - Can be < 1% in non-prerenal AKI states (e.g., early glomerulonephritis)
        - Therefore, the FeNa is not diagnostic of prerenal AKI by itself
    - Low FeNa suggests, but does not confirm, volume depletion (should not be the sole guide for fluid management)
    - FeNa > 1% indicates ischemic intrinsic AKI from tubular injury and impaired sodium reabsorption
      - Some ischemic intrinsic or nephrotoxic AKIs (sepsis, early rhabdomyolysis, contrast nephropathy) may present with FeNa < 1%

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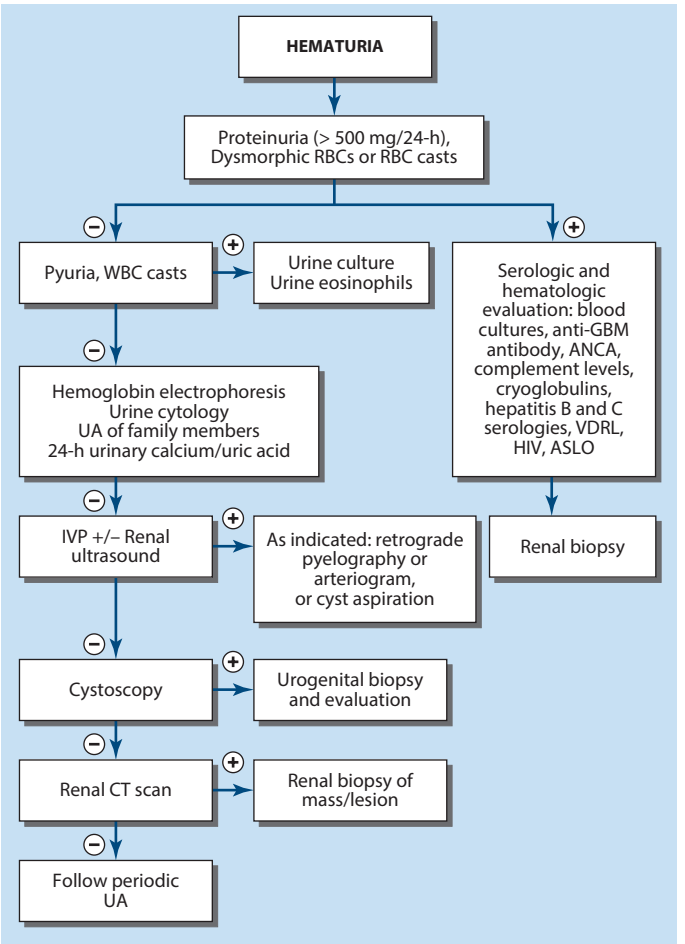

FIGURE 26-4 Approach to the patient with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; GBM, glomerular basement membrane; IVP, intravenous pyelography; VDRL, Venereal Disease Research Laboratory. (Reproduced with permission from Mount DB. Azotemia and urinary abnormalities, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Urine osmolality
  - Measures the ability of the kidney to produce a concentrated urine (dependent on good blood flow and tubular function)
  - Urine osmolality > 500 mOsm/kg usually reflects prerenal AKI
    - Reflects intact medullary concentration gradient and elevated vasopressin leading to passive water reabsorption in the collecting duct and appropriate concentration of urine
- CBC
  - Evaluate for anemia, thrombocytopenia, and leukocytosis
    - Severe anemia with AKI in the absence of bleeding may reflect
      - Hemolysis
      - Multiple myeloma
      - Thrombotic microangiopathy (e.g., hemolytic uremic syndrome [HUS] or thrombotic thrombocytopenic purpura [TTP])
    - Thrombocytopenia may be a clue to thrombotic microangiopathy
    - Leukocytosis may indicate prerenal or intrinsic AKI from sepsis
  - Peripheral eosinophilia can accompany
    - Interstitial nephritis

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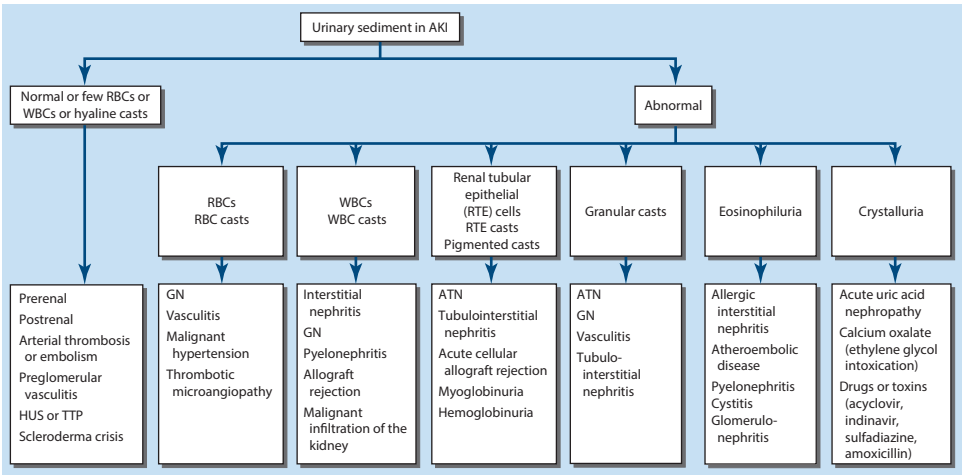

FIGURE 26-5 Interpretation of urinary sediment findings in AKI. ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura. (Adapted from L Yang, JV Bonventre: Diagnosis and clinical evaluation of acute kidney injury. In Comprehensive Nephrology, 4th ed. J Floege et al [eds]. Philadelphia, Elsevier, 2010.) (Reproduced with permission from Waikar SS, Bonventre JV. Acute kidney injury, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

        - Atheroembolic disease
        - Polyarteritis nodosa
        - Eosinophilic granulomatosis with polyangiitis
- Peripheral smear
    - Evaluate for schistocytes, which may indicate
        - HUS, TTP, and disseminated intravascular coagulation (DIC)
        - Pre-eclampsia
        - Antiphospholipid antibody syndrome
        - Malignant hypertension
        - Scleroderma renal crisis
- LDH and haptoglobin
    - Abnormalities are seen in DIC, TTP, HUS, pre-eclampsia
- ANA and antineutrophil cytoplasmic antibodies (ANCAs) if suspicious for
    - SLE
    - Granulomatosis with polyangiitis

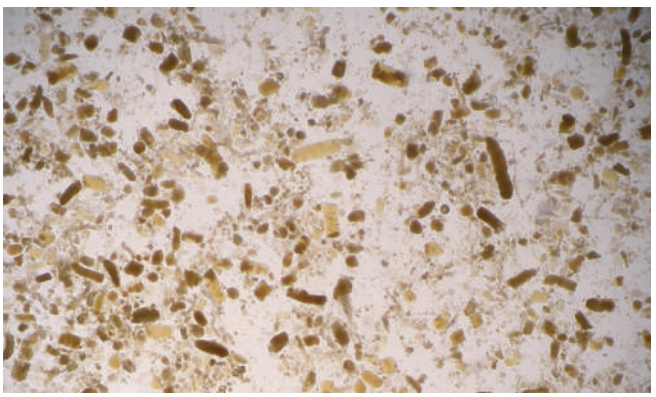

FIGURE 26-6 Urine microscopy, showing muddy brown casts of acute tubular necrosis (ATN). (Courtesy of Dr. Serban Nicolescu.) (Modified with permission from Singh AK et al. Acute kidney injury, in *Principles and Practices of Hospital Medicine,* 2nd ed, SC McKean et al (eds). New York, McGraw Hill, 2017.)

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TABLE 26-2 Urine Diagnostic Indices in Differentiation of Prerenal versus Intrinsic Kidney Injury

DIAGNOSTIC INDEX	TYPICAL FINDINGS	
	PRERENAL AZOTEMIA	INTRINSIC RENAL AZOTEMIA
Fractional excretion of sodium (%)[a] $U_{Na} \times P_{Cr}/P_{Na} \times U_{Cr} \times 100$	< 1	> 1
Urine sodium concentration (mEq/L)	< 10	> 20
Urine creatinine to plasma creatinine ratio	> 40	> 20
Urine urea nitrogen to plasma urea nitrogen ratio	> 8	< 3
Urine specific gravity	> 1.018	< 1.015
Urine osmolality (mosmol/kg H_2O)	> 500	< 300
Plasma BUN/creatinine ratio	> 20	< 10–15
Renal failure index $U_{Na}/U_{Cr}/P_{Cr}$	< 1	> 1
Urinary sediment	Hyaline casts	Muddy brown granular casts

[a]Most sensitive indices.
P_{Cr}, plasma creatinine concentration; P_{Na}, plasma sodium concentration; U_{Cr}, urine creatinine concentration; U_{Na}, urine sodium concentration.
Reproduced with permission from Jameson JL et al. Acute renal failure, in *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). New York, McGraw Hill Education, 2020.

    - Microscopic polyangiitis
    - Eosinophilic granulomatosis with polyangiitis
- Antiglomerular antibodies if suspecting anti–glomerular basement membrane disease
- Immunoelectrophoresis or free light chain assay if multiple myeloma suspected
- Cryoglobulins if suspecting mixed cryoglobulinemia
- Creatine kinase and uric acid if suspecting rhabdomyolysis or tumor lysis syndrome

IMAGING

- Bladder and renal ultrasound and CT abdomen/pelvis
    - Renal ultrasound is the initial imaging of choice
        - Small shrunken kidneys are observed in CKD
        - Asymmetric kidneys can be a sign of unilateral renal artery stenosis
        - Hydronephrosis may indicated obstruction which then would need to be confirmed with a CT
        - Enlarged kidneys in a patient with AKI suggests the possibility of allergic interstitial nephritis or infiltrative disease
- Postvoid residual if suspect bladder obstruction and urinary retention
- Vascular imaging may be useful if venous or arterial obstruction suspected

PROCEDURE

- Renal biopsy is performed if
    - All other workup fails to identify an etiology
    - Glomerulonephritis or vasculitis is suspected

DIAGNOSTIC APPROACH

After lab and ultrasound studies result, the causes of AKI can further be delineated (Fig. 26-7).

MANAGEMENT

SEVERITY OF AKI

- Based on kidney lab results and urine output, the severity of the AKI using Kidney Disease: Improving Global Outcomes' (KDIGO's) definition can be grouped into three stages
    - Stage 1
        - SCr 1.5–1.9 times above baseline or ≥ 0.3 mg/dL increase
        - Urine output < 0.5 mL/kg/h for 6–12 h
    - Stage 2
        - SCr 2.0–2.9 times above baseline
        - Urine output < 0.5 mL/kg/h for ≥ 12 h
    - Stage 3
        - SCr 3.0 times above baseline, or

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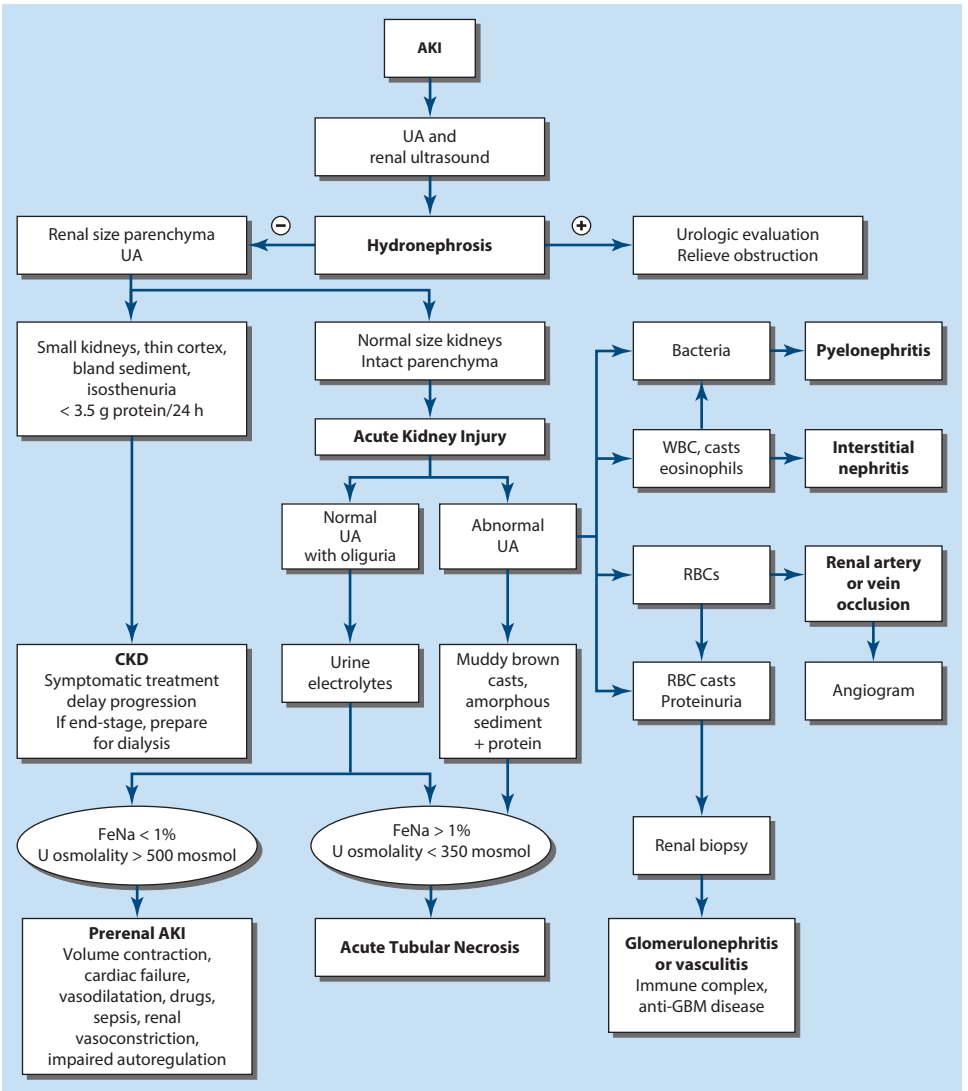

FIGURE 26-7 Approach to the patient with AKI. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane; U, urine. (Reproduced with permission from Mount DB. Azotemia and urinary abnormalities, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Increase in SCr to ≥ 4.0 mg/dL
- Initiation of renal replacement therapy
- In patients < 18 years of age, a decrease in eGFR to < 25 mL/min per 1.73 m^2)

- Urine output < 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

GENERAL PRINCIPLES IN THE MANAGEMENT OF ALL AKIs

- Treat the underlying cause of the AKI
  - Review history, medications, fluid balance, and exposure to contrast
- Optimize hemodynamics with fluids or vasopressors
- Correct fluid, electrolyte, and acid-base abnormalities daily
- Optimize nutrition status
  - Patients with AKI should achieve a total energy intake of 20–30 kcal/kg/d

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- Protein intake should vary, depending on the severity of AKI
  - 0.8–1.0 g/kg/d in noncatabolic AKI without the need for dialysis
  - 1.0–1.5 g/kg/d in patients on dialysis
  - Up to a maximum of 1.7 g/kg/d if hypercatabolic and receiving continuous renal replacement therapy
- Discontinue nephrotoxic medications, including but not limited to
  - NSAIDs
  - ACE-Is/ARBs
  - Aminoglycosides
  - Amphotericin
  - Cisplatin
- Adjust medication doses for renal clearance
- Daily monitoring of weight and Ins and Outs (*I*s/*O*s)
- Volume and hemodynamic management
  - Hypovolemia
    - Administer IV fluid boluses
      - LR is preferred over NS to avoid hyperchloremic acidosis
    - Monitor response to fluids via urine output, BP, and lactate monitoring
  - Hypervolemia
    - Restrict fluids and administer loop diuretics
    - Combine loop diuretics + a thiazide for diuretic synergy in resistant cases
    - Dialysis is indicated if a patient develops refractory pulmonary edema
  - Hypotension and shock
    - Vasopressors (norepinephrine is first choice in septic shock)
    - Avoid dopamine (it is not renoprotective and increases the risk of dysrhythmias)
    - Target a mean arterial pressure of ≥ 65 mm Hg
- Consider a Foley catheter if suspecting postrenal AKI
  - Monitor how much urine is produced, as you may need to replace that amount with fluids to prevent a prerenal AKI from developing
    - Sometimes occurs in postobstructive AKI from excessive diuresis after the obstruction is relieved
- In cases of oliguric AKI
  - The urinary flow rate in response to bolus IV furosemide 1.0–1.5 mg/kg can be used as a prognostic test
    - Urine output < 200 mL over 2 h after IV furosemide may identify patients at higher risk of progression to more severe AKI and the need for renal replacement therapy
- After the AKI has improved, consider ACE-I/ARB therapy
  - A study demonstrated lower mortality associated with ACE-I/ARB use in patients with diabetes, proteinuria, and AKI, regardless of recovery
  - Results favored earlier ACE-I/ARB initiation [1]
- General questions to ask
  - Is the patient septic and have borderline shock?
    - Administer fluids and antibiotics
  - Does the patient have HF and is hypervolemic
    - Administer IV furosemide
  - Does the patient have multiple sclerosis (or another neurologic disease), a distended, painful bladder, and the inability to void?
    - Insert a Foley catheter

PREVENTIVE STRATEGIES TO DECREASE THE RISK OF AKI

- Hydrate before and after IV contrast
  - Administer LR at 1 mL/kg/h beginning 1 h before contrast administration and continuing for 3–12 h after
- Use the lowest possible contrast dose with iso-osmolar agents
- Avoid nephrotoxins in high-risk patients
- Monitor kidney function daily in ICU and postop patients

PRERENAL AKI

- There is no parenchymal damage in prerenal AKI
- It is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored
- Discontinue potential precipitating medications
- If blood loss → replace with PRBCs

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- Isotonic crystalloid, or fluid/sodium restriction and diuretics depending on fluid status
  - If hypovolemic, administer IV fluids (LR preferred)
  - Bicarbonate-containing solutions like dextrose water with 150 mEq sodium bicarbonate can be used in those with metabolic acidosis
  - If hypervolemic, administer IV furosemide (e.g., in acute HF)
- Treat underlying HF causing cardiorenal syndrome, cirrhosis causing hepatorenal syndrome, or sepsis (see **Chaps. 20**, **24**, **and 36**, respectively)

INTRINSIC AKI

- Identify and treat the underlying cause
- Remove offending agents (Table 26-1)
- Rhabdomyolysis
  - Aggressive fluids and supportive care
  - May need diuretics to help augment urinary output
- Tumor lysis syndrome
  - Aggressive fluids and allopurinol and/or rasburicase administration
- Multiple myeloma
  - Treat with cancer-directed therapies
- Vasculitis/glomerulonephritis/hemolytic anemia
  - Treatment depends on the cause
- Acute tubular necrosis
  - Supportive care and optimize hemodynamics
- Glomerulonephritis
  - May need steroids, cytotoxic medications, and/or plasmapheresis depending on the cause
- Acute interstitial nephritis
  - Stop the offending agent and administer steroids if severe
- Vascular causes
  - Anticoagulation for thrombosis
  - Plasmapheresis for thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) (see **Chap. 33**)
  - Tight BP control for malignant hypertension
- Scleroderma renal crisis
  - Treat with ACE-Is (e.g., captopril)

POSTRENAL AKI

- Postrenal AKI occurs when
  - The normally unidirectional flow of urine is acutely blocked either partially or totally
  - This leads to increased retrograde hydrostatic pressure and interference with glomerular filtration
- Normal urinary flow rate does not rule out the presence of partial obstruction
  - The GFR is normally two orders of magnitude higher than the urinary flow rate and hence a preservation of urine output may be misleading in hiding the postrenal partial obstruction
  - For moderate to severe AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr
  - Unilateral obstruction may cause AKI in the setting of significant underlying CKD with loss of renal reserve or, in rare cases, from reflex vasospasm of the contralateral kidney
- The site of obstruction defines the treatment approach
  - Transurethral or suprapubic catheterization may be all that is needed for urethral strictures or functional bladder impairment
  - Percutaneous nephrostomy tube placement or ureteral stents may be used for ureteric obstructions
- Relief of obstruction may be followed by an appropriate diuresis for several days
  - In rare cases, severe polyuria persists due to tubular dysfunction and may require continued administration of IV fluids (to prevent a superimposed prerenal AKI) and electrolytes for a period of time

DIALYSIS INDICATIONS

- *AEIOU*
  - *A*cidosis: pH < 7.1
  - *E*lectrolyte disorders: hyperkalemia (> 6.5 mEq/L or rapidly increasing, tumor lysis syndrome)
  - *I*ntoxication: methanol, ethylene glycol, lithium, salicylates
  - *O*verload (fluid): pulmonary edema which is refractory to diuretics
  - *U*remia (symptomatic): pericarditis, encephalopathy, bleeding, asterixis

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- When to start dialysis is not straightforward, even if the above criteria are met
- You must attempt medical management prior to initiating dialysis
- Late initiation of dialysis carries the risk of avoidable volume overload and electrolyte and metabolic complications
- Early initiation of dialysis, however, may expose individuals to
    - Catheters from invasive procedures
    - Risk of infection
    - Bleeding
    - Procedural complications
    - Hypotension
- In randomized controlled trials, earlier versus later initiation of dialysis has not been shown to improve survival and may increase the risk of adverse events
- The initiation of dialysis should not await the development of a life-threatening complication of renal failure
- One of the major complications of hemodialysis is hypotension, which can perpetuate AKI by causing ischemic injury to the recovering organ
    - Continuous renal replacement therapy (CRRT) is often preferred in patients with
        - Severe hemodynamic instability (to avoid hypotension)
        - Cerebral edema
        - Significant volume overload
- There are two trials in ICU patients that showed different results on when to start dialysis in critically ill patients
    - Among ICU patients with AKI, there is no mortality difference between early versus delayed renal replacement therapy (RRT) [2]
    - Among critically unwell patients with AKI, early RRT compared with delayed initiation of RRT reduced mortality over the first 90 days [3]
    - Overall, nephrology consultation is important in deciding when/if dialysis should be initiated
- A trial was performed in critically ill patients and severe AKI specifically associated with septic shock
    - There was no significant difference in overall mortality at 90 days between patients assigned to an early strategy for the initiation of RRT and those who were assigned to a delayed strategy [4]

COMPLICATIONS

- Uremia
    - Seen with BUN > 100 mg/dL causing mental status changes, pericarditis, and bleeding complications
    - Treat with management of the etiology of AKI and possibly dialysis
- Malnutrition
    - AKI is often a severely hypercatabolic state
    - Provide 20–30 kcal/kg/d and 0.8–1.0 g/kg/d of protein in the diet
- Hypervolemia
    - Expansion of the extracellular fluid is a major complication of oliguric and anuria AKI
    - Treat with salt and water restriction, diuretics, and dialysis if severe
- Anemia and bleeding
    - Administer desmopressin for uremic bleeding and IV iron
    - Among patients undergoing hemodialysis, a high-dose IV iron regimen administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered [5]
- Hyponatremia
    - Restrict free water if hypervolemic and administer IV diuretics
    - Administer IV fluids if hypovolemic
- Hyperkalemia
    - Restrict dietary potassium
    - Stop potassium-sparing diuretics (ACE-Is, ARBs, spironolactone)
    - Stop NSAIDs
    - Administer IV calcium gluconate, insulin + glucose, inhaled β_2-agonists, if ECG changes are present
- Metabolic acidosis
    - Administer $NaHCO_3^-$ only if pH < 7.2 to keep serum HCO_3^- > 15 mg/L
- Hyperphosphatemia
    - Decrease dietary phosphate and administer calcium acetate
- Hypocalcemia
    - Can lead to perioral paresthesias, muscle cramps, seizures, carpopedal spasms, and prolongation of the QTc interval
    - If symptomatic give calcium carbonate or calcium gluconate

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- Hypermagnesemia
  - Stop magnesium-containing antacids
- Hyperuricemia
  - If tumor lysis syndrome is present, administer IV fluids, allopurinol, and/or rasburicase
- Infections
  - Patients with AKI are more susceptible to infections
  - Treat the underlying infection
- Dysrhythmias, pericarditis, and pericardial effusion
  - Treat electrolyte abnormalities; the patient may require dialysis
- Increased risk of later cardiovascular disease events

PROGNOSIS

- AKIs are associated with
  - Significantly increased risk of in-hospital and long-term mortality
  - Longer length of stay
  - Increased costs
- Oliguria in the disease course is associated with worse clinical outcomes
- Intrinsic AKI carries a worse prognosis than pre- and postrenal AKI (except in cardiorenal and hepatorenal syndrome)
- AKI and CKD are interrelated syndromes: when one develops, the other is more likely to occur
- Hospitalized patients who develop AKI have higher morbidity and mortality rates than those who do not develop an AKI
- The morbidity of AKI in those admitted to the ICU exceeds 50% in many studies

PATHOPHYSIOLOGY

- Mechanisms of AKI vary by etiology (**Fig. 26-8**)

PRERENAL AKI

- Caused by inadequate renal plasma flow and increased intraglomerular hydrostatic pressure, impairing the GFR
- There is no structural kidney damage, and the AKI is rapidly reversible if perfusion is restored
- A prolonged prerenal state can lead to ischemia and acute tubular necrosis
- Autoregulatory mechanisms that preserve the GFR
  - Systemic vasoconstriction and renal sodium/water reabsorption maintain BP and perfusion of vital organs
    - Mediated by angiotensin II, norepinephrine, and vasopressin
  - Angiotensin II sustains filtration pressure via efferent arteriole vasoconstriction
  - Vasodilators (prostacyclin, kinins, and nitric oxide [NO]) enhance flow to the kidneys via afferent arteriole vasodilation
  - Tubuloglomerular feedback occurs (as the macula densa senses low solute delivery) further vasodilating the afferent arteriole, partly via NO
  - Autoregulatory responses usually fail once the systolic BP falls below 80 mm Hg
- Factors that impair autoregulation, increasing the risk of prerenal AKI
  - Atherosclerosis
  - Chronic hypertension
  - Aging
  - All lead to hyalinosis and myointimal hyperplasia, causing structural narrowing of the intrarenal arterioles and impaired capacity for renal afferent vasodilation
  - In patients with CKD, the afferent vasodilation mechanism has little reserve capabilities as it is already maximized
  - NSAID use inhibits prostaglandin synthesis, blocking the afferent vasodilation response
  - ACE-Is/ARBs block the efferent vasoconstriction response and decrease glomerular pressure
- HF causing cardiorenal syndrome is described in **Chap. 20**
- Hepatorenal syndrome is described in **Chap. 24**

INTRINSIC AKI

- Results from
  - Direct renal interstitial damage (from medications, infections, and infiltrative/inflammatory processes)

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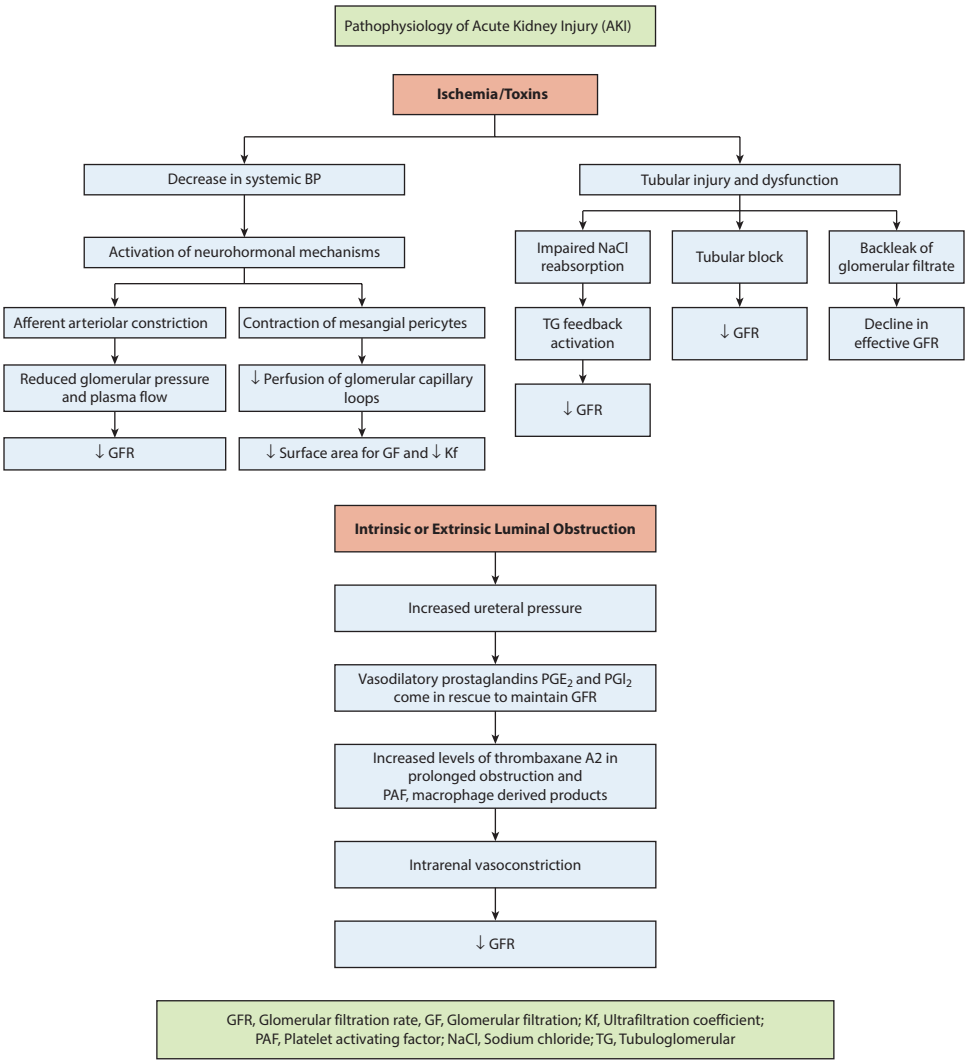

FIGURE 26-8 Pathophysiology of AKI. (Reproduced with permission from Singh AK et al. Acute kidney injury, in *Principles and Practices of Hospital Medicine,* 2nd ed, SC McKean et al (eds). New York, McGraw Hill, 2017.)

  - Disruption of small or large vessels
  - Injury to the tubules with endogenous and exogenous products
- Mechanisms
  - Vascular: small/large vessel disease
  - Tubular: endogenous (myoglobin, hemoglobin, uric acid) or exogenous toxins (aminoglycosides, contrast)
  - Intratubular obstruction: precipitation of crystals or proteins
  - Interstitial: drugs, infections, infiltrative or inflammatory disorders
- The specific pathophysiology varies by cause (and is too extensive for this text)
- Ischemic acute tubular necrosis involves tubular cell injury, loss of polarity, and backleak of filtrate

POSTRENAL AKI

- Due to acute obstruction of urinary outflow (partial or complete), which leads to increased retrograde hydrostatic pressure and interference with glomerular filtration in the glomeruli, causing interstitial edema

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- Pathophysiology
  - Early: afferent dilation causes transient hyperemia
  - Later: intrarenal vasoconstriction from the generation of angiotensin II, thromboxane A2, vasopressin, and a reduction in NO production
  - Secondary reductions in glomerular function are due to underperfusion of glomeruli and, possibly, changes in the glomerular ultrafiltration coefficient

RISK FACTORS

- Older age (> 65 years)
- Baseline CKD
- Chronic hypertension
- Diabetes
- HF and cirrhosis
- Vascular disease
- Benign prostatic hyperplasia
- Prostate cancer
- Sepsis and shock
- Major surgery
- Burns, pancreatitis, and systemic inflammation
- NSAIDs, ACE-Is/ARBs, aminoglycosides, amphotericin, and contrast media administration

ADMITTING ORDERS

- Admit to floor
- Diagnosis: AKI
- Condition: guarded
- Vital signs: routine, check orthostatic vital signs on admission
- Nursing: place Foley (if postrenal AKI is suspected), strict inputs/outputs, daily weights, call for urinary output < 200 mL/shift or oxygen saturation < 92%
- Diet: renal (low sodium, low potassium, low phosphate)
- Fluids: depends on whether the patient is hypovolemic or hypervolemic
- Diagnostic tests
  - CBC
  - CMP
  - Calcium
  - Magnesium
  - Phosphate
  - FeNa (calculated from measuring the SCr, serum sodium, urine sodium, and urine creatinine)
  - Urinary osmolality
  - Urinary specific gravity
  - UA with microscopy
  - Renal ultrasound
- Medications
  - Discontinue nephrotoxic medications
  - IV diuretics may be necessary in hypervolemic causes of AKI

DISCHARGE INFORMATION

- Follow renal diet and measure weight daily at home
- Avoid dehydration and drugs that worsen renal function (e.g., NSAIDs)
- Adjust medications for the eGFR when indicated
- Follow up with primary care clinician within 2 weeks with kidney and electrolyte testing performed prior to visit

CASE ANSWERS

1. This patient is presenting with muscle pain and tightness after starting a new and intense workout regimen. With the findings of dark-colored urine (classically described as tea- or cola-colored), AKI, and an elevated creatine kinase, the patient likely has rhabdomyolysis.
2. The UA in rhabdomyolysis classically reveals the presence of heme-positive urine in the absence of hematuria (i.e., < 3 RBCs per high-powered field). Urine sediment will often reveal myoglobinuria, but its absence does not rule out rhabdomyolysis as myoglobin is rapidly cleared.

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3. The mainstay of rhabdomyolysis management with AKI is early and aggressive IV crystalloid fluid resuscitation. Initial boluses of LR or NS, followed by a continuous infusion of NS at a rate of 1–2 L/h, is common practice. Fluids should be titrated according to the patient's volume status and urine output. Frequent electrolyte monitoring and repletion also are necessary. The creatine kinase level may be measured daily to ensure the levels are decreasing with fluids. Infusion of fluids containing bicarbonate solution to alkalinize the urine may be necessary in select patients. Patients with severe AKI, hyperkalemia, severe acidemia, and uremia may require dialysis.

LANDMARK TRIALS

[1] Murphy DP et al. Renin-angiotensin-aldosterone system blockade after AKI with or without recovery among US veterans with diabetic kidney disease. J Am Soc Nephrol 34:1721, 2023. [PMID: 37545022]
- *Summary:* This study demonstrated lower mortality associated with ACE-I/ARB use in patients with diabetes, proteinuria, and AKI, regardless of recovery. Results favored earlier ACE-I/ARB initiation.

[2] Gaudry S et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 375:122, 2016. [PMID: 27181456]
- *Summary:* Among ICU patients with AKI, there is no mortality difference between early or delayed renal replacement therapy (RRT).

[3] Zarbock A et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. JAMA 315:2190, 2016. [PMID: 27209269]
- *Summary:* Among critically unwell patients with AKI, early RRT compared with delayed initiation of RRT reduced mortality over the first 90 days.

[4] Macdougall IC et al. Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med 380:447, 2019. [PMID: 30365356]
- *Summary:* Among patients undergoing hemodialysis, a high-dose IV iron regimen administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered.

[5] Barbar SD et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med 379:1431, 2018. [PMID: 30304656]
- *Summary:* Among patients with septic shock who had severe AKI, there was no significant difference in overall mortality at 90 days between patients assigned to an early strategy for the initiation of RRT and those assigned to a delayed strategy.

FURTHER READING

- Mount DB. Azotemia and urinary abnormalities, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- Waikar SS, Bonventre JV. Acute kidney injury, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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29 Hyponatremia

KEY POINTS

1. Hyponatremia is the result of decreased serum sodium concentration levels in the blood, primarily from abnormalities in water homeostasis, leading to changes in the relative ratio of sodium to body water. It can be categorized into acute (if develops in < 48 h) or chronic (if develops > 48 h), and its severity can be categorized by degree (mild if serum sodium is 130–134 mEq/L, moderate if it is 125–129 mEq/L, and severe if it is < 125 mEq/L), or by severity of symptoms.
2. Most patients (~ 98%) present with chronic hyponatremia with mild symptoms (nausea, headache, weakness, gait abnormalities, and falls). The other 2% have life-threatening severe symptoms, including somnolence, vomiting, acute pulmonary edema, seizures, coma, or cardiorespiratory arrest. Hyponatremia has no specific physical exam findings to suggest the diagnosis, but volume status is important, as it guides diagnosis and eventually treatment of the underlying condition.
3. Hyponatremia is found on screening serum testing, and the clinician should have a low threshold to test for it given hyponatremia's vague symptoms and lack of specific physical exam findings. After confirming hyponatremia, the serum osmolality, urine osmolality, and urine Na^+ are vital in understanding the underlying pathophysiology in conjunction with a volume status assessment. Certain populations will need further testing with a TSH and ACTH stimulation test.
4. Treatment depends on the cause and should include hypertonic saline for acute symptomatic hyponatremia, IV NS for hypovolemic hyponatremia, diuretics and renin-angiotensin-aldosterone system inhibitors for hypervolemic hyponatremia, or fluid restriction for SIAD.
5. Complications of acute or severe hyponatremia include cerebral edema, seizures, coma, brain herniation, cardiorespiratory arrest, and death. Chronic hyponatremia, if overcorrected too quickly, can lead to osmotic demyelination syndrome. Even mild hyponatremia is associated with increased length of hospitalization, greater resource use, and higher mortality.

EPIDEMIOLOGY & DEFINITIONS

Disorders of serum sodium are caused by abnormalities in water homeostasis leading to changes in the relative ratio of sodium to body water. Hyponatremia is the most common electrolyte disorder, affecting ~ 5% of adults. About 20% of people > 65 years of age have hyponatremia, as well as 35% of patients who are hospitalized, 30% of patients with HF, and 50% of patients with cancer or cirrhosis. This disorder is almost always the result of an increase in circulating arginine vasopressin (AVP) and/or increased renal sensitivity to AVP combined with an intake of free water.

Hyponatremia: serum sodium < 135 mEq/L; mild if serum sodium is 130–134 mEq/L, moderate if it is 125–129 mEq/L, and severe if it is < 125 mEq/L.

Acute hyponatremia: hyponatremia occurring within the last 48 h; usually presents with severe symptoms.

Chronic hyponatremia: hyponatremia occurring > 48 h; usually presents with mild symptoms.

Hypertonic hyponatremia: hyponatremia with serum osmolality > 295 mOsm/kg.

Hypotonic hyponatremia: hyponatremia with serum osmolality < 275 mOsm/kg (the most common type of hyponatremia).

Isotonic hyponatremia: hyponatremia with serum osmolality 275–295 mOsm/kg.

CLINICAL VIGNETTE

A 72-year-old woman with epilepsy on carbamazepine and HF with reduced ejection fraction on metoprolol succinate, sacubitril/valsartan, spironolactone, empagliflozin, and furosemide presents to the ED with a week of fatigue, weakness, and an unsteady gait resulting in a fall today. She felt weak while walking, then fell onto her knees, catching her upper body with her hands as she fell to the ground. She describes no seizure- like activity and no loss of consciousness. She also denies palpitations or chest pain. Her apartment has no air conditioning, and the temperature has been warmer than usual over the last week. She is diligent about taking her medications. On physical exam, she is afebrile, BP is 98/64 mm Hg, heart rate is 108 beats/min, and oxygen saturation is 98% on room air. Her weight is 4.5 kg lower than her last recorded weight at the cardiology clinic when she was recorded to be euvolemic. She appears tired on general

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exam but is not somnolent. Her JVP is not visualized, and there is no peripheral edema. Skin turgor has prolonged tenting. Her neurologic exam is nonfocal, and she is not confused. Initial lab data are significant for a BUN of 58 mg/dL, SCr of 2.2 mg/dL (baseline SCr 1.4 mg/dL), and sodium of 121 mEq/L (last recorded sodium was 133 mEq/L 6 months ago).

GUIDING QUESTIONS

1. What other diagnostic tests would you order?
2. Does this patient have acute/symptomatic hyponatremia or chronic hyponatremia?
3. What initial management strategies would you employ?
4. How quickly would you correct this patient's sodium, and what major complication can develop if the sodium correction is too rapid?
5. What medication(s) is this patient prescribed that may lead to chronic hyponatremia?

HISTORY

Hyponatremia can present with a wide variety of symptoms; therefore, a high clinical suspicion and low threshold to order a serum sodium should be at the forefront of clinicians' minds. It is important to know

- If the hyponatremia is acute or chronic
- How severe the symptoms are
- If the patient has risks for neurologic complications (e.g., alcohol use disorder, malnourishment, cirrhosis, hypoxemia, and hypokalemia)

Symptoms can be nonspecific (nausea, weakness, headache, gait abnormalities, and falls) but knowing whether the patient has acute and/or symptomatic hyponatremia (vomiting, acute pulmonary edema [especially from endurance exercise or intoxication with ecstasy], somnolence, seizures, coma, or cardiorespiratory arrest) will change the level of care and the initial treatment approach.

Most patients present with chronic hyponatremia, but acute hyponatremia is a medical emergency due to cerebral swelling. Volume status can be difficult to assess, but it is important to help determine the cause and diagnostic evaluation. A thorough medication review is essential.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - An older patient with comorbidities of HF, cirrhosis, and alcohol use disorder who is on several medications and presents with several days of weakness, nausea, and confusion
  - A young patient with rapid onset of somnolence, vomiting, and dyspnea after intense exercise or MDMA ("ecstasy", "molly") use
- Nausea or vomiting?
  - Depending on the severity, can be present in mild or severe hyponatremia
- Headache?
  - By itself, usually indicates chronic hyponatremia
- Confusion?
  - Depending on the acuity and severity (e.g., coma), can present as acute or chronic hyponatremia
- Seizures? Obtundation or coma?
  - Sign of severe cerebral edema and acute symptomatic hyponatremia
- Unsteadiness on feet or falls?
  - Older patients with chronic hyponatremia are at risk of gait abnormalities and falls
- Any new medications, or changes to old medications?
  - Several medications are reported to cause hyponatremia

PAST MEDICAL HISTORY

- History of HF, cirrhosis, or CKD?
  - Common causes of hypervolemic hyponatremia
- History of hypothyroidism or adrenal insufficiency?
  - Can cause euvolemic hyponatremia

SURGICAL HISTORY

- Recent surgery?
  - Transurethral resection of the prostate (TURP) and uterine surgeries may use glycine irrigation (hypotonic fluid administration), causing hyponatremia

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- Recent colonoscopy prep?
  - Colonoscopy prep can cause hyponatremia

SOCIAL HISTORY

- Use of alcohol
  - Beer potomania causes hyponatremia
- Smoking
- Use of recreational drugs
  - MDMA can cause acute hyponatremia
- Occupation
- Living situation
- Sexual history

MEDICATIONS

- Many different medications can cause hyponatremia
  - Diuretics (especially thiazides)
  - Antidepressants (e.g., SSRIs and tricyclic antidepressants)
  - Antipsychotics
  - Carbamazepine
  - Antineoplastics (e.g., vincristine and ifosfamide)
  - Arginine vasopressin (AVP) analogues (e.g., desmopressin)
  - Oxytocin
  - Vasopressin
  - Chlorpropamide
  - Clofibrate
  - Nicotine
  - NSAIDs
  - Opiates
  - Cyclophosphamide

PHYSICAL EXAM

Once hyponatremia has been established, it is important to assess the fluid status of the patient. A key concept in sodium disorders is that the absolute serum sodium concentration tells one nothing about the volume status of a given patient. The patient's volume status must be taken into account in the diagnostic and therapeutic approach.

- Vital signs
  - Tachycardia and hypotension suggest hypovolemia
  - Hypoxemia and respiratory distress can suggest acute pulmonary edema from intense exercise or ecstasy use, or related to an acute decompensation of HF
- Neurologic
  - Assess mental status thoroughly
    - Confusion and obtundation can be signs of severe symptomatic hyponatremia
  - Are they having seizures (sign of acute/symptomatic hyponatremia)?
- Volume exam
  - Orthostatic vital signs
  - JVP assessment
  - Skin turgor and capillary refill time
  - Mucous membrane exam
  - Assess for signs of edema

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

- Low sodium levels are discovered on lab evaluation
- Determine from the history the acuity of hyponatremia
  - Table 29-1 lists causes of acute hyponatremia that can be life-threatening and need emergent management
  - Patients with acute hyponatremia usually present with euvolemia unless it is obvious that they have exercise-induced hyponatremia
- The etiologies of chronic hyponatremia can be separated based on the tonicity, volume status, and urine sodium levels
  - *Hypertonic* hyponatremia (tonicity > 295 mOsm/kg)
    - Hyperglycemia from diabetic ketoacidosis or hyperosmolar hyperglycemic state
    - Mannitol or sucrose administration

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TABLE 29-1 Causes of Acute Hyponatremia

Iatrogenic
Postoperative: premenopausal women
Hypotonic fluids with cause of ↑ vasopressin
Glycine irrigation: TURP, uterine surgery
Colonoscopy preparation
Recent institution of thiazides
Polydipsia
MDMA ("ecstasy," "molly") ingestion
Exercise-induced
Multifactorial, e.g., thiazide and polydipsia

MDMA, 3,4-methylenedioxymethamphetamine; TURP, transurethral resection of the prostate.
Reproduced with permission from Mount DB. Fluid and electrolyte disturbances, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- *Isotonic* hyponatremia (tonicity 275–295 mOsm/kg)
  - Hyperlipidemia or hyperproteinemia
- *Hypotonic* hyponatremia (tonicity < 275 mOsm/kg, *the most common form of hyponatremia*)
  - Separate based on volume status evaluation and urine Na^+ levels
  - Hypovolemic hypotonic hyponatremia
    - Urinary Na^+ < 20 mEq/L
      - Extrarenal losses from vomiting, diarrhea, burns, pancreatitis
    - Urinary Na^+ > 20 mEq/L
      - Diuretic therapy
      - Renal salt wasting
      - Primary adrenal insufficiency
      - Cerebral salt wasting
  - Euvolemic hypotonic hyponatremia
    - Severe hypothyroidism
    - Glucocorticoid deficiency
    - SIAD (causes of SIAD are listed in Table 29-2)
      - In SIAD, the urine sodium is high (commonly > 40 mEq/L)
    - Infections: HIV and Rocky Mountain spotted fever
  - Hypervolemic hypotonic hyponatremia
    - Urinary Na^+ < 20 mEq/L
      - Chronic HF
      - Cirrhosis
      - Nephrotic syndrome
    - Urinary Na^+ > 20 mEq/L
      - AKI, AKI on CKD, or CKD
  - If urine osmolality < 100–200 mOsm/kg
    - Excessive water intake (primary polydipsia) or low solute intake (beer potomania)
    - Patients are usually euvolemic
    - The urine osmolality < 200 mOsm/kg stands out more than the volume exam

DIAGNOSTIC TESTS

LABS

- Comparison with recent sodium levels, if available, is vital as it can help differentiate the acuity of hyponatremia or show that the patient has a chronically mild low sodium
- Serum osmolality (indirect measurement of tonicity)
  - First step in hyponatremia evaluation; gives an indirect measurement of circulating serum arginine vasopressin (AVP) levels (Fig. 29-1)
  - To formally calculate the tonicity
    - Serum tonicity = $2 \times [Na^+] + [\text{Glucose}]/18$
  - Normal serum osmolality is 275–295 mOsm/kg
    - Elevated osmolality → evaluate for hyperglycemia, mannitol, sucrose

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TABLE 29-2 Causes of SIAD

Malignant Diseases
Carcinoma
Lung
Small cell
Mesothelioma
Oropharynx
GI tract
Stomach
Duodenum
Pancreas
Genitourinary tract
Ureter
Bladder
Prostate
Endometrium
Endocrine thymoma
Lymphomas
Sarcomas
Ewing's sarcoma
Pulmonary Disorders
Infections
Bacterial pneumonia
Viral pneumonia
Pulmonary abscess
Tuberculosis
Aspergillosis
Asthma
Cystic fibrosis
Respiratory failure associated with positive-pressure breathing
Disorders of the CNS
Infections
Encephalitis
Meningitis
Brain abscess
Rocky Mountain spotted fever
AIDS
Bleeding and masses
Subdural hematoma
Subarachnoid hemorrhage
Cerebrovascular accident
Brain tumors
Head trauma
Hydrocephalus
Cavernous sinus thrombosis
Other
Multiple sclerosis
Guillain-Barré syndrome
Shy-Drager syndrome
Delirium tremens
Acute intermittent porphyria

(*Continued*)

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TABLE 29-2 Causes of SIAD (*Continued*)

Drugs & Medications
Drugs that stimulate release of AVP or enhance its action
Chlorpropamide
SSRIs
Tricyclic antidepressants
Clofibrate
Carbamazepine
Vincristine
Nicotine
Narcotics
Antipsychotic drugs
Ifosfamide
Cyclophosphamide
Nonsteroidal anti-inflammatory drugs
MDMA ("ecstasy," "molly")
AVP analogues
Desmopressin
Oxytocin
Other Causes
Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Idiopathic
Transient
Endurance exercise
General anesthesia
Nausea
Pain
Stress

AVP, arginine vasopressin; MDMA, 3,4-methylenedioxymethamphetamine.
From DH Ellison, T Berl: The syndrome of inappropriate antidiuresis. N Engl J Med 356:2064, 2007. Copyright © 2007 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

        - Isotonic osmolality → evaluate for hyperlipidemia or hyperproteinemia
        - Hypotonic osmolality → assess volume status and measure urine osmolality and urine Na^+ levels
    - If there is an osmolar gap (i.e., the measured osmolality is higher than the calculated osmolality)
        - Evaluate for uremia or ethylene glycol ingestion
        - Calculated osmolality = $2 \times [Na^+] + ([Glucose]/18) + ([BUN]/2.8)$
        - A patient with hyponatremia in conjunction with uremia or severe ethanol intoxication may have high osmolality but low tonicity
- Urine osmolality
    - If urine osmolality is low (< 100–200 mOsm/kg), this is consistent with appropriately suppressed AVP release
        - Think of primary polydipsia or low solute intake (e.g., beer potomania)
    - If urine osmolality is > 200 mOsm/kg, this is consistent with inappropriately increased AVP levels
        - A volume status assessment along with urine Na^+ levels are the next steps in evaluation
- Urinary Na^+
    - Helps to determine the cause of hypotonic hyponatremia
    - Urinary Na^+ is affected by volume regulation (Table 29-3)
- TSH
    - Tests for severe hypothyroidism causing euvolemic hypotonic hyponatremia

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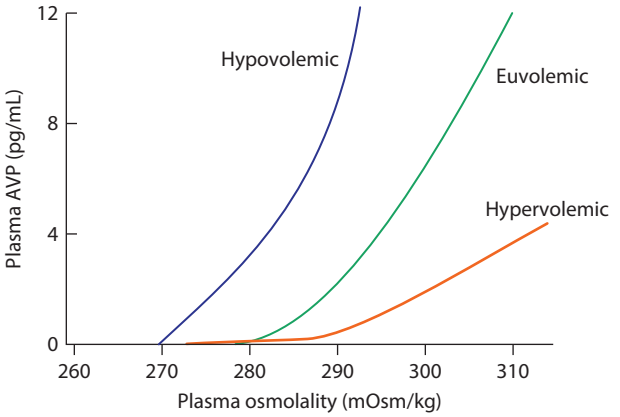

FIGURE 29-1 Circulating levels of arginine vasopressin (AVP) in response to changes in osmolality. Plasma AVP becomes detectable in euvolemic, healthy individuals at a threshold of ~285 mOsm/kg, above which there is a linear relationship between osmolality and circulating AVP. The AVP response to osmolality is modulated strongly by volume status. The osmotic threshold is thus slightly lower in hypovolemia, with a steeper response curve; hypervolemia reduces the sensitivity of circulating AVP levels to osmolality. (Reproduced with permission from Mount DB. Fluid and electrolyte disturbances, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- AM cortisol and ACTH stimulation test if indicated
  - Tests for glucocorticoid insufficiency causing euvolemic hypotonic hyponatremia
- HIV Ab
  - Tests for HIV causing euvolemic hypotonic hyponatremia

DIAGNOSTIC APPROACH

- A detailed step-by-step approach in the diagnostic evaluation of hyponatremia is imperative (Fig. 29-2)

MANAGEMENT

MANAGEMENT OF ACUTE SYMPTOMATIC HYPONATREMIA

- ~ 2% of patients with hyponatremia require emergency treatment
  - These patients need to be treated emergently in the ICU if
    - The symptoms are severe (seizures, obtundation, central herniation)
    - The hyponatremia is acute (< 48 h in development)
- *Hypertonic saline* administration is the treatment of choice
  - A bolus of 3% NS 100 mL over 30 min is more effective than an infusion, rapidly improving both serum sodium and mental status [1]
    - Administration of 3% NS infusion at a rate of 30 mL/h is an alternative

TABLE 29-3 Osmoregulation versus Volume Regulation

	OSMOREGULATION	VOLUME REGULATION
What is sensed	Plasma osmolality	Arterial filling
Sensors	Hypothalamic osmoreceptors	Carotid sinus
		Afferent arteriole
		Atria
Effectors	AVP	Sympathetic nervous system
	Thirst	Renin-angiotensin-aldosterone system
		ANP/BNP
		AVP
What is affected	Urine osmolality	Urinary sodium excretion
	H_2O intake	Vascular tone

ANP, atrial natriuretic peptide; AVP, arginine vasopressin.
Modified from Jameson JL et al. Electrolytes, in *Harrison's Manual of Medicine*, 20th ed, JL Jameson et al (eds). New York, McGraw-Hill Education, 2020.

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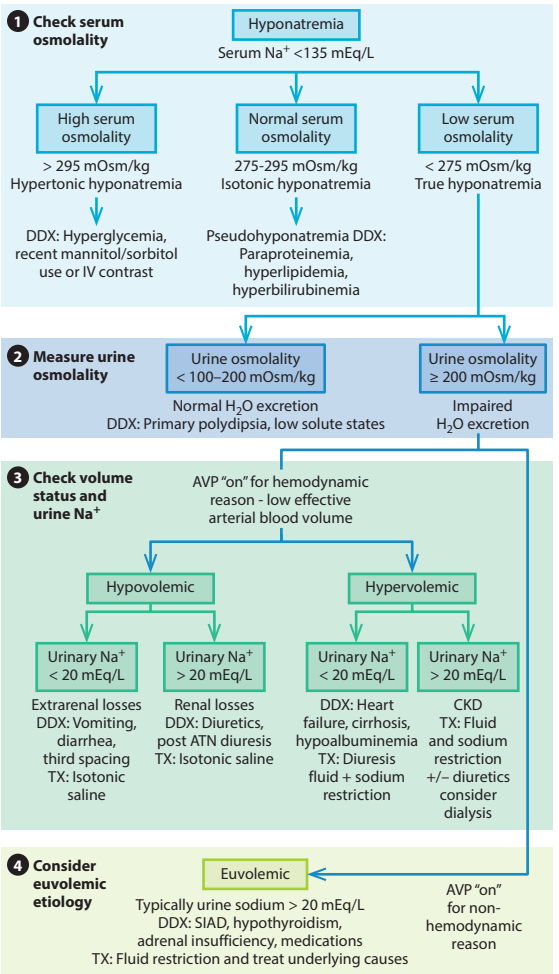

FIGURE 29-2 Workup of hyponatremia. This diagram depicts one strategy to work up hyponatremia. See text for additional details. ATN, acute tubular necrosis; DDX, differential diagnosis; TX, treatment. (Reproduced with permission from Huppert LA, Dyster TG. Diseases and pathophysiology in nephrology, in *Huppert's Notes: Pathophysiology and Clinical Pearls for Internal Medicine,* LA Huppert, TG Dyster (eds). New York, McGraw Hill, 2021.)

- Goal: sodium increase with hypertonic saline administration
  - Increase sodium by 1–2 mEq/L/h to a total 4–6 mEq/L in the first 4 h
  - Then, do not increase the serum sodium levels by more than 6–8 mEq/L in the first 24 h, and no more than 6 mEq/L each subsequent 24 h
- Measure sodium levels and perform neuro exams q2–4h
  - Sodium responses to hypertonic saline are highly unpredictable and require frequent serum sodium checks
  - If not at goal, can consider another 100 mL bolus of 3% NS
  - Administer supplemental oxygen and ventilatory support in acute hyponatremia in the event the patient develops acute pulmonary edema or hypercapnic respiratory failure
  - IV loop diuretics help treat acute pulmonary edema and will also increase free water excretion

MANAGEMENT OF ASYMPTOMATIC CHRONIC HYPONATREMIA

- Patients with asymptomatic or mild symptoms generally present with chronic hyponatremia (> 48 h in development) and can be treated on the medical floor
- For all patients with chronic hyponatremia

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- Do not increase serum sodium levels more than
  - 6–8 mEq/L in the first 24 h, and
  - No more than 6 mEq/L each subsequent 24 h
- The risk of osmotic demyelination syndrome increases with the severity of the hyponatremia

- Measure serum sodium levels q4–8h, depending on how low the initial serum sodium level is
- Measure strict *I*s/*O*s and frequently assess the patient's volume status

HYPERTONIC HYPONATREMIA

- Etiology: hyperglycemia from diabetic ketoacidosis or hyperosmolar hyperglycemic state, mannitol, sucrose
- Treat the underlying cause

HYPOTONIC HYPONATREMIA WITH URINE OSMOLALITY < 100–200 MOSM/KG

- Etiology: primary polydipsia or decreased solute intake (beer potomania or tea and toast diet)
- Correct the underlying cause
  - Sodium levels correct rapidly in beer potomania if given fluids
    - Eating a balanced diet alone corrects these patients' sodium levels
  - If NS is needed, be judicious and check serum sodium levels often
  - Beer potomania has a high risk of osmotic demyelination syndrome given the associated hypokalemia, alcohol use disorder, malnutrition, and risk of overcorrection of the serum sodium concentration

ISOTONIC HYPONATREMIA

- Etiology: hyperlipidemia or hyperproteinemia
- Correct the underlying etiology

HYPOVOLEMIC HYPOTONIC HYPONATREMIA

- Urinary Na^+ < 20 mEq/L
  - Etiology: nonrenal losses from vomiting, diarrhea, burns, pancreatitis
  - Initial bolus of IV NS, then maintenance NS
    - Fluids suppress circulating arginine vasopressin (AVP), inducing water diuresis
  - Treat the underlying etiology
- Urinary Na^+ > 20 mEq/L
  - Etiology: renal losses from diuretic therapy, renal salt wasting, adrenal insufficiency, cerebral salt wasting
  - Initial bolus of IV NS, then maintenance IV fluids with NS to suppress circulating AVP and induce water diuresis
    - Sodium corrects very quickly in cerebral salt wasting if given fluids; be judicial with fluid administration and check serum sodium levels often
  - Treat the underlying etiology

EUVOLEMIC HYPOTONIC HYPONATREMIA

- Urinary Na^+ is usually > 40 mEq/L
- Etiology: severe hypothyroidism, glucocorticoid deficiency, SIAD
  - Treat underlying hypothyroidism (with levothyroxine) or glucocorticoid insufficiency (with glucocorticoids), if present
- Treatment of SIAD
  - Free water restriction is the cornerstone of therapy (< 1 L free water per day)
    - The urine-to-plasma electrolyte ratio (urinary $[Na^+]$ + $[K^+]$/plasma $[Na^+]$) can be exploited as a quick indicator of electrolyte-free water excretion
      - Patients with a ratio of > 1 should be more aggressively restricted (< 500 mL/d) if possible
      - Those with a ratio of ~ 1 should be restricted to 500–700 mL/d
      - Those with a ratio < 1 should be restricted to < 1 L/d
  - *NS worsens the serum sodium level and is not indicated in SIAD*
  - Potassium replacement as needed
  - Oral salt tablets can be used if concern about low solute intake from the diet
  - In patients who fail therapy with free water restriction
    - Potassium replacement, and/or increased solute intake, combined with oral furosemide, 20 mg, and oral salt tablets may be beneficial
      - Furosemide inhibits the renal countercurrent mechanism and blunts the urinary concentrating ability
      - Salt tablets counteract diuretic-associated natriuresis

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- Demeclocycline
  - Inhibits principal cells
  - Can be used in patients whose sodium levels do not increase in response to furosemide and salt tablets
  - Avoid in patients with cirrhosis
- Oral urea (15–60 g/d)
  - Can be administered to promote water diuresis
  - Can be a substitute for sodium chloride tablets and furosemide
- AVP antagonists (e.g., tolvaptan, 15 mg/d initially with a max dose of 60 mg/d)
  - Block the vasopressin receptor 2 located in the collecting duct, promoting water diuresis [2]
  - Increases the sodium very quickly
    - Caution: ~10% of patients who receive an AVP antagonist correct their sodium levels too quickly
    - Do not prescribe tolvaptan > 30 days, as it causes liver function abnormalities chronically
  - Thirst increases substantially with vaptans
    - Fluid restriction should be liberalized
- Treat the underlying etiology of SIAD (Table 29-2)

HYPERVOLEMIC HYPOTONIC HYPONATREMIA

- Urinary Na^+ < 20 mEq/L
  - Etiology: nonrenal losses from chronic HF, cirrhosis, nephrotic syndrome
  - Treatment
    - Fluid and sodium restriction
    - Adequate diuretic therapy
    - ACE-I, ARB, or ARNI therapy if due to HF
    - If hyponatremia is resistant to the above measures in a patient with HF, consider an AVP antagonist
    - Consult nephrology if nephrotic syndrome is the etiology
- Urinary Na^+ > 20 mEq/L
  - Renal losses from AKI, AKI on CKD, or CKD
  - Fluid and Na^+ restriction with diuretics if hypervolemic
  - IV NS if prerenal AKI
  - Nephrology consult if severe hypervolemia is resistant to diuretic therapy for consideration of dialysis

MANAGEMENT OF RAPIDLY OVERCORRECTED SODIUM

- D_5W at ~ 150 mL/h and/or desmopressin 2 μg IV q6h
- Serum sodium measurements q2h

COMPLICATIONS

- Cerebral edema
- Brain herniation
- Cardiopulmonary arrest
- Seizure
- Coma
- Death
- *Osmotic demyelination syndrome (ODS)*
  - Chronic hyponatremia is associated with the loss of osmotically active organic osmolytes from astrocytes, which provide protection against brain cell swelling
  - As you correct sodium back into the circulation, water will be pulled out of these cells, causing brain volume to decrease
    - This results in demyelination of brain cells, leading to apoptosis
  - The lesions of ODS classically affect the pons, a neuroanatomic structure wherein the delay in the reaccumulation of osmotic osmolytes is particularly pronounced (**Fig. 29-3**)
  - Patients with chronic hyponatremia and lower sodium on presentation are at higher risk of overcorrection of the serum sodium
    - Correcting the serum sodium by > 8–10 mEq/L within the first 24 h, and/or > 18 mEq/L within the first 48 h, increases the risk of ODS
  - If overcorrection occurs, attempt to prevent ODS by administering
    - D_5W at ~ 150 mL/h, and
    - Desmopressin, 2 μg IV q6h

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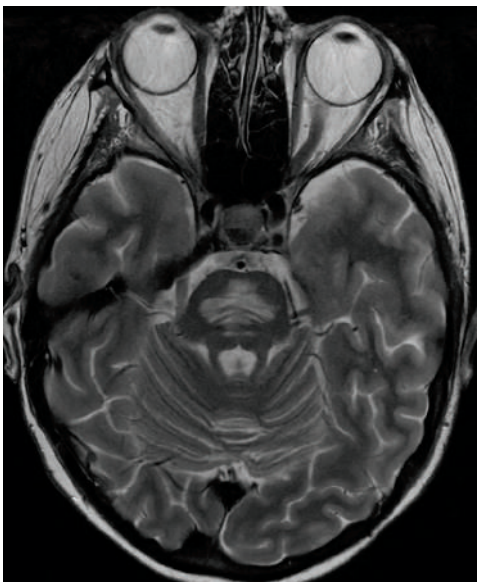

FIGURE 29-3 Osmotic demyelination syndrome. Axial T2-weighted magnetic resonance scan through the pons reveals a symmetric area of abnormal pontine high signal intensity that characteristically involves transverse pontine fibers and spares the descending corticospinal tracts. (Image courtesy of Dr. Jared Narvid, Department of Radiology & Biomedical Imaging, University of California, San Francisco.) (Used with permission from Hemphill J III et al. Nervous system disorders in critical care, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

PROGNOSIS

- Even mild hyponatremia is associated with increased length of hospitalization, greater resource use, and higher mortality
- The severity of hyponatremia in conditions causing hypervolemia (e.g., cirrhosis and HF) provides an indirect index of the associated neurohumoral activation and is an important prognostic indicator

PATHOPHYSIOLOGY

- Disorders of serum sodium concentrations are caused by abnormalities in water homeostasis, leading to changes in the relative ratio of sodium to body water
- Water intake and circulating arginine vasopressin (AVP) constitute the two key effectors in the defense of serum osmolality
  - Defects of one or the other can lead to hyponatremia
- Hyponatremia is almost always due to an increase in circulating AVP levels and/or increased renal sensitivity to AVP
  - A notable exception is hyponatremia due to low solute intake (e.g., beer potomania)
- Water homeostasis regulation
  - Sensors in the anterior third ventricle respond to tonicity and angiotensin II → regulates thirst and AVP
  - AVP
    - Secreted with hypertonicity or a decreased effective arterial blood volume
    - Acts on V_2 receptors in the collecting duct, inserting water channels and increasing water reabsorption (**Fig. 29-4**)
- Hypovolemia
  - Associated with higher circulating levels of AVP from the pituitary, leading to relatively increased water reabsorption compared with sodium in the nephron
  - Leads to reduced arterial blood flow, increasing AVP levels (Fig. 29-4)
  - The increase in circulating AVP helps preserve BP via vascular and baroreceptor V_{1A} receptors and increases in water reabsorption through renal V_2 receptors by increasing the number of aquaporin channels
  - In nonrenal causes of hypovolemic hyponatremia, urine sodium levels typically become < 20 mEq/L
    - AVP also leads to sodium reabsorption (**Fig. 29-5**)

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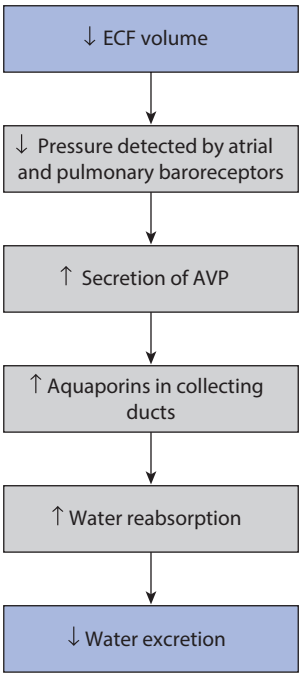

FIGURE 29-4 Decreased water excretion in response to decreased plasma volume. Low pressure is sensed by neural baroreceptors. Their reduced firing removes inhibition of the hypothalamic cells whose axons release AVP (vasopressin) from the posterior pituitary gland. The subsequent increase in AVP increases water reabsorption in the collecting ducts and helps preserve existing volume. (Reproduced with permission from Eaton DC, Pooler JP. Regulation of sodium and water excretion, in *Vander's Renal Physiology,* 10th ed, DC Eaton, JP Pooler (eds). New York, McGraw Hill, 2023.)

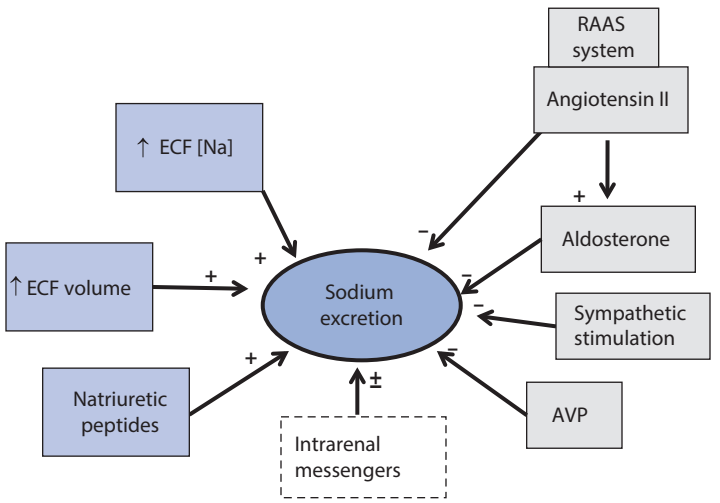

FIGURE 29-5 Major controllers of sodium excretion. Controllers on the left side increase sodium excretion, while controllers on the right side inhibit sodium excretion. A major means to increase sodium excretion is to decrease activity of the controllers that stimulate sodium reabsorption, particularly the renin-angiotensin-aldosterone system. Intrarenal controls both stimulate and inhibit sodium excretion. (Reproduced with permission from Eaton DC, Pooler JP. Regulation of sodium and water excretion, in *Vander's Renal Physiology,* 10th ed, DC Eaton, JP Pooler (eds). New York, McGraw Hill, 2023.)

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- In renal causes of hypovolemic hyponatremia, urine sodium levels are typically > 20 mEq/L from inappropriate loss of sodium chloride in the nephron (still leading to increasing AVP levels)
  - Primary adrenal insufficiency leads to a deficiency of circulating aldosterone
    - Results in less sodium reabsorption in the nephron
  - Thiazide diuretics cause hyponatremia from a number of mechanisms, including
    - Polydipsia
    - Diuretic-induced volume depletion
- Cerebral salt wasting induces clinical hypovolemia and inappropriate natriuresis in association with intracranial disease
  - Disorders include
    - Subarachnoid hemorrhage
    - Traumatic brain injury
    - Encephalitis
    - Meningitis

- Hypervolemia
  - Causes arterial underfilling (e.g., HF and cirrhosis), leading to an increase in circulating AVP
  - This again leads to a relatively increased water reabsorption compared with Na^+ in the nephron
  - Urine Na^+ concentration is typically very low (< 10 mEq/L) in nonrenal causes of hypervolemic hyponatremia, such as HF and cirrhosis
  - Acute and chronic renal failure are renal causes of sodium loss in the nephrons, increasing the urine Na^+ concentration (> 20 mEq/L)
- Euvolemic hyponatremia
  - Occurs via a variety of mechanisms based on its etiology (hypothyroidism, glucocorticoid deficiency, drugs, SIAD)
  - Hyponatremia from SIAD requires an intake of free water with persistent intake at serum osmolalities that are lower than the usual threshold for thirst
  - The osmotic threshold and osmotic response curves for the sensation of thirst are shifted downward (Fig. 29-1)
  - Four distinct patterns of AVP secretion have been recognized, independent of the underlying cause
    - Unregulated, erratic AVP secretion is seen in about a third of patients
    - Failure to suppress AVP secretion at lower serum osmolalities with a normal response curve to hyperosmolar conditions
    - A "reset osmostat" is a lower threshold osmolality and a left-shifted osmotic response curve
    - Some patients have undetectable AVP levels, suggesting either a gain in function in renal water reabsorption or a circulating antidiuretic substance that is distinct from AVP
      - Gain-in-function mutations of a single specific residue in the V_2 ADH receptor have been described in some of these patients, leading to activation of the receptor in the absence of AVP and "nephrogenic" SIAD
- Low solute intake
  - Hyponatremia can occasionally occur in patients with a very low intake of dietary solutes
  - Classically, these patients' sole nutrient is alcohol (beer potomania), which is low in protein and salt content (1–2 mEq/L of sodium)
  - These patients present with a
    - Very low urine osmolality (< 100–200 mOsm/kg) and
    - Very low urine sodium < 10–20 mEq/L
  - Inadequate intake of solutes reduces urinary solute excretion, causing inadequate water diuresis

RISK FACTORS

- Medications (see History section)
- Poor oral intake or diet (tea and toast diet)
- Alcohol use disorder (beer potomania)
- Psychiatric history (e.g., for primary polydipsia)
- HF, cirrhosis, or CKD
- Heat and excessive exercise
- Older patients

ADMITTING ORDERS

- Admit to floor or ICU
- Diagnosis: chronic/asymptomatic hyponatremia or acute/severe hyponatremia

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- Condition: stable/guarded/critical
- Vital signs: routine per unit, orthostatic vitals
- Activity: as tolerated with fall precautions
- Nursing: call for hypoxemia, seizures, obtundation; perform frequent neurochecks
- Diet: sodium restriction and fluid restriction if indicated
- Fluids: NS, hypertonic saline, or fluid restriction depending on clinical context
- Diagnostic tests
  - BMP
  - Sodium measurements q2–6h initially, dependent on severity of hyponatremia and risk of osmotic demyelination syndrome
  - Serum osmolality
  - Urine osmolality
  - Urine Na^+
  - TSH
  - A.M. cortisol
  - ACTH stimulation test
  - HIV antibody
- Medications
  - Depends on the cause
  - Diuretics if hypervolemic
  - ACE-I, ARB, or ARNI if due to HF

DISCHARGE INSTRUCTIONS

- Follow-up sodium level 1–2 weeks after discharge
- Educate to seek medical help if signs and symptoms of hyponatremia recur (weakness, gait abnormalities, nausea and vomiting, confusion)
- Education on any special diets (low-sodium diet, free water restriction) if necessary

CASE ANSWERS

1. Additional initial diagnostic studies to help identify the underlying etiology of hyponatremia include
   a. Serum osmolality
   b. Urine osmolality
   c. Urine sodium
2. *Symptomatic hyponatremia* refers to severe symptoms that can result from hyponatremia. These include vomiting, acute pulmonary edema, somnolence, seizures, coma, or cardiorespiratory arrest. This patient has none of these features; therefore, she is classified as having asymptomatic hyponatremia. The duration of hyponatremia is commonly vague like in this patient. However, given that her symptoms have been ongoing for a week, it should be assumed this episode of hyponatremia is chronic (≥ 48 h since onset).
3. Given the history and physical exam findings of weight loss, continued use of diuretics despite warm temperature, unmeasurable JVP, and skin turgor tenting, this patient likely has hypovolemic hyponatremia. An IV NS bolus, followed by a continuous infusion of NS and temporarily discontinuing her furosemide, is a reasonable initial management strategy.
4. When the serum sodium is corrected too quickly, osmotic demyelination can occur. In order to prevent this devastating complication in chronic hyponatremia, the serum sodium should not be corrected by 6–8 mEq/L in the first 24 h. After the initial 24 h, the sodium should not be increased more than 6 mEq/L for each subsequent 24 h.
5. Several medications can lead to chronic hyponatremia, including from SIAD. The medications this patient takes that may lead to hyponatremia include carbamazepine, sacubitril/valsartan (a rare cause of hyponatremia), spironolactone, and furosemide.

LANDMARK TRIALS

[1] Baek SH et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: The SALSA randomized clinical trial. JAMA Intern Med 181:81, 2021. [PMID: 33104189]
  - *Summary:* This study showed that treating hyponatremia with either rapid intermittent bolus (RIB) or slow continuous infusion (SCI) hypertonic saline was effective and safe and there was no difference in

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the overcorrection risk. However, RIB had a lower incidence of therapeutic relowering treatment and tended to have a better efficacy in achieving serum Na^+ within 1 h than SCI. RIB could be suggested as the preferred treatment of symptomatic hyponatremia, which is consistent with the current consensus guidelines.

[2] Berl T et al. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 21:705, 2010. [PMID: 20185637]
- *Summary:* Normalization of the serum sodium level at day 30 occurred in 66.6% of patients receiving tolvaptan (15 mg/d initially with a max dose of 60 mg/d) and in 26.8% of patients receiving placebo ($P < 0.05$).

FURTHER READING

- Adrogué HJ et al. Diagnosis and management of hyponatremia: A review. JAMA 328:280, 2022. [PMID 35852524]
- Eaton DC, Pooler JP. Regulation of sodium and water excretion, in *Vander's Renal Physiology*, 10th ed, DC Eaton, JP Pooler (eds). New York, McGraw Hill, 2023.
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32 Anemia

KEY POINTS

1. Anemia is a decreased circulating RBC mass in the body and has a diverse etiology. It is defined as a decrease in the hemoglobin level below 11 g/dL in children and pregnant women, and below 12 g/dL in others. Anemia can be categorized into types by the RBC size (using the mean corpuscular value [MCV]), or from mechanisms producing the anemia. Categorizing the type of anemia aids in narrowing the differential to identify the underlying etiology.
2. The clinical history should include information about symptoms, such as fatigue, shortness of breath, and dizziness, as well as any relevant medical conditions or medications. The physical exam should assess skin pallor, mucous membranes, nail beds, and palmar creases. Check for tachycardia, yellow sclera, and splenomegaly.
3. The most common causes of anemia include blood loss, decreased red cell production, and increased red cell destruction. These can be further classified into categories such as nutritional deficiencies, chronic diseases, and genetic disorders. The CBC will show a reduction in circulating RBCs, and the MCV categorizes the RBC size into microcytic, normocytic, or macrocytic. The peripheral smear is invaluable in assessing the etiology of anemia. An absolute reticulocyte count helps differentiate anemias from blood loss and hemolysis from underproduction. LDH, haptoglobin, and indirect bilirubin are markers that evaluate for hemolysis. If microcytic, iron studies can help identify an etiology. Other diagnostic tests are ordered based on the history and initial evaluation.
4. The treatment of anemia depends on the underlying cause. Iron-deficiency anemia requires iron replacement (either IV or PO supplementation) and correction of the underlying etiology. Acute blood loss anemia requires aggressive fluid resuscitation, packed RBC (PRBC) transfusion when indicated, and control of the source of bleeding. A restrictive transfusion strategy should be used in deciding when to provide PRBCs in most patients.
5. Complications of anemia mostly involve worsening of other comorbidities, leading to greater symptoms and a reduced quality of life. Some etiologies have specific complications (e.g., sickle cell anemia can have painful crises, acute chest syndrome, strokes, pulmonary hypertension, and nephropathy from microinfarctions). Chronic anemia can also lead to high-output HF.

EPIDEMIOLOGY & DEFINITIONS

Anemia is one of the most common medical problems in the world, affecting ~ 2 billion people, and it is a significant source of morbidity and reduced quality of life. Many causes of anemia are treatable, and some forms of anemia can be a clue to other underlying disorders. Iron-deficiency anemia is especially common worldwide.

Anemia: a decrease in circulating RBCs defined as a decrease in the hemoglobin level below 11 g/dL in children and pregnant women, and below 12 g/dL in others.

Microcytic anemia: anemia with small RBCs (mean corpuscular volume [MCV] < 80 fL).

Normocytic anemia: anemia with normal-sized RBCs (MCV 80–99 fL).

Macrocytic anemia: anemia with large RBCs (MCV > 100 fL).

Hemolytic anemia: anemia caused by the destruction of RBCs within the body.

CLINICAL VIGNETTE

A 66-year-old man presents to the ED at the request of his primary care physician for a hemoglobin level of 5.4 g/dL. He expresses several months of progressively worsening fatigue, generalized weakness, and dyspnea on exertion. He denies any bleeding, chest pain, paroxysmal nocturnal dyspnea, or orthopnea. He has also noticed weight loss over the past few months with decreased appetite and reflux symptoms but maintains a well-balanced diet. His past medical history is notable for hypothyroidism, CKD stage 3, hypertension, and a prior cerebrovascular accident with residual right foot drop and right-sided weakness. He is adherent to his medications, including levothyroxine, lisinopril, and aspirin. He used to drink alcohol, but he quit 15 years ago. The vital signs are normal without fever, tachycardia, hypotension, or hypoxemia. Conjunctival and palmar crease pallor are present. His tongue is enlarged and mildly painful with palpation. He has reduced sensation on both legs with associated hyperreflexia. Repeat lab

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data reveal a hemoglobin of 5.3 g/dL, mean corpuscular volume of 119.4 fL, platelet count of 250,000/μL, WBC count of 9200 cells/μL, and absolute reticulocyte count of 1.2% (low). A peripheral blood smear reveals macro-ovalocytes and hypersegmented neutrophils.

GUIDING QUESTIONS

1. What is your leading etiology of this patient's anemia?
2. What additional diagnostic tests would you order?
3. Would you transfuse PRBCs for this patient?

HISTORY

Anemia is usually first noted on screening laboratory tests. A good history is the first step in the diagnosis of anemia and should include

- If the patient has had any previous episodes of anemia
- Any previous therapy such as iron pills or transfusions
- A family history of anemia
- If they have been a blood donor

Focus on any disease symptoms that could cause anemia (e.g., diarrhea for celiac or inflammatory bowel disease). Females who menstruate require a good menstrual history taken. In chronic anemia, symptoms are vague and include fatigue and dyspnea on exertion, but patients can also be asymptomatic. In contrast, acute anemia from blood loss presents with hypovolemia and symptoms related to it (e.g., dizziness, syncope, dyspnea at rest, weakness, encephalopathy). Always ask about recent bleeding, such as from the GI tract.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Chronic anemia can be asymptomatic; classic symptoms are
    - Fatigue
    - Headache
    - Poor concentration
    - Dyspnea
    - Nausea
    - Vague abdominal discomfort
    - Dyspnea on exertion
  - Acute anemia (e.g., from blood loss or hemolysis) symptoms can include
    - Dizziness
    - Syncope
    - Dyspnea
    - Chest pain (if the patient has CAD)
    - Encephalopathy
- Fatigue?
  - Common symptom of anemia
- Dyspnea on exertion?
  - Oxygen delivery to tissues and heart with exertion may be reduced
  - Dyspnea at rest suggests acute blood loss
- Chest pain?
  - May occur from low oxygen supply to the heart in patients with CAD
- Bleeding (e.g., in the stool or urine, from the mouth)?
  - A possible acute source of the anemia
- Recent trauma
  - May reveal nonobvious internal bleeding
- Recent illness?
  - Many illnesses can cause anemia (e.g., *Mycoplasma pneumoniae*, mononucleosis)
- Fever?
  - Possible sign of infection-induced anemia
- Weight loss?
  - Colon cancer with iron-deficiency anemia
  - Any malignancy can cause anemia

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- Weakness and balance issues?
  - B_{12} deficiency can cause subacute combined degeneration
- Night sweats?
  - Can be a sign of anemia from cancer
- Skin changes?
  - Petechiae can be a sign of mucosal bleeding and/or associated thrombocytopenia with anemia

REVIEW OF SYSTEMS

- A full review of systems is necessary given the diverse underlying conditions that can lead to anemia, and can help identify other conditions that can cause anemia

PAST MEDICAL HISTORY

- History of anemia?
  - How has it been treated?
  - What was the diagnosis previously?

SURGICAL HISTORY

- Recent surgery (potential cause of acute blood loss)?
- Prior gastric bypass surgery (potential cause of malabsorption-related anemia)

SOCIAL HISTORY

- Use of alcohol
  - Chronic alcohol use may lead to macrocytic anemia from B_{12} and folate deficiencies
- Smoking
- Use of recreational drugs
- Occupation
- Living situation
- Sexual history
- Diet (e.g., pica, vegan diet, lack of vitamins and minerals)
  - Potential cause of nutrition-related anemia
- Geographic background (e.g., Middle Eastern and Black Americans are at higher risk of glucose-6-phosphate dehydrogenase [G6PD] deficiency, α-thalassemia, and hereditary spherocytosis)

FAMILY HISTORY

- Family history of anemia?
  - Was a diagnosis made that is genetic?

MEDICATIONS

- Many medications can cause anemia, including, but not limited to
  - Antibiotics
    - Cephalosporins
    - Sulfonamides
    - Rifampin
    - Ribavirin
  - Cardiovascular medications
    - Methyldopa
    - Procainamide
    - Quinidine
    - Thiazides
  - Tricyclic antidepressants
  - Phenothiazines
  - NSAIDs
  - Sulfonylureas
  - Methotrexate
  - 5-fluorouracil
  - Rasburicase
  - G6PD deficiency–precipitating medications
    - Sulfonamides
    - Dapsone

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- Primaquine
- Doxorubicin
- Methylene blue
- Many others; review each medication the patient takes when considering G6PD deficiency flare

PHYSICAL EXAM

There is a wide variety of physical exam findings in anemia that could be present based on the cause of the anemia. It could range from minor abnormalities of the skin to neurologic symptoms. It is important to keep in the back of your head the etiologies of anemia and what their physical exam findings may be.

Likelihood ratios for individual positive or negative findings on physical exam can be clinically useful in determining whether anemia exists. When a finding can be either positive or negative, then the likelihood ratios are called the *positive likelihood ratio* (PLR) or the *negative likelihood ratio* (NLR). A finding that has a PLR > 1 indicates that the positive finding is associated with the presence of anemia; a finding that has an NLR of < 1 indicates that the finding is associated with the absence of anemia. The further either ratio is from 1, the more likely anemia is either present or absent. For example, a PLR of 3 = 20% probability patient has condition, a PLR of 4 = 25% probability patient has condition, a PLR of 5 = 30% probability patient has condition, and a PLR of 10 = 45% probability patient has condition.

- Vital signs
  - Patients with chronic anemia may have normal vital signs
  - Signs of severe and acute anemia
    - Tachycardia
    - Hypoxemia
    - Orthostatic hypotension
    - Hypotension
  - Fever may indicate an infectious cause to the anemia
- General
  - Pallor at any site (PLR 3.8)
- HEENT
  - Conjunctival rim pallor (PLR 16.7)
  - Tongue pallor (PLR 3.7)
  - Glossitis (iron, folate, or B_{12} deficiency)
- Cardiac
  - Forceful heartbeat and a flow murmur may be found in anemia
  - Dullness on chest percussion may suggest intrapleural bleeding
- Abdominal
  - Jaundice (in hemolytic anemias and cirrhosis)
  - Splenomegaly (thalassemia, hereditary spherocytosis, chronic hemolysis, myelofibrosis)
  - Grey Turner sign (flank ecchymosis) may reflect retroperitoneal bleeding
  - Cullen sign (umbilical ecchymosis) may suggest intraperitoneal or retroperitoneal bleeding
- Skin
  - Nailbed pallor (4.3)
  - Palmar crease pallor (PLR 7.9)
  - Palmar pallor (PLR 5.6)
  - Evaluate for petechiae and purpura (bleeding disorder)
  - Koilonychia (iron-deficiency anemia)
- Neurologic
  - B_{12} deficiency may cause subacute combined degeneration
    - Decreased position and vibratory senses, especially in the lower extremities
    - Spasticity and hyperreflexia
    - Ataxia
    - Tactile pain and temperature sensations
    - Irritability and mild depression
  - Encephalopathy may develop from decreased oxygen supply to the brain from anemia

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

There are two general ways of classifying anemia (**Table 32-1**). The most common way is to categorize based on the size of the red cell by using the mean corpuscular volume, as this can help guide the diagnostic workup. The other method is through the mechanism of anemia categorization.

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TABLE 32-1 Classification of Anemia	
By Size of Red Cell	
Microcytic	Anemia of inflammation, iron deficiency, sideroblastic anemia, thalassemia
Macrocytic	*Oval Macrocytes:* Vitamin B_{12} deficiency, folate deficiency, medications (chemotherapy, some antiseizure medications), myelodysplasia
	Round Macrocytes: Alcohol use, dysproteinemia, hypothyroidism, hypoxia, liver disease, reticulocytosis, smoking
Normocytic	Aplastic anemia, endocrinopathies, marrow invasion, myeloma, pure red cell aplasia, renal disease
By Mechanism	
Hyperproduction	Bleeding, hemolysis
	Acquired: Autoimmune, mechanical
	Congenital: Hemibrain defect, hemoglobinopathies, enzyme defects
Underproduction	*Nutritional Deficiency:* Vitamin B_{12}, copper, folate, iron, vitamin C
	Absence of Red Cell Precursors: Aplastic anemia, pure red cell aplasia
	Failure of Iron Reutilization: Anemia of inflammation
	Lack of Erythropoietin: Renal disease, anemia of aging
	Marrow Replacement: Granulomatous disease, infection, neoplasm
	Stem Cell Defects: Acute leukemia, chronic leukemia, myelodysplasia

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MICROCYTIC ANEMIA

- Due to any process that interferes with hemoglobin production
  - Less hemoglobin leads to smaller red cells
- Etiologies include
  - Thalassemia (defects of hemoglobin protein synthesis)
  - Iron-deficiency anemia (unable to make heme)
  - Sideroblastic anemia (defects of heme synthesis)
  - Anemia of inflammation (lack of iron delivery to red cells)
    - Multifactorial anemia in a heterogeneous group of disorders, including
      - Infections
      - Autoimmunity
      - Malignancies
      - Inflammatory bowel disease
- Table 32-2 describes the causes of iron deficiency with or without anemia

MACROCYTIC ANEMIA

- Due to defects in DNA synthesis, and has two subdivisions
  - Round macrocytes: due to defects in DNA synthesis
  - Oval macrocytes: due to membrane defects
- Many processes can lead to macrocytosis
  - Vitamin deficiencies (B_{12}/folate)
  - Liver disease
  - Hypothyroidism
  - GI disorders (Crohn's disease, celiac disease, small-intestinal bacterial overgrowth)
  - Bone marrow disorders (myelodysplasia)
  - Reticulocytosis
  - Medications (the anticonvulsants phenytoin and valproate, methotrexate, metformin, trimethoprim/sulfamethoxazole, HIV medications)
  - Chronic alcohol use
  - Post-splenectomy
- *Megaloblastic anemia* is a group of disorders characterized by the presence of distinctive morphologic appearances of developing red cells in the bone marrow (Table 32-3 lists causes of megaloblastic anemia)
  - *Hypersegmented neutrophils and macro-ovalocytes* are present on the peripheral smear
  - If you diagnose B_{12} or folate deficiency, you must understand the root cause of the deficiency, which includes
    - Dietary deficiencies
    - Malabsorption

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TABLE 32-2 Causes of Absolute Iron Deficiency with or without Anemia

MECHANISM	CONDITIONS
Increased iron needs	• Children, adolescents (growth spurt) • Pregnancy and breastfeeding • Treatment with erythropoiesis-stimulating agents
Inadequate iron intake	• Vegan or vegetarian diet • Malnutrition, poverty • Prolonged breastfeeding
Decreased iron absorption	• Gastrectomy, bariatric surgery • Celiac disease • *Helicobacter pylori* gastritis • Atrophic/autoimmune gastritis • Proton pump inhibitors[a] • Excess consumption of iron absorption inhibitors (e.g., tea, calcium) • IRIDA (*TMPRSS6* mutations)
Chronic blood losses	*GI* • Erosive esophagitis/gastritis • Peptic ulcer • Large hiatal hernia • Antral gastric ectasia (watermelon stomach) • Benign lesions (e.g., large polyps) • Meckel's diverticulum • Angiodysplasias (including Heyde's syndrome with concurrent aortic stenosis and acquired von Willebrand disease) • Malignancy (especially right colon cancer) • Large hemorrhoids • Inflammatory bowel diseases • Parasites (hookworms, others) *Gynecologic* • Heavy menstrual bleeding[b] • Fibroids • Uterine cancers *Urinary* • Intravascular hemolysis (e.g., PNH, prosthetic heart valves, march hemoglobinuria) • Urinary schistosomiasis (*Schistosoma haematobium*) • Bladder or renal cancer *Pulmonary* • Pulmonary hemosiderosis • Severe hemoptysis *Iatrogenic* • Hemodialysis • Surgical blood losses • Excess blood drawn for diagnostic testing • Drugs inducing or facilitating GI bleeding (aspirin, NSAIDs, corticosteroids, antithrombotic drugs) *Bleeding disorders* • von Willebrand disease, other coagulation defects, platelet disorders • Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) *Frequent blood donors* *Self-inflicted in psychiatric disorders* (Munchausen's syndrome)

[a]Unlikely the sole cause. [b]May be exacerbated by undiagnosed von Willebrand disease or platelet disorders.
IRIDA, iron-refractory iron deficiency anemia; PNH, paroxysmal nocturnal hemoglobinuria.
Reproduced with permission from Camaschella C, Girelli D. Iron deficiency and other acquired anemias due to decreased erythrocyte production, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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TABLE 32-3 Causes of Megaloblastic Anemia
Cobalamin (Vitamin B_{12}) deficiency or abnormalities of cobalamin metabolism
Folate deficiency or abnormalities of folate metabolism
Therapy with antifolate drugs (e.g., methotrexate)
Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy:
Some cases of acute myeloid leukemia, myelodysplasia
Therapy with drugs interfering with synthesis of DNA (e.g., cytosine arabinoside, hydroxyurea, 6-mercaptopurine, azidothymidine [AZT])
Orotic aciduria (responds to uridine)
Thiamine-responsive

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        - Gastric and intestinal causes (including pernicious anemia)
        - Medication side effects
        - Excessive utilization or loss

NORMOCYTIC ANEMIA

- Normocytic anemia includes all other causes of anemia
- The broad differential for this classification of anemia is a drawback for categorizing anemias based on the mean corpuscular volume
- Start with evaluating renal function and erythropoietin levels

DISORDERS OF HEMOGLOBIN

- Result from changes in the amino acid sequence of globin, composing the most common Mendelian genetic diseases
- They are also responsible for most instances of hemolytic anemia
- Sickle cell disease and the hemoglobin E (HbE)–associated syndromes are the most prevalent hemoglobinopathies
    - β- and α-thalassemia are the most prevalent thalassemias
- Table 32-4 lists the disorders of hemoglobin

HEMOLYTIC ANEMIA

- Due to increased destruction of red cells within the body
- The anemia results from overconsumption of red cells from the peripheral blood, while the supply of cells from the bone marrow is normal (and usually increased)
- The mean corpuscular volume, absolute reticulocyte count, LDH, and indirect bilirubin are elevated; haptoglobin is low
- Hemolytic anemias can be either inherited or acquired and are classified into intracorpuscular defects or from extracorpuscular factors
    - Inherited intracorpuscular defects
        - Hemoglobinopathies
        - Enzymopathies
        - Membrane-cytoskeletal defects
    - Inherited extracorpuscular factors
        - Familial (atypical) hemolytic-uremic syndrome (Evans syndrome)
    - Acquired intracorpuscular defects
        - Paroxysmal nocturnal hemoglobinuria (PNH)
    - Acquired extracorpuscular factors
        - Mechanical destruction (microangiopathic)
        - Toxic agents
        - Drugs
        - Infections
        - Autoimmune

ANEMIA FROM ACUTE BLOOD LOSS

- Blood loss causes anemia by two main mechanisms
    - By the direct loss of red cells
    - If the loss of blood is protracted, it will gradually deplete iron stores, eventually resulting in iron deficiency

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TABLE 32-4 Disorders of Hemoglobin

I. Hemoglobinopathies—hemoglobin variants with amino acid sequence variants that alter the physical, chemical, or functional properties of hemoglobin
   A. Common variants with unusual properties
      1. HbS—polymerization
      2. HbE—reduced biosynthesis
      3. HbC—hemoglobin-membrane interaction
   B. Altered oxygen affinity
      1. High affinity—erythrocytosis
      2. Low affinity—cyanosis, anemia
   C. Hemoglobins that oxidize readily
      1. Unstable hemoglobins—hemolytic anemia, jaundice
      2. M hemoglobins—methemoglobinemia, cyanosis
II. Thalassemias—defective biosynthesis of globin chains
   A. α-Thalassemias
   B. β-Thalassemias
   C. Complex thalassemias
III. Hereditary persistence of fetal hemoglobin—persistence of higher than normal levels of HbF into adult life
   A. Deletions within the HBB cluster—15–30% HbF in heterozygotes, pancellular HbF
   B. Point mutations in HBG2/1 promoters—5–30% HbF in heterozygotes; pancellular or heterocellular HbF
IV. Acquired hemoglobinopathies
   A. Methemoglobin due to toxic exposures
   B. Sulfhemoglobin due to toxic exposures
   C. Carboxyhemoglobin
   D. HbH in erythroleukemia
   E. Elevated HbF in myelodysplasia

Reproduced with permission from Sankaran VG, Steinberg MH. Disorders of hemoglobin, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- The cause is directed by the history and physical exam
  - Most cases are usually straightforward, but internal bleeding, even when large, may not be immediately obvious
  - Grey Turner sign (flank ecchymosis) may reflect retroperitoneal bleeding
  - Cullen sign (umbilical ecchymosis) may suggest intraperitoneal or retroperitoneal bleeding
  - Dullness on chest percussion may suggest intrapleural bleeding

PATIENTS WITH PANCYTOPENIA

- Decreased RBCs, platelets, granulocytes (WBCs), and possibly neutropenia
- Table 32-5 describes the differential diagnosis of pancytopenia

DIAGNOSTIC TESTS

- CBC
  - Evaluates the hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelets
  - Current testing of the blood count is performed by electronic cell counters that can directly measure red cell size (MCV), number of red cells, and hemoglobin levels with a variety of measurements derived from these values
  - Normal RBC indices are listed in Table 32-6
    - The index most commonly used is the MCV because the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration will trend with the MCV
- Peripheral blood smear for morphology
  - *One of the most informative exercises clinicians can perform in the diagnosis of anemia*
  - Automated technology advances have made exam of smears by a physician less important

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TABLE 32-5 Differential Diagnosis of Pancytopenia	
Pancytopenia with Hypocellular Bone Marrow	
Acquired (immune) aplastic anemia	
Constitutional aplastic anemia (Fanconi anemia, telomere biology disorders, and others)	
Hypoplastic myelodysplastic syndrome	
Rare aleukemic leukemia	
Some acute lymphoid leukemia	
Rare lymphomas of bone marrow	
Copper deficiency	
Pancytopenia with Cellular Bone Marrow	
Primary bone marrow diseases	Myelodysplastic syndromes Paroxysmal nocturnal hemoglobinuria (PNH) Myelofibrosis Aleukemic leukemia Myelophthisis
Bone marrow lymphoma	
Hairy cell leukemia	
Secondary to systemic diseases	SLE Hypersplenism B_{12}, folate deficiency Copper deficiency Alcohol use disorder HIV infection Brucellosis Sarcoidosis Tuberculosis Leishmaniasis Sepsis
Hypocellular Bone Marrow ± Pancytopenia	
Q fever	
Legionnaires' disease	
Anorexia nervosa, starvation	
Mycobacterium	

Reproduced with permission from Young NS, Groarke EM. Bone marrow failure syndromes including aplastic anemia and myelodysplasia, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- However, the technology is not a completely satisfactory replacement for a blood smear interpretation by a trained professional who takes into account the patient's history and exam
- *Steps in examining a blood smear*
  - Examine the feathered edge of the blood smear where red cells lie in a single layer, barely touching one another, but not overlapping

TABLE 32-6 Red Cell Indices			
INDEX	**FORMULA**	**NORMAL VALUES**	**COMMENT**
MCV	Hct/RBC count × 10	80–100 fL	RBC size
MCH concentration	Hgb/Hct × 100	33.8–34.2 g/dL	Changes very little in most cases of anemia; therefore, of limited value
MCH	Hgb/RBC count × 10	28.5–32.3 pg	Varies linearly with MCV; therefore, of limited additional value

Hct, hematocrit; Hgb, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.
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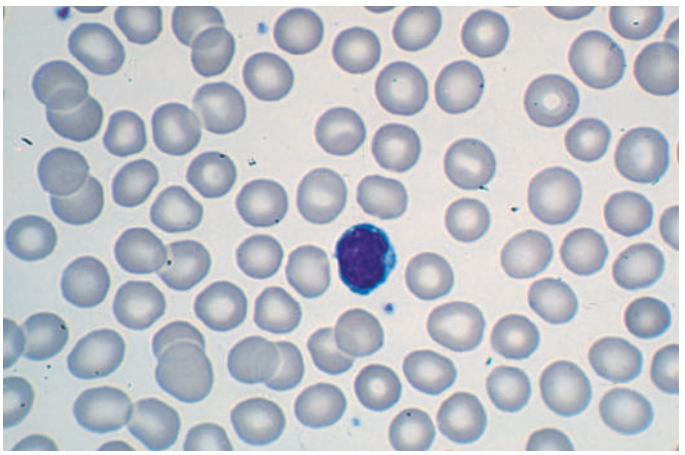

FIGURE 32-1 Normal peripheral blood smear. Small lymphocyte in center of field. Note that the diameter of the red blood cell is similar to the diameter of the small lymphocyte nucleus. (From M Lichtman et al (eds): *Williams Hematology, 7th ed*. New York, McGraw-Hill, 2005; RS Hillman, KA Ault, *Hematology in General Practice, 4th ed*. New York, McGraw-Hill, 2005.)

- Examine platelets first, then red cells, and finally, white cells
- Use an oil immersion lens that magnifies cells 100-fold
- Figure 32-1 depicts a normal peripheral smear
- Platelets are usually 1–2 μm in diameter and have a blue granulated appearance
- Red cells are usually 8 μm wide and are similar in size to the nucleus of a small lymphocyte
  - *Microcytic* red cells are smaller than the nucleus of a small lymphocyte
  - *Macrocytic* red cells are larger and usually more oval-shaped (macro-ovalocytes)
  - *Anisocytosis* is when red cells vary greatly in size (reported as "red cell distribution width" [RDW])
  - *Poikilocytosis* is when red cells vary greatly in shape
- After red cell size is assessed, examine the hemoglobin content of the cells
  - *Normochromic*: normal in color (normal hemoglobin content)
  - *Hypochromic*: pale in color (low hemoglobin content), seen in
    - Iron-deficiency anemia
    - Sideroblastic anemia
    - Thalassemia
    - Anemia of inflammation
- Examine red cells for their shape, the presence of inclusions, and distribution on the smear (Table 32-7)
  - For images of blood smears, refer to *Harrison's Principles of Internal Medicine,* 22nd ed, Chap. 65
- Examine the white cells (neutrophils, eosinophils, and basophils)
  - Neutrophils
    - Usually the most abundant of the three white cells
    - 10–14 μm wide
    - Contain a lobulated nucleus with 2–5 lobes connected by a thin chromatin thread
  - The presence of neutrophils with > 5 nuclear lobes (hypersegmentation) suggests megaloblastic anemia
  - Eosinophils
    - Are slightly larger than neutrophils
    - Have bilobed nuclei, and
    - Contain red granules

- Absolute reticulocyte count
  - Red cells still contain mRNA for about 24 h after being released by the marrow
    - This mRNA can be detected by staining, and these cells are called *reticulocytes*
  - The number of reticulocytes present is a measure of red cell production and is helpful in separating increased destruction and blood loss from anemias due to impaired red cell production
  - The reticulocyte count, because of how it is calculated, needs to be corrected for the hematocrit
    - Corrected reticulocyte count = measured reticulocyte count × (hematocrit/45%) (normal hematocrit)

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TABLE 32-7 Blood Smear Terminology, Characteristics, and Their Associated Clinical Entities

BLOOD SMEAR TERMINOLOGY	CHARACTERISTICS	CLINICAL ENTITIES
Basophilic stippling	Diffuse, fine or coarse blue dots in the red cell usually representing RNA residue	Lead poisoning, thalassemia
Howell-Jolly bodies	Dense blue circular inclusions that represent nuclear remnants	Splenic dysfunction
Nucleated RBCs	Premature release of red cells from the bone marrow prior to nuclear extrusion	Myelophthisic processes or a vigorous response to anemia (usually hemolytic anemias)
Parasites	Parasites seen within the RBC	Malaria and babesia
Polychromatophilia	The cytoplasm has a bluish hue, reflecting the persistence of ribosomes making hemoglobin in an immature red cell	Hemolytic anemias, anemia from blood loss, megaloblastic anemia, iron-deficiency anemia (after iron stores have been adequately restored), myelofibrosis, leukemia and other cancers
Heinz bodies (use supravital stain)	Clumps of damaged hemoglobin	G6PD deficiency
Bite cells	RBCs with part of the cell broken off	G6PD deficiency
Spherocytes	Small red cells without central pallor	Hereditary spherocytosis, hemolytic anemias, severe iron-deficiency anemia, clostridial sepsis
Dacrocytes	Teardrop-shaped cells	Hemolytic anemias, severe iron deficiency, thalassemia, myelofibrosis, myelodysplastic syndrome
Schistocytes	Helmet-shaped cells	Microangiopathic hemolytic anemias or fragmentation on an artificial heart valve
Echinocytes (Burr cells)	Spiculated red cells with evenly spaced spikes	Abnormal drying of the blood smear, renal failure, malnutrition
Acanthocytes (Spur cells)	Spiculated red cells with irregularly spaced spikes	Cholestatic liver disease, renal disease, abetalipoproteinemia, post-splenectomy
Elliptocytes	Elliptical shaped red cells	Inherited defect in the cell membrane, iron-deficiency anemia, myelodysplastic syndrome, megaloblastic anemia, thalassemia
Stomatocytes	Central pallor with a slit shape instead of the usual round shape	Inherited membrane defects and alcoholism
Target cells	Central pallor that contains a dense center (or bull's eye)	Thalassemia, iron-deficiency anemia, cholestatic liver disease, some hemoglobinopathies, improper making of a slide
Agglutination	Red cells that are clumped together	Paraproteinemias and autoimmune hemolytic anemia
Rouleaux formation	Red cells lying in a single row on top of one another	Abnormal serum protein levels (e.g., multiple myeloma)
Megaloblastic anemia	Neutrophils that have more than five nuclear lobes	Megaloblastic anemia (see Table 32-3)

G6PD, glucose-6-phosphate dehydrogenase.

        - Many newer CBC machines can directly quantitate the reticulocytes present in a given volume of blood, and this is the *absolute reticulocyte count*
    - The normal reticulocyte count is 0.5–2.0% in patients without anemia
    - High reticulocyte counts → hemolytic anemia or blood loss
    - Low reticulocyte counts → anemia from impaired red cell production
- Iron studies
    - Serum iron, total iron-binding capacity (TIBC), TIBC saturation %, and ferritin
    - Table 32-8 describes how to interpret laboratory markers in the differential diagnosis of iron deficiency
- LDH, haptoglobin, and indirect bilirubin
    - Markers to help evaluate for the presence of hemolytic anemia

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TABLE 32-8 Laboratory Biomarkers for Differential Diagnosis of Iron Deficiency

	IRON DEFICIENCY	ANEMIA OF INFLAMMATION	MIXED FORMS	THALASSEMIA TRAIT
Ferritin (μg/L)	Low (≤ 15–30)	Normal to high (> 100)	Low to normal (< 70–100)	Normal to high
Serum iron (μmol/L)	Low	Low	Low	Normal to high
Transferrin saturation (%)	Low (< 10)	Low (< 20)	Low (< 20)	Normal to high
MCV (fL)	Low (< 80)	Low to normal	Low to normal	Low
RDW	High	Normal	Normal to high	Low to normal
% HYPO	High (> 6%)	High	High	High
CHr	Low	Low	Low	Low
sTfR	High	Low to normal	Normal to high	Normal to high
sTfR/log ferritin	> 2	< 1	> 2	NA
Hepcidin[a]	Very low	Normal to high	Low	Low to normal
Zn-PP[b] (μM/mol heme)	High (> 80)	Normal to high	High (> 80)	High

[a]Serum hepcidin levels are not routinely measured; reference values are not standardized. [b]Zn-PP indicate zinc protoporphyrins, which reflect iron/zinc competition in the last step of heme synthesis; used in screening programs.
Note: % HYPO (percentage of hypochromic RBCs) and CHr (hemoglobin content of reticulocytes) are measured by automated analyzers and available upon request.
MCV, mean corpuscular volume; NA, not assessed; RDW, red cell distribution width; sTfR, soluble transferrin receptor.
Reproduced with permission from Camaschella C, Girelli D. Iron deficiency and other acquired anemias due to decreased erythrocyte production, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- LDH and indirect bilirubin are increased in hemolytic anemia
- Haptoglobin is low in hemolytic anemia

- CMP
  - May give clues to underlying chronic conditions (e.g., cirrhosis, CKD)
- Other laboratory tests
  - Other tests may be needed after the history, physical, and initial laboratory workup provide clues to diagnosis
  - These may include
    - Erythropoietin
    - Copper
    - Vitamin C, B_{12}, and folate
    - Serum and urine protein electrophoresis
    - TSH levels
  - With B_{12} and folate deficiency, methylmalonic acid and homocysteine levels should be ordered
    - Anti-intrinsic factor antibody is ordered in patients with B_{12} deficiency and no other identifiable cause to evaluate for pernicious anemia
  - Genetic testing and/or an evaluation of the bone marrow may be necessary

PROCEDURE

- Bone marrow aspirate/biopsy
  - A bone marrow biopsy disturbs the marrow architecture but allows for an examination of
    - Individual cell morphology
    - Determination of a differential cell count
    - Determination of the myeloid-to-erythroid ratio
  - A "core" sample
    - Keeps the marrow architecture intact
    - Is useful for the determination of cellularity and the presence of abnormal marrow infiltrates or fibrosis
  - Samples can also be drawn for specialized testing such as
    - Flow cytometry
    - Genetic testing
    - Microbiologic testing

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- Indications for bone marrow biopsy
  - Circulating immature cells (blasts)
  - Severe pancytopenia
  - Very low reticulocyte counts (< 0.1%)
  - Circulating nucleated RBCs
  - Evidence of marrow infiltration (teardrop red cells, nucleated red cells)
  - Staging of certain malignancies (e.g., lymphoma)
  - Unexplained severe anemia

DIAGNOSTIC APPROACH

- After the absolute reticulocyte count, mean corpuscular volume, iron studies, and peripheral smear have been examined, Fig. 32-2 describes an approach to diagnosing the underlying etiology of patients with anemia

MANAGEMENT

PRINCIPLES OF BLOOD TRANSFUSIONS

- Goals of blood transfusions
  - Increase oxygen delivery to tissues
  - Relieve symptomatic anemia
- Basic principles
  - The decision to transfuse should not be based on hemoglobin value; think of the whole clinical picture
  - 1 unit of packed RBCs increases the hemoglobin by 1 g/dL if there is an adequate response

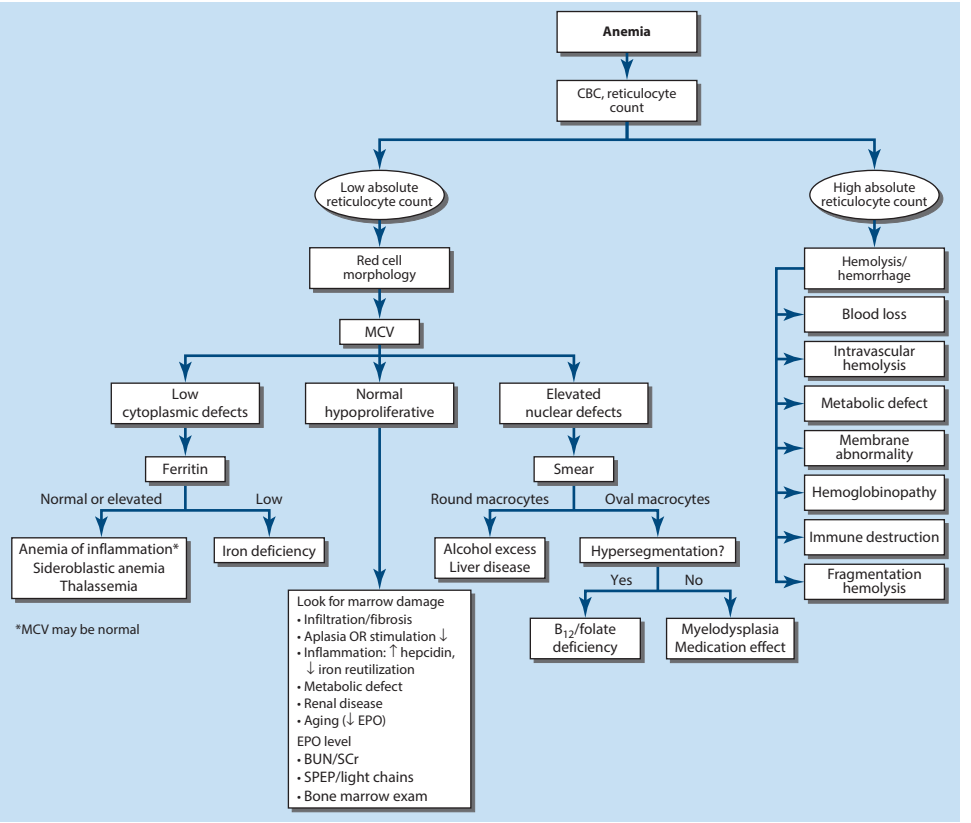

FIGURE 32-2 The physiologic classification of anemia. EPO, erythropoietin level; MCV, mean corpuscular volume; SPEP, serum protein electrophoresis. (Reproduced with permission from DeLoughery TG, Longo DL. Anemia and polycythemia, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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        - For example, if the patient is bleeding and the hemoglobin increases by 0.5, they may have adequately responded but have ongoing bleeding
- The American Association of Blood Banks (AABB) 2023 guidelines should be used in guiding decisions when to transfuse
    - *A restrictive transfusion strategy should be used for most hemodynamically stable adults*
        - In critically ill patients, a restrictive transfusion strategy (hemoglobin > 7 g/dL) is associated with better survival compared with a liberal strategy (hemoglobin > 10) [1]
    - Hemoglobin < 6 g/dL → transfusion recommended
    - Hemoglobin 6–7 g/dL → transfusion likely recommended
    - Hemoglobin 7–8 g/dL → transfusion likely not recommended for stable patients (strong recommendation)
        - Consider transfusion for hemoglobin 7–8 g/dL only if postop or symptomatic (chest pain or history of CAD, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, or HF)
        - In patients with acute MI, the AABB has chosen not to recommend for or against a liberal or restrictive transfusion threshold
            - In patients with acute MI and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent MI or death at 30 days [2]
                - However, potential harms of a restrictive transfusion strategy couldn't be excluded
    - Hemoglobin > 10 g/dL → transfusion not indicated

MANAGEMENT OF SPECIFIC ETIOLOGIES & THEIR CHARACTERISTICS

MICROCYTIC ANEMIAS

IRON-DEFICIENCY ANEMIA

- Decreased marrow iron and depleted body iron → decreased heme synthesis → microcytes → anemia
- Decreased ferritin and iron, increased total iron-binding capacity (TIBC)
- Treatment
    - Always try to find an underlying etiology (see Table 32-2) and treat accordingly
    - If severe or cannot absorb oral iron, administer IV iron (e.g., iron sucrose 200–300 mg single dose with repeated doses as needed)
    - Oral iron (ferrous sulfate 325 PO every other day for 3–6 months)
    - Supplement with vitamin C, which facilitates GI absorption of oral iron

THALASSEMIAS

- Decreased synthesis of α or β globin chains of hemoglobin → subunits are made incorrectly → destruction of RBCs and erythroid precursors, therefore, anemia from hemolysis and ineffective erythropoiesis
- α-Thalassemia → 3,2,1,0 traits
- β-Thalassemia → 1 or 2 mutations
- Findings
    - Chipmunk facies
    - Crew-cut appearance on x-ray
    - Fractures
    - Hepatosplenomegaly (extramedullary hematopoiesis)
    - High-output HF
    - Bilirubin gallstones
    - Chronic transfusions
- MCV < 70 fL (usually a *very low MCV*), normal iron studies, + abnormal hemoglobin electrophoresis
- Treatment of β-thalassemia
    - Transfusions every 2–4 weeks (goal hemoglobin of 9–10.5 g/dL)
    - Iron chelation with IV deferoxamine, or PO options of deferasirox or deferiprone
    - Luspatercept is a fusion protein that binds growth factor β superfamily ligands, reducing Smad2/3 signaling, ultimately enhancing late-stage erythropoiesis
        - Reduces transfusion requirements by 33%
    - Hematopoietic stem cell transplantation (improves quality of life more than transfusions and chelation therapy)
    - Gene therapy is emerging as a treatment option
    - Splenectomy if transfusion needs increase by ≥ 50%

ANEMIA OF INFLAMMATION (ANEMIA OF CHRONIC DISEASE)

- Decreased RBC production from impaired iron reutilization and functional iron deficiency from increased hepcidin

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- Etiologies
  - Autoimmune disorders
  - Chronic infection
  - Inflammation
  - HIV
  - Malignancy
  - CKD
  - HF
- Decreased iron, decreased TIBC, + increased ferritin; can be microcytic or normocytic
- Treatment
  - Treat underlying disease + iron preparations and/or EPO
  - Iron supplementation if ferritin < 100 or TIBC sat < 20%
  - Hepcidin and IL-6 antagonists are being explored

SIDEROBLASTIC ANEMIA

- Defective heme synthesis in RBC precursors
- Findings: hepatosplenomegaly and iron overload syndromes
- Etiologies
  - Hereditary/X-linked (ALAS2 mutation)
  - Idiopathic
  - Myelodysplastic syndrome with refractory anemia with ring sideroblasts (MDS-RARS)
  - Reversible causes (alcohol use, lead poisoning, isoniazid, chloramphenicol, copper deficiency, hypothermia)
- Increased iron, normal/high ferritin, normal TIBC
- *Ringed sideroblasts* in bone marrow biopsy (iron-laden mitochondria), Pappenheimer bodies (iron inclusions)
- Treatment
  - Treat reversible causes
  - Trial of vitamin B6 pyridoxine, 25–50 mg by mouth daily
  - Luspatercept for congenital sideroblastic anemia and MDS/myeloproliferative neoplasm variants
  - Supportive transfusions

NORMOCYTIC ANEMIAS

- Anemia of inflammation: see above
- Sideroblastic anemia: see above

PURE RED CELL APLASIA

- Destructive antibodies or lymphocytes → *ineffective erythropoiesis*
- Associated with thymoma, chronic lymphocytic leukemia (CLL), and parvovirus
- Lack of erythroid precursors on bone marrow biopsy
- Treatment
  - Thymectomy if thymoma present
  - IVIG if parvovirus
  - Immunosuppression for CLL
  - Supportive therapy with transfusions

PANCYTOPENIA

- See Table 32-5 for the differential diagnosis of pancytopenia
- Findings: fatigue and recurrent infections (increased susceptibility from neutropenia)
- Treat the underlying cause

APLASTIC ANEMIA

- Due to stem cell failure
- Pancytopenia with decreased reticulocytes, bone marrow biopsy showing a fatty bone marrow
- Etiologies
  - Idiopathic (33–50% of cases)
  - Radiation
  - Chemotherapy
  - Chemicals
  - Chloramphenicol
  - NSAIDs
  - Sulfonamides
  - Drugs
  - Gold

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- Carbamazepine
- Antithyroid
- Human herpesvirus 6, HIV, Epstein-Barr virus, parvovirus B19 (especially if they have sickle cell anemia)
- Post-hepatitis
- SLE
- Graft-versus-host disease
- Thymoma
- Post–hematopoietic stem cell transplant
- Paroxysmal nocturnal hemoglobinuria
- Fanconi anemia
- Shortened telomeres (telomerase mutations)

- Treatment
  - Allogenic hematopoietic stem cell transplant for younger patients
  - Cyclosporine/tacrolimus
  - Antithyroid globulin
  - Thrombopoietin mimetics (eltrombopag, 50–150 mg by mouth daily) for refractory anemia
  - Supportive transfusions

MACROCYTIC ANEMIAS

MEGALOBLASTIC ANEMIA

- Impaired DNA synthesis → cytoplasm matures before nucleus → ineffective erythropoiesis and macrocytosis due to folate/ B_{12}/myelodysplastic syndrome
- Peripheral smear shows neutrophil hypersegmentation and macro-ovalocytes
- Treatment is dependent on the etiology

B_{12} DEFICIENCY

- B_{12} is found in animal foods
  - The body has 2–3 years of storage in individuals who ingest adequate B_{12}
  - Required for the production of thymidylate from uridylate
- Binds to intrinsic factor from parietal cells, absorbed in the terminal ileum
- Etiologies
  - Malnutrition (vegans, alcohol users)
  - Pernicious anemia
  - Decreased absorption (gastrectomy, Crohn's, celiac)
  - *Diphyllobothrium latum*
  - Liver disease (impaired cholesterol synthesis in the B_{12} molecule)
  - Thyroid disease
- Findings: neurologic changes (subacute combined degeneration), affects peripheral nerves
- Decreased B_{12}, increased homocysteine, increased methylmalonic acid, anti-intrinsic factor antibodies, Schilling's test (a cumbersome test)
- Treatment
  - B_{12}, 1 mg IM daily × 7 days, then every week × 4–8 weeks, then every month for life

FOLATE DEFICIENCY

- Folate is found in vegetables
  - Body stores last 2–3 months
- Etiologies
  - Malnutrition (chronic alcohol use)
  - Decreased absorption (celiac disease)
  - Methotrexate, pyrimethamine, and trimethoprim use
- Decreased folate, decreased RBC folate, increased homocysteine, normal methylmalonic acid
- Treatment
  - Critical to rule out B_{12} deficiency first
  - Folate, 1–5 mg PO daily × 1–4 months
  - Treat the underlying cause

HEMOLYTIC ANEMIAS

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

- X-linked recessive pathogenic variant causing RBCs to be more susceptible to oxidative stress
- Variant more common in Black or Mediterranean males

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- Precipitants of hemolysis
  - Drugs (sulfonamides, dapsone, primaquine, doxorubicin, methylene blue)
  - Infections
  - Diabetic ketoacidosis
  - Fava bean ingestion
- Heinz bodies (oxidized Hemoglobin), bite cells, decreased G6PD levels
  - G6PD levels may be normal during an acute attack; not ideal to test during flares
- Treatment
  - Prevention of triggers and avoidance of susceptible medications
    - Remove any offending agents during acute flares
    - As there are many drugs that can precipitate hemolysis, check every medication before initiating
  - If severe anemia → transfuse
  - Regular folate supplementation

SICKLE CELL ANEMIA

- Recessive β-globulin mutation
  - Decreased O_2 causes hemoglobin to polymerize → *RBCs sickle* → decreased RBC deformability → *hemolysis and microvascular occlusion*
- Vaso-occlusion and infarction cause
  - Painful crises
  - Acute chest syndrome
  - Cerebrovascular accidents
  - Dactylitis
  - Renal papillary necrosis
  - Aseptic necrosis
  - Priapism
- Infection risk increases
  - Splenic infarction, which leads to infection susceptibilities from encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenza*, *Neisseria meningitidis*, *Klebsiella*, *Salmonella typhi*, cryptococcus, *Pseudomonas*)
  - Infarcted bone → osteomyelitis (*Salmonella* and *Staphylococcus*)
- Sickled RBCs, Howell Jolly bodies, abnormal hemoglobin electrophoresis
- Treatment
  - Hydroxyurea, 15–35 mg/kg PO daily (increases hemoglobin F)
  - Folate, 1 mg daily to prevent megaloblastic erythropoiesis
  - Crizanlizumab: a P-selectin–blocking monoclonal antibody given IV monthly
    - Reduces acute painful episodes by ~45% [3]
  - L-glutamine: presumed to reduce oxidative stress in sickle cell
    - Reduces painful episodes by ~25% and reduces hospitalizations by 33%
  - Transfusions for severe symptomatic anemia
  - Treatment and prevention of stroke and severe acute chest syndrome
  - Stem cell transplantation
  - Gene therapy is potentially a treatment in the future
  - Ensure adequate hydration
  - Oxygen and analgesia for acute pain syndromes
  - Vaccinations for *Pneumococcus*, *Meningococcus*, *H influenza*, hepatitis B
  - Children should receive prophylactic penicillin until age 5 years

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- Acquired clonal stem cell disorder → inactivating somatic mutations of PIG-A gene → deficiency of GPI-anchor for *CD55/99* (inhibitors of complement) → complement-mediated RBC lysis with platelet aggregation and subsequent hypercoagulable state
- Triad of findings
  - Hemolysis
  - Pancytopenia
  - Distinct tendency to venous thrombosis
- Intravascular hemolytic anemia with hypercoagulability (venous > arterial, especially intra-abdominal [hepatic veins] and cerebral), deficient hematopoiesis, and evolution to acute myelogenous leukemia
- During the night, the body retains more CO_2, which creates an acidic environment
  - This leads to *red urine* in the morning from increased complement and the destruction of RBCs

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- Treatment
  - Folate, 3 mg/d
  - Eculizumab, 900 mg IV every 2 weeks
    - Binds to the complement component of C5 near the site that triggers the distal part of the complement cascade, inhibiting intravascular hemolysis [4]
  - Pegcetacoplan, an inhibitor of C3, and iptacopan, an inhibitor of factor B, inhibit complement activation more upstream, at the level of C3
  - A short course of prednisone may be useful when an inflammatory process exacerbates hemolysis

HEREDITARY SPHEROCYTOSIS

- Defect in cytoskeletal RBC membrane → membrane loss and mutations in ankyrin and α/β spectrins
- Northern European descent family history in 75% of patients
- Findings: anemia, jaundice, splenomegaly, pigmented gallstones
- Spherocytes, + *osmotic fragility test, decreased eosin-5-maleimide test*
- Increased MCHC
- Treatment
  - Folate
  - Supportive transfusions
  - Splenectomy in moderate-severe cases

AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)

- An acquired antibody-mediated RBC destruction
- Warm (IgG) and cold (IgM) AIHA causes are listed in **Table 32-9**
- Diagnosis
  - *Spherocytes, + Coombs test, cold agglutinin titer,* splenomegaly
- Treatment
  - Treat underlying disease
  - Warm AIHA
    - Corticosteroids and rituximab (first line)
    - Splenectomy (+), IVIG, azathioprine, cyclophosphamide, cyclosporine, and/or mycophenolate (second line)
  - Cold AIHA
    - Avoid cold environments
    - Rituximab (first line)
    - Plasma exchange
    - Venetoclax, ibrutinib, bortezomib, and sutimlimab can be used in relapses
    - Steroids and splenectomy are not effective

DRUG-INDUCED HEMOLYTIC ANEMIA

- An acquired antibody-mediated RBC destruction precipitated by a medication
- Antibiotics: cephalosporins, sulfonamides, rifampin, ribavirin
- Cardiovascular drugs: methyldopa, procainamide, quinidine, thiazides
- TCAs, phenothiazines, NSAIDs, sulfonylureas, methotrexate, 5-fluorouracil, rasburicase
- Diagnosis: Coombs negative, increased LDH
- Treatment: discontinue the medication causing the hemolytic anemia

MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)

- See **Chap. 33** for further details
- Intra-arteriolar fibrin damages RBCs → acquired intravascular hemolysis
- Etiologies
  - Hemolytic uremic syndrome (HUS)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Disseminated intravascular coagulation (DIC)
  - Malignancy
  - Malignant hypertension
  - Eclampsia
  - HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome
  - Mechanical heart valves
  - Scleroderma renal crisis
- Diagnosis
  - *Schistocytes* + thrombocytopenia + abnormalities in specific diseases (e.g., increased PT in DIC; increased SCr in HUS; increased liver enzymes and low platelets in HELLP)

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TABLE 32-9 Classification of Acquired Immune Hemolytic Anemias

CLINICAL SETTING	TYPE OF ANTIBODY	
	COLD, MOSTLY IgM, OPTIMAL TEMPERATURE 4°C–30°C	WARM, MOSTLY IgG, OPTIMAL TEMPERATURE 37°C; OR MIXED
Primary	Cold agglutin disease	AIHA (idiopathic)
Secondary to viral infection	EBV CMV Other	Parvovirus B19 HIV HCV EBV Viral vaccines
Secondary to other infection	Mycoplasma infection: paroxysmal cold hemoglobinuria	Babesia
Secondary to/ associated with other disease	Cold agglutin disease in: Waldenström's disease Lymphoma	AIHA in: SLE, scleroderma, RA CLL Lymphoproliferative disorders Multiple myeloma Other malignancy Chronic inflammatory disorders (e.g., IBD) Thyroiditis (including Hashimoto) After allogeneic HSCT Common variable immunodeficiency After immune checkpoint modulating drugs
Secondary to drugs: drug-induced immune hemolytic anemia	Small minority (e.g., with lenalidomide)	Majority: currently most common culprit drugs are cefotetan, ceftriaxone, piperacillin, methyldopa, fludarabine
	Drug-dependent: antibody destroys red cells only when drug present (e.g., rarely penicillin)	
	Drug-independent: antibody can destroy red cells even when drug no longer present (e.g., methyldopa)	
Associated with	Pregnancy	

AIHA, autoimmune hemolytic anemia; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; RA, rheumatoid arthritis.
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- Treatment
  - Treat underlying disease
  - Emergent therapeutic plasma exchange for TTP, possibly for HUS as well (and eculizumab for atypical HUS)
  - Glucocorticoids, rituximab, and caplacizumab are other options for TTP

ACUTE BLOOD LOSS ANEMIA

- Management requires aggressive fluid resuscitation, packed RBC transfusion when indicated, and control of the source of bleeding
- See **Chap. 23** for the details on managing acute GI bleeding

COMPLICATIONS

- Severe fatigue
- High-output cardiac failure and worsening of existing HF
- Dysrhythmias
- Complications of sickle cell disease
  - Acute anemic episodes
  - Acute pain crisis and chest syndrome
  - Gallstones

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  - Hepatic disease
  - Multiorgan failure
  - Nephropathy
  - Priapism
  - Retinopathy
  - Restrictive lung disease and pulmonary hypertension
  - Stroke and silent infarction
- Complications of thalassemias
  - Bone disease
  - Cardiac disease, including HF and dysrhythmias
  - Delayed puberty; secondary amenorrhea
  - Endocrinopathies, including diabetes, hypothyroidism, hypoparathyroidism, and adrenal insufficiency
  - Growth retardation
  - Hepatic disease
  - Infections: from transfusions, linked to iron overload (*Yersinia*), and malaria
  - Leg ulcers
  - Splenomegaly
  - Thromboembolism
- Risks of blood transfusion
  - Transfusion of transmitted pathogens (HIV, hepatitis C virus, hepatitis B virus, cytomegalovirus, West Nile virus, bacteria, parasites)
    - HIV: 1 in 1,600,000
    - HCV: 1 in 1,200,000
    - HBV: 1:1,100,00
  - Febrile reaction (1:161 patients)
  - Allergic reaction (1:345 patients)
  - Transfusion-associated circulatory overload (1:125 patients)
  - Transfusion-related acute lung injury (1:1,250 patients)
  - Electrolyte abnormalities, hyperkalemia, and citrate toxicity (metabolic alkalosis or ionized hypocalcemia/hypomagnesemia)

PROGNOSIS

- The prognosis for anemia depends on its cause
- Usually, nutritional deficiencies have a good prognosis if treated early and adequately
- Anemia due to acute blood loss, if treated and stopped early, has a good prognosis
- Patients with anemia have worsened morbidity of other comorbidities and reduced quality of life compared to matched patients without anemia

PATHOPHYSIOLOGY

- Based on the underlying disorder (see the Management section for selected etiologies and a brief description of their pathophysiology)
- Basics
  - RBCs are produced in the bone marrow and released into the circulation (**Fig. 32-3**) via a feedback loop mechanism
    - Deficiencies in the feedback loops in Figure 32-3 lead to anemia
  - ~ 1% of RBCs are removed from the circulation per day
  - Imbalance in production to removal or destruction of RBCs leads to anemia
  - The kidneys produce erythropoietin (EPO), and its production is stimulated by tissue hypoxia
  - EPO is the major stimulator of RBC production
  - EPO levels are generally inversely proportional to the hemoglobin concentration
  - EPO levels are lower than expected in anemic patients with renal failure
  - In anemia of inflammation, EPO levels are generally elevated, but not as high as they should be, demonstrating a relative deficiency of EPO

RISK FACTORS

- Diets deficient in iron, vitamins, and minerals
- Older age
- Chronic alcohol use
- Prior gastric bypass surgery

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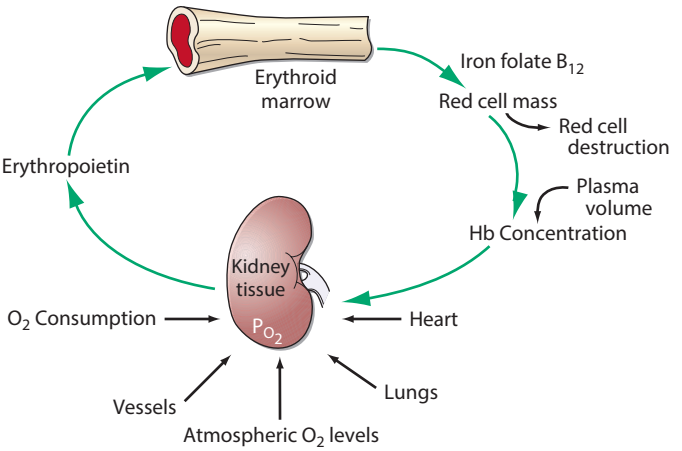

FIGURE 32-3 The physiologic regulation of red cell production by tissue oxygen tension. Hb, hemoglobin. (Reproduced with permission from DeLoughery TG, Longo DL. Anemia and polycythemia, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Certain medications (see Medications in the History section)
- Genetic conditions
- Chronic illnesses (e.g., CKD, inflammatory bowel disease, diabetes, liver disease, rheumatoid arthritis, HF)
- Autoimmune disorders
- Infections
- Cancer

ADMITTING ORDERS

- Admit to floor
- Diagnosis: anemia
- Condition: stable-guarded
- Vital signs: routine
- Activity: ad lib; bed rest if bleeding
- Nursing: call for rapidly dropping hemoglobin < 7 g/dL, heart rate > 110 beats/min, systolic BP < 90 mm Hg, oxygen saturation < 90%
- Diet: regular or tailored to comorbidities
- Fluids: may need PRBC transfusion and IV fluid boluses (if bleeding)
- Diagnostic tests
  - CBC with diff
  - CMP
  - Reticulocyte count
  - Red cell distribution width
  - Iron studies
    - Iron, total iron-binding capacity (TIBC), TIBC sat %, ferritin
  - Peripheral blood smear
  - B_{12} and folate
  - LDH
  - Indirect bilirubin
  - Haptoglobin
  - Possible bone marrow aspirate/biopsy
- Medications
  - Medications depend on the etiology (see the Management section)
  - Folate 1–5 mg orally daily for folate deficiency or in hemolytic anemias
  - B_{12}, 1 mg IM daily × 7 days for B_{12} deficiency
  - Ferrous sulfate, 325 mg orally every other day, for iron-deficiency anemia (or IV iron for severe iron-deficiency anemia) with supplemental vitamin C
  - Transfusion of packed RBCs using a restrictive strategy in most patients

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DISCHARGE INSTRUCTIONS

- Ensure the patient's vital signs are normal on discharge and, if admitted for bleeding, the source of bleeding has been controlled
- Planned outpatient follow-up with primary care and hematologist if necessary
- Educate the patient about the cause of anemia and its corresponding management
- Discuss any precipitating causes that can worsen a patient's anemia, if necessary (e.g., medications to avoid for patients with glucose-6-phosphate dehydrogenase deficiency)
- Stop any offending medications, if applicable

CASE ANSWERS

1. This patient has a macrocytic anemia that is likely chronic in nature given the elevated mean corpuscular volume and normal hemodynamics. Macro-ovalocytes and hypersegmented neutrophils (megaloblastic anemia) on peripheral smear, along with glossitis, reduced sensation in the lower extremities, and hyperreflexia, suggest a diagnosis of B_{12} deficiency.
2. In patients with suspected B_{12} deficiency, B_{12}, methylmalonic acid, and homocysteine levels should be measured. Etiologies of B_{12} deficiency (Table 32-3) should be assessed. If an underlying etiology is not identified, anti-intrinsic factor antibodies to evaluate for pernicious anemia are recommended.
3. A restrictive transfusion strategy (goal hemoglobin of > 7 g/dL) is recommended for most patients without active hemorrhage. This patient's hemoglobin of 5.3 mg/dL is an indication for a packed RBC transfusion.

LANDMARK TRIALS

[1] Hébert PC et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 340:409, 1999. [PMID: 9971864]
- *Summary:* In critically ill patients, a restrictive transfusion strategy (hemoglobin > 7 g/dL) is associated with better survival compared with a liberal strategy (hemoglobin > 10 g/dL).

[2] Carson JL et al. Restrictive or liberal transfusion strategy in myocardial infarction and anemia. N Engl J Med 389:2446, 2023. [PMID: 37952133]
- *Summary:* In patients with acute MI and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent MI or death at 30 days. However, potential harms of a restrictive transfusion strategy cannot be excluded.

[3] Ataga KI et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med 376:429, 2017. [PMID: 27959701]
- *Summary:* In patients with sickle cell disease, crizanlizumab therapy resulted in a significantly lower rate of sickle cell–related pain crises than placebo and was associated with a low incidence of adverse events.

[4] Hillmen P et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 355:1233, 2006. [PMID: 16990386]
- *Summary:* Eculizumab is an effective therapy for paroxysmal nocturnal hemoglobinuria. Eculizumab reduced intravascular hemolysis, as shown by the 85.8% lower median area under the curve for LDH plotted against time (in days) in the eculizumab group compared with the placebo group (58,587 vs 411,822 U/L; $p < .001$). Clinically significant improvements also were found in quality of life, as measured by scores on the Functional Assessment of Chronic Illness Therapy-Fatigue instrument ($p < .001$) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

[5] Hillmen P et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 384:1028, 2021.
- *Summary:* C5 inhibition with eculizumab is effective in controlling intravascular hemolysis but does not address extravascular hemolysis. In this phase 3 randomized comparison of the C3 inhibitor, pegcetacoplan, with eculizumab, pegcetacoplan resulted in higher hemoglobin levels and a higher percentage of patients becoming transfusion independent (85% vs 15%). FACIT-F quality of life assessment scores increased on pegcetacoplan and decreased on eculizumab.

FURTHER READING

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- Carson JL et al. Red blood cell transfusion: 2023 AABB international guidelines. JAMA 330:1892, 2023. [PMID: 37824153]

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- Sankaran VG, Steinberg MH. Disorders of hemoglobin, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
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33 Thrombocytopenia

KEY POINTS

1. Thrombocytopenia is defined as a platelet count < 150,000/μL. It has a wide variety of causes and is generally categorized based on acuity and the underlying pathophysiology (decreased bone marrow production, sequestration of platelets in an enlarged spleen, increased platelet destruction or clearance, or dilutional thrombocytopenia).
2. Thrombocytopenia in most patients is asymptomatic, especially if chronic in nature. However, severe and acute thrombocytopenia can lead to bleeding of mucocutaneous sites and within the GI system, or it can manifest as intracranial or spinal cord hemorrhage in severe cases. A thorough medication review is necessary. Petechiae, wet purpura, and retinal hemorrhages may herald life-threatening bleeding. Other physical exam findings may give clues to the underlying etiology (e.g., a small liver and splenomegaly with caput medusae suggest cirrhosis).
3. A CBC reveals thrombocytopenia. Pseudothrombocytopenia should be ruled out with a peripheral smear and non-EDTA blood collection tubes. The peripheral smear is also helpful to visualize the morphology of red and white cells to provide clues to diagnosis. Coagulation studies (PT/PTT/INR) and hemolysis labs should be performed in most patients. In the right setting, HIV testing, hepatitis C RNA levels, autoimmune serologies, and antibody testing in specific conditions (e.g., ADAMTS13 levels in thrombotic thrombocytopenic purpura [TTP] or anti–heparin/platelet factor 4–heparin complex antibody and serotonin release assay in heparin-induced thrombocytopenia [HIT]) may be necessary.
4. Platelet transfusions are necessary in patients with active bleeding or if the platelet count is severely low. The active management is always directed toward the underlying etiology and may involve simply stopping an offending medication. Argatroban is used in the management of HIT. Therapeutic plasma exchange and glucocorticoids are used for TTP. Glucocorticoids and IVIG are used for immune thrombocytopenic purpura (ITP) in acute flares and/or with bleeding.
5. Severe life-threatening bleeding is the major complication of thrombocytopenia. Spontaneous bleeding is more likely with a platelet count < 10,000/μL. The prognosis for ITP is normal when platelet counts are > 30,000/μL. Therapeutic plasma exchange has improved the mortality of TTP from 85–100% to 10–30%.

EPIDEMIOLOGY & DEFINITIONS

Thrombocytopenia may be associated with a variety of conditions, with clinical presentations ranging from asymptomatic to life-threatening bleeding (e.g., in immune thrombocytopenic purpura [ITP]) or thrombosis (e.g., in heparin-induced thrombocytopenia [HIT]). The prevalence and incidence vary with the underlying etiology. For example, the incidence rate of ITP is 1.6 to 3.9 per 100,000 patient-years, which increases with age and has a slight female predominance, whereas HIT can occur in up to 5% of patients exposed to heparin products, but its incidence and prevalence are largely unknown.

Thrombocytopenia is a platelet count < 150,000/μL (mild: 100,000–149,000/μL, moderate: 50,000–99,000/μL, severe: < 50,000/μL) due to

- Decreased bone marrow production
- Sequestration of platelets in an enlarged spleen
- Increased platelet destruction or clearance, or
- Dilutional thrombocytopenia

Clinical consequences are worse as the platelet count decreases:

- > 100,000/μL
  - Usually asymptomatic
  - Normal hemostasis even with trauma/surgery
- 50,000–100,000/μL
  - Patients typically are asymptomatic
  - May have bleeding with significant trauma or major surgery
- 20,000–50,000/μL
  - Easy bruising, petechiae, and purpura may be observed
  - Prolonged bleeding after minor trauma
  - Risk of bleeding with invasive procedures

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- 10,000–20,000/μL
  - Spontaneous mucocutaneous bleeding (epistaxis, gingival bleeding, menorrhagia) may occur
  - Hematuria and GI bleeding are also possible
- < 10,000/μL
  - High risk of spontaneous and severe bleeding
  - Intracranial hemorrhage risk increases significantly
  - This is a hematologic emergency

CLINICAL VIGNETTE

A 72-year-old woman presents to the ED with severe pain and redness of her left leg that has progressively worsened over the last 3 days. It is associated with fever and chills, and sometimes her body shakes. She confirms that she takes no medications, has not been exposed to heparin, and has not been hospitalized recently. On physical exam, the temperature is 38.6°C (101.4°F), heart rate 122 beats/min, respiratory rate 20 breaths/min, BP 92/68 mm Hg, and oxygen saturation 94% on room air. She appears fatigued and has rigors.

Her left dorsal lower leg is erythematous with small nonhemorrhagic bullae present. It is warm on palpation and moderately tender to palpation without crepitus. You notice she has blood oozing from her IV site. Laboratory data reveal the following:

- WBC: 18,400 cells/μL
- Hemoglobin: 12.4 g/dL
- Platelets: 43,000/μL
- Sodium: 132 mEq/L
- Potassium: 3.8 mEq/L
- BUN: 43 mg/dL
- Creatinine: 1.8 mg/dL
- HCO_3^-: 18 mEq/L
- Lactic acid: 3.4 mg/dL

Blood cultures are obtained, and the patient is administered 2 L of LR and IV antibiotics to treat a skin and soft tissue infection.

GUIDING QUESTIONS

1. How would you confirm the thrombocytopenia is real?
2. What is on your differential for the cause of the thrombocytopenia?
3. What additional diagnostic tests would you order if pseudothrombocytopenia is ruled out?

HISTORY

Thrombocytopenia has a wide range of symptoms depending on the cause and can range from asymptomatic to overt bleeding with organ dysfunction or clotting. It can be suspected based on physical exam findings, suspected from the past medical history if a patient has a condition that makes the person susceptible to thrombocytopenia, or found on lab workup. A healthy young adult with thrombocytopenia will have a much more limited differential diagnosis than an ill hospitalized patient who is receiving multiple medications. It is important to ask about a history of bleeding, family history, recent illnesses, and medications. Another important step is to rule out pseudothrombocytopenia (see Diagnostic Tests section).

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - A wide variety of clinical presentations but may present with bleeding from mucocutaneous sites (e.g., nosebleeds, menorrhagia, GI bleed), with easy bruising or petechiae
- Bleeding?
  - Where (e.g., nosebleed, blood in stool, menorrhagia) and how much?
- Recent illness?
  - Immune thrombocytopenic purpura can be caused by viral infections, or by hemolytic-uremic syndrome (HUS) from bacteria, and infections themselves can cause thrombocytopenia through inflammation
- Diarrhea?
  - Symptom of HUS as a potential etiology

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- Fever or chills?
  - Infectious source can be a cause of thrombocytopenia
  - Fever can be present in hematologic malignancies
- Bruising?
  - Any trauma that caused it, or was it spontaneous?
- Confusion?
  - Symptom of thrombotic thrombocytopenic purpura (TTP) or intracranial hemorrhage
- Pregnant?
  - Pregnancy can cause dilutional thrombocytopenia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome

PAST MEDICAL HISTORY

- History of bleeding in the past?
  - Describe the bleeding
  - Was a diagnosis made?
- History of thrombocytopenia?
  - Was a diagnosis made?
  - How was it treated?
  - Have your platelets been chronically low?
- History of anemia?
  - Was a diagnosis made?
  - How was it treated?
- History of renal disease?
  - Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) can cause kidney injury
- History of cirrhosis? SLE? HIV?
  - Common conditions associated with thrombocytopenia
- Recent illnesses
  - Mononucleosis, HUS, immune thrombocytopenic purpura (ITP), and sepsis may cause thrombocytopenia
- History of chronic lymphocytic leukemia (CLL) or other cancers?
  - What is the current treatment?
  - Malignancies, as well as their chemotherapy regimens, can cause thrombocytopenia

SURGICAL HISTORY

- Recent invasive procedure (can have dilutional thrombocytopenia after surgery)?
- Prosthetic heart valve (can cause platelet destruction)?

SOCIAL HISTORY

- Use of alcohol and recreational drugs, smoking
  - Chronic alcohol use can cause thrombocytopenia (potential B_{12} deficiency or cirrhosis)
- Occupation
- Living situation
- Sexual history
  - Pregnancy can cause dilutional anemia

FAMILY HISTORY

- History of thrombocytopenia, anemia?
  - Anything diagnosed?
  - Genetic conditions?

MEDICATIONS

- Heparin treatment in the last 5–14 days? Recent hospitalization and heparin administration?
  - Heparin-induced thrombocytopenia may need to be ruled out
- See Table 33-1 for medications reported to cause isolated thrombocytopenia

PHYSICAL EXAM

The physical exam should look for findings that are sequelae of thrombocytopenia or for findings that can be associated with diseases causing thrombocytopenia (e.g., splenomegaly, evidence of chronic liver diseases). Some exam findings may give you a clue as to the severity of the thrombocytopenia.

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TABLE 33-1 Drugs Reported as Definitely or Probably Causing Isolated Thrombocytopenia[a]

Abciximab	Gold	Quinidine
Acetaminophen	Haloperidol	Quinine
Amiodarone	Heparin	Ranitidine
Amlodipine	Ibuprofen	Rosiglitazone
Ampicillin	Lorazepam	Roxifiban
Carbamazepine	Mirtazapine	Sulfisoxazole
Ceftriaxone	Naproxen	Suramin
Cefamandole	Oxaliplatin	Tirofiban
Ciprofloxacin	Penicillin	Tranilast
Diazepam	Phenytoin	Trimethoprim/sulfamethoxazole
Eptifibatide	Piperacillin	Vancomycin
Furosemide		

[a]Based on scoring requiring a compatible clinical picture and positive laboratory testing. Note, this is not inclusive of newer medications.
Reproduced with permission from Konkle BA. Disorders of platelets and vessel wall, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- Vital signs
  - Fever (potential infection-related thrombocytopenia or a hematologic malignancy)?
  - Sepsis itself can cause thrombocytopenia
- HEENT
  - Retinal hemorrhages?
    - Poor prognostic sign in immune thrombocytopenic purpura (ITP)
  - Wet purpura (blood blisters) on the oral mucosa?
    - Denotes an increased risk of life-threatening hemorrhage in thrombocytopenic patients
- Cardiac
  - Murmurs?
    - Prosthetic heart valves can cause platelet destruction
- Abdominal
  - Enlarged spleen?
    - Cirrhosis, ITP, thrombotic thrombocytopenic purpura (TTP), chronic lymphocytic leukemia, etc., have an enlarged spleen due to splenic sequestration
  - Examine for signs of cirrhosis
    - Small and nodular liver
    - Stigmata of cirrhosis such as spider angiomata, caput medusae, palmar erythema, and ascites
- Skin
  - Petechiae (pinpoint, nonblanching hemorrhages in areas of increased venous pressure [such as the ankles and feet])?
    - Finding of severe thrombocytopenia (~ 5000–10,000/μL)
  - Lymph node examination
    - Lymphadenopathy in a patient with thrombocytopenia may suggest infection, lymphoma, or other malignancy
  - Excessive bruising?
    - Seen in disorders of both platelet number and function
- Neurologic
  - Focal neurologic symptoms?
    - Can be a sign of TTP or intracranial hemorrhage in severe thrombocytopenia
  - Altered mental status?
    - HUS and TTP can cause encephalopathy
    - Severe thrombocytopenia can lead to intracranial hemorrhage

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Always make sure to rule out pseudothrombocytopenia (see Diagnostic Tests section)

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ETIOLOGY

The following is a list of potential causes of thrombocytopenia based on their mechanisms. The management section will describe select etiologies and their key features. Drugs reported to cause isolated thrombocytopenia are listed in Table 33-1.

DECREASED BONE MARROW PRODUCTION

- Inherited thrombocytopenia (usually diagnosed in children)
- Bone marrow disorders
  - B_{12}, folate, or copper deficiency
  - Myelodysplastic syndrome or clonal cytopenias of undetermined significance
  - Hematologic malignancies
  - Bone marrow infiltration by cancer cells
  - Paroxysmal nocturnal hemoglobinuria (PNH) with associated reduced bone marrow function
  - Aplastic anemia and other bone marrow failure syndromes
  - Infections (e.g., HIV, hepatitis C, infectious mononucleosis, gram-negative rods)
  - Acquired megakaryocyte loss (drug-induced)
  - Liver disease (e.g., cirrhosis)
  - Sepsis-induced bone marrow dysfunction

SEQUESTRATION OF PLATELETS IN AN ENLARGED SPLEEN

- Lymphoproliferative disorders
- Conditions causing splenic congestion through portal hypertension, including
  - Cirrhosis
  - Alcohol-related or metabolic dysfunction–associated steatotic liver disease [MASLD]

INCREASED PLATELET DESTRUCTION OR CLEARANCE

- Increased destruction
  - Disseminated intravascular coagulopathy (DIC)
  - Heparin-inducted thrombocytopenia (HIT)
  - Platelet factor 4–associated immune thrombocytopenia and thrombosis (PITT)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic-uremic syndrome (HUS)
  - Drug-induced thrombotic microangiopathy
  - Prosthetic heart valves
  - Sepsis
  - Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
- Increased clearance
  - Immune thrombocytopenic purpura (ITP)
  - Drug-induced ITP
  - Autoimmune hemolytic anemia with ITP (Evans syndrome)
  - Posttransfusion purpura

DILUTIONAL THROMBOCYTOPENIA

- Fluid resuscitation or massive transfusion
- Postoperative thrombocytopenia
- Gestational thrombocytopenia

DIAGNOSTIC TESTS

LABS

- CBC with differential
  - Initial test to evaluate the platelet count
    - Also important to note if the thrombocytopenia is acute or chronic (compare with recent prior platelet counts)
  - Also evaluates if other cell lines are abnormal (which may indicate a hematologic disorder or malignancy), such as
    - Anemia
    - Leukopenia
    - Neutropenia

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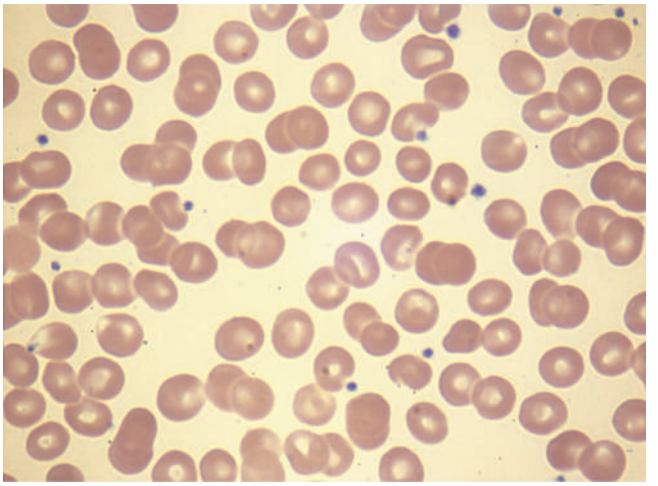
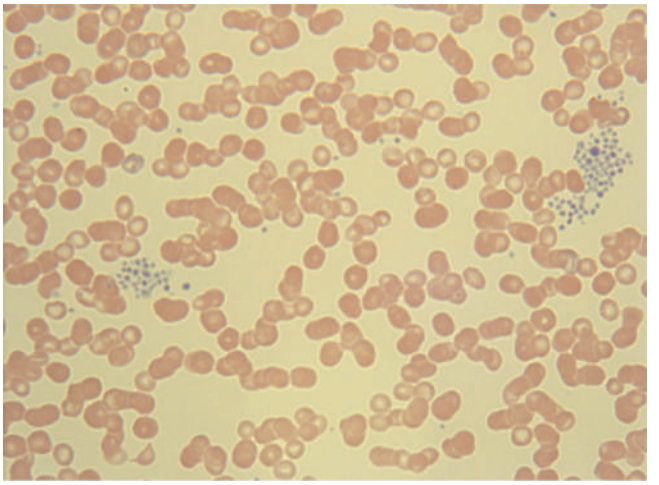
- Peripheral smear (see Chap. 32 for further details about interpreting the peripheral smear)
  - Figure 33-1A depicts thrombocytopenia on peripheral smear
  - Pseudothrombocytopenia (Fig. 33-1B) is an in vitro artifact resulting from platelet agglutination via antibodies (usually IgG, but also IgM and IgA) when the calcium content is decreased by blood collection in EDTA tubes (purple top) used to collect blood for CBCs
    - A peripheral smear will show clumped platelets in pseudothrombocytopenia
    - Use a sodium citrate (blue top) or heparin (green top) tube for CBC collection
  - *Schistocytes* suggest increased destruction of a microangiopathic hemolytic anemia
  - *Blasts* suggest decreased bone marrow production from several conditions, which may include
    - Acute leukemia
    - Myelodysplastic syndrome
    - Chronic myeloproliferative disorders
  - *Spherocytes* may suggest immune-mediated hemolytic anemia or hereditary spherocytosis
  - *Teardrop cells*, *nucleated RBCs*, or *immature granulocytes* suggest an infiltrative process in the bone marrow



A



B

FIGURE 33-1 Photomicrographs of peripheral blood smears. A. Normal peripheral blood. **B.** Platelet clumping in pseudothrombocytopenia. (Used with permission from Konkle BA. Disorders of platelets and vessel wall, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- CMP
  - Evaluates for liver disease as a clue to diagnosis
  - Abnormal kidney function and electrolytes may be present in hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (TTP)
- Absolute reticulocyte count (if also anemic)
- If concerned about hemolytic anemia
  - PT, PTT, INR
  - LDH
  - Haptoglobin
  - Indirect bilirubin
  - Fibrinogen: decreased in disseminated intravascular coagulation (DIC)
  - D-dimer: elevated in DIC
  - Coombs test: positive in autoimmune hemolytic anemia with immune thrombocytopenic purpura (ITP) (Evans syndrome)
  - ANA: screens for SLE, when indicated
- Blood cultures if concerned about sepsis-induced thrombocytopenia
- HIV testing if has risk factors for HIV/AIDS
- Hepatitis C RNA
  - Hepatitis C can cause cirrhosis
  - Chronic hepatitis C can also cause secondary ITP
- If concerned for heparin-induced thrombocytopenia, order
  - Anti–heparin/platelet factor 4–heparin complex antibody assay with ELISA (high sensitivity) and serotonin release assay (lower sensitivity, but higher specificity)
- ADAMTS13 level if concerned about TTP

IMAGING
- Liver ultrasound if suspecting cirrhosis
- Spleen ultrasound for sequestration assessment

PROCEDURE
- Bone marrow biopsy for
  - Unexplained thrombocytopenia
  - If a primary hematologic disorder is suspected, especially if other cell lines are affected

DIAGNOSTIC ALGORITHM OF THROMBOCYTOPENIA EVALUATION
After a history, physical exam, and initial diagnostic testing has been performed, Fig. 33-2 describes a diagnostic algorithm to help narrow the differential diagnosis of thrombocytopenia.

MANAGEMENT

THROMBOCYTOPENIC EMERGENCIES REQUIRING IMMEDIATE MANAGEMENT
- An expert in these disorders, typically a hematologist, should be consulted
  - Bleeding with severe thrombocytopenia (platelet count < 50,000/μL)
  - Urgently needing an invasive procedure with severe thrombocytopenia
  - Pregnancy with severe thrombocytopenia
  - Suspected heparin-induced thrombocytopenia (HIT) or platelet factor 4–associated immune thrombocytopenia and thrombosis (PITT)
  - Suspected posttransfusion purpura
  - Suspected thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), or drug-induced thrombotic microangiopathy
  - Acute disseminated intravascular coagulation (DIC)
  - Suspected acute leukemia, aplastic anemia, or other bone marrow failure syndrome
  - Hemophagocytic lymphohistiocytosis (HLH)

GENERAL CONSIDERATIONS FOR PLATELET TRANSFUSIONS
- Indications for platelet transfusion
  - Actively bleeding patients with platelet counts < 50,000/μL
  - Patients with CNS bleeding with platelet counts < 100,000/μL

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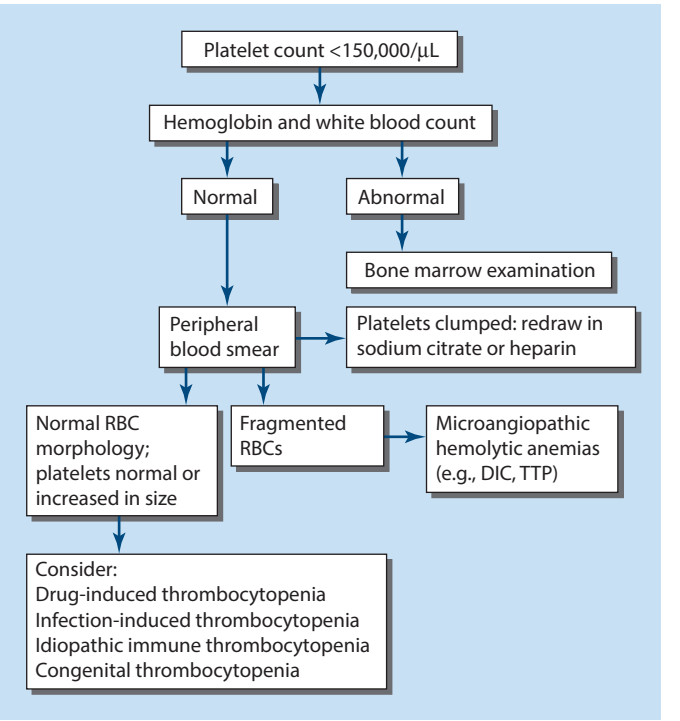

FIGURE 33-2 Algorithm for evaluating the thrombocytopenic patient. DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura. (Reproduced with permission from Konkle BA. Disorders of platelets and vessel wall, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Prevention of bleeding when patients have platelet counts < 10,000/μL—however:
        - If the patient has fever, infection, or inflammation, transfuse if the platelet count is < 15,000–20,000/μL (due to bone marrow suppression)
        - If the patient has acute promyelocytic leukemia, transfuse at platelet counts < 30,000–50,000/μL
    - In preparation for an invasive procedure
        - At what levels to transfuse depends on the type of procedure being performed
- Specific clinical scenarios
    - Immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), and heparin-induced thrombocytopenia (HIT)
        - Transfuse for bleeding, rather than according to a specific platelet count
    - Massive blood loss
        - Transfuse PRBCs, fresh frozen plasma, and platelets in a 1:1:1 ratio

MANAGEMENT & KEY FEATURES OF SELECTED THROMBOCYTOPENIA ETIOLOGIES

INFECTION-INDUCED THROMBOCYTOPENIA

- The most common noniatrogenic cause of thrombocytopenia
- May be associated with disseminated intravascular coagulation (DIC)
- Viral infections are the most common cause (HIV, hepatitis C, parvovirus B19, COVID-19)
- Can be from gram-negative rods, infectious mononucleosis, or any cause of sepsis
- Treatment
    - Treat the underlying infection
    - The thrombocytopenia is usually self-limited

DRUG-INDUCED THROMBOCYTOPENIA

- Chemotherapy, herbal, and over-the-counter drugs
- Quinine and sulfonamides can cause drug-dependent antibodies that react with platelet surface antigens
    - Takes a median of 21 days of drug exposure, or may occur upon re-exposure, and resolves after 7–10 days of stopping the drug

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- Treatment
  - Stop the offending medication (see Table 33-1)

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

- Usually not severe thrombocytopenia (rarely < 20,000/μL)
- Not associated with bleeding, but rather a markedly increased risk of thrombosis (arterial or venous) called heparin-induced thrombocytopenia thrombosis (HITT)
- The pathophysiology is complex, but anti–heparin/platelet factor 4–heparin complex activates platelets
- Can occur with exposure to low-molecular-weight heparin or UFH, usually 5–14 days after starting the medication (Fig. 33-3)
  - It can occur earlier than 5 days if the patient has been exposed to heparin in the prior few weeks or months and has circulating anti–heparin/platelet factor 4–heparin complex antibodies
- Rarely, thrombocytopenia and thrombosis begin several days after all heparin has been stopped (termed *delayed-onset HIT*)
- Platelet transfusions are not helpful
  - Transfuse only if bleeding is present
- When suspected, use the *"4Ts" score* (each category earns a score of 0–2)
  - Categories
    - Severity of thrombocytopenia
    - Timing of the platelet count drop
    - Thrombosis or other sequelae such as localized skin reactions
    - Other causes of thrombocytopenia (either definite, possible, or not evident)
  - Score is sum of values for each of above four categories
  - Score interpretation
    - Scores 0–3 indicate an extremely unlikely diagnosis of HIT
      - No further testing is recommended
      - Evaluate other etiologies of thrombocytopenia
    - Scores 4–5 indicate an intermediate probability of HIT and scores 6–8 indicate a high probability
      - Stop heparin
      - Start a nonheparin anticoagulant (e.g., argatroban)
      - Order HIT antibody testing
- Diagnosis
  - Anti–heparin/platelet factor 4–heparin complex antibody assay with ELISA (high sensitivity)
  - Serotonin release assay (lower sensitivity, higher specificity)
  - HIT remains a clinical diagnosis
- Treatment
  - Early recognition is key
  - *Discontinue heparin as soon as suspected and HIT score ≥ 4*
  - Replace with the direct thrombin inhibitor *argatroban,* 2 μg/kg/min IV, if bleeding risk does not outweigh the thrombotic risk [1]
  - Bivalirudin, fondaparinux, or a DOAC (rivaroxaban) are alternatives and appear to have efficacy but are not FDA- approved for this indication
  - Order imaging (at least a lower extremity Doppler) to evaluate for thrombosis
  - Anticoagulate for at least 3 months if thrombosis is diagnosed
  - Patients without thrombosis should also be considered for anticoagulation, given the risk of thrombosis
  - If needs warfarin therapy for another indication, do not start until the platelet count has recovered



FIGURE 33-3 Time course of heparin-induced thrombocytopenia (HIT) development after heparin exposure. The timing of development after heparin exposure is a critical factor in determining the likelihood of HIT in a patient. HIT occurs early after heparin exposure in the presence of preexisting heparin/platelet factor 4 (PF4) antibodies, which disappear from circulation by ~ 100 days following a prior exposure. Rarely, HIT may occur later after heparin exposure (termed *delayed-onset HIT*). In this setting, heparin/PF4 antibody testing is usually markedly positive. HIT can occur after exposure to either UFH or low-molecular-weight heparin (LMWH). (Reproduced with permission from Konkle BA. Disorders of platelets and vessel wall, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

- Acquired thrombocytopenia with immune-mediated destruction of platelets and inhibition of platelet release from megakaryocytes
- Children: post-infection and self-limited
- Adults: more chronic in nature
    - Can be from underlying disorders (e.g., SLE, HIV, hepatitis C, *Helicobacter pylori*)
        - Termed *secondary* ITP
- Insidious onset of mucocutaneous bleeding (oral mucosa, nosebleeds, GI bleeding, menorrhagia), but may be asymptomatic
- Rarely, life-threatening CNS bleeding can occur
- *Very low platelet counts* are seen in ITP
- Normal blood cells and peripheral smear
    - Or may show large platelets
- Wet purpura and retinal hemorrhages may herald life-threatening bleeding
- Platelet transfusions do not help
    - Transfuse only if bleeding
- Diagnosis
    - Serologic testing for antibodies is usually not helpful (low sensitivity and specificity)
    - Bone marrow examination is reserved for
        - Patients with other signs or laboratory abnormalities not explained by ITP
        - Patients who do not respond to initial therapy
    - Test for the following to rule in/out secondary ITP from
        - HIV
        - Hepatitis C
        - SLE
        - Monoclonal lymphoproliferative disorders (serum protein electrophoresis)
        - Hypogammaglobulinemia (testing IgA levels)
        - *Helicobacter pylori* (if geographically indicated)
        - Combined autoimmune hemolytic anemia with ITP (Coombs test) if anemia is present
- Treatment
    - With severe ITP and bleeding, admit the patient and administer
        - *High-dose glucocorticoids*
            - IV methylprednisolone, 1 g daily, or PO/IV dexamethasone, 40 mg daily
        - *IVIG* (1–2 g/kg given over 1–5 days)
            - IVIG increases platelet count more rapidly than glucocorticoids
        - Additional immunosuppressive agents (e.g., rituximab, daratumumab, rilzabrutinib) as needed
    - With no bleeding, platelet count > 5000 μL, and no signs of impending bleeding
        - Manage as an outpatient with *prednisone, 1 mg/kg/d*, or Rho(D) immune globulin therapy (50–75 μg/kg)
            - Rho(D) immune globulin therapy must be used only in Rh-positive patients
            - It has a black box warning for hemolytic anemia and is now used less often for ITP
    - *TPO receptor agonists* (eltrombopag or romiplostim)
        - Effective in raising platelet counts in patients with chronic ITP
        - More commonly used than rituximab and/or splenectomy [2]
    - Rituximab has shown efficacy in refractory ITP [3]
    - Other B-cell-directed antibodies have also been shown to be effective
    - Splenectomy for patients who relapse after other treatment modalities have been tried
        - Vaccinate against encapsulated organisms (pneumococcus, meningococcus, and *Haemophilus influenzae*) after splenectomy

DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC), THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP), & HEMOLYTIC-UREMIC SYNDROME (HUS)

ABNORMALITIES FOUND IN DIC, TTP, AND HUS

- *Schistocytes*
- Lab evidence of hemolysis (*increased LDH, decreased haptoglobin, increased indirect bilirubin*)
- Microvascular thrombosis

DIC

- All coagulation lab values are abnormal (increased PTT, increased PT, decreased fibrinogen)
- *Bleeding/oozing from everywhere* (including IV sites)

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- If the patient has cirrhosis, check the factor VIII level (will be increased in cirrhotic patients, normal in DIC patients)
- *Treat the underlying cause of the DIC, and administer blood products*
  - Administer cryoprecipitate if the fibrinogen is decreased (goal > 100 g/dL)
  - Administer fresh frozen plasma if the INR is increased
  - Administer platelets if platelets are < 50,000/μL
  - Transfuse packed RBCs if hemoglobin is < 7 g/dL

TTP

- *Pentad of symptoms (most patients do not have all five)*
  - Fever
  - Anemia (microangiopathic hemolytic anemia)
  - Thrombocytopenia
  - Renal failure
  - Neurologic symptoms
- Other symptoms may include
  - Nausea, vomiting, and diarrhea (from bowel ischemia)
  - Chest pain and dysrhythmias (from myocardial ischemia)
- The *PLASMIC score* can help estimate the probability of TTP (must already have the presence of microangiopathic hemolytic anemia with schistocytes before using this scoring system)
  - Platelet count < 30,000/μL
  - Hemolysis (reticulocytes > 2.5%, indirect bilirubin > 2 mg/dL, and haptoglobin < 50 mg/dL)
  - No active cancer
  - No history of organ or stem cell transplantation
  - Mean corpuscular volume < 90 fL
  - INR < 1.5
  - Creatinine < 2 mg/dL
  - Score interpretation
    - Low-risk patients have 0–4 of the above
    - Order an ADAMTS13 level in patients with ≥ 5 of the above
      - Treat for TTP until the ADAMTS13 level results
      - Typical turnaround time to result is several days
- Caused by a deficiency of or antibodies to ADAMTS13
  - ADAMTS13 normally cleaves von Willebrand factor (VWF) units (**Fig. 33-4**)
  - This causes VWF to be very large, as the units cannot be cleaved
  - These long VWF units will fragment RBCs, causing schistocytes, as well as causing platelet adhesion and aggregation and *microvascular thrombosis*
  - ADAMTS13 levels < 10% are diagnostic of TTP
- Normal PT/PTT, fibrinogen, and normal split products
- Idiopathic TTP
  - Etiology: HIV, pregnancy, ticlopidine, and clopidogrel use
- Platelet transfusions do not help
  - Transfuse only if bleeding
- Treatment of TTP
  - Rule out DIC with hemolysis and coagulation studies
  - *Therapeutic plasma exchange* is the mainstay of treatment and continues until the platelet count is normal and signs of hemolysis are resolved for at least 2 days
  - *Glucocorticoids* (IV methylprednisolone, 1000 mg daily) are used as an adjunct to plasma exchange
  - The addition of *rituximab* to initial therapy decreases the risk of relapse, but it is used only if an inhibitor is present
  - *Caplacizumab*
    - An anti-VWF antibody
    - Decreases mortality and burden of care when used in patients with ADAMTS13 < 10% or with high clinical probability of disease [4]
  - Recombinant ADAMTS13 has become available and is effective in congenital and acquired TTP [5]
  - If refractory TTP, rituximab, vincristine, cyclophosphamide, and splenectomy may be necessary

HUS

- Worse renal injury is observed in HUS than TTP, and usually no neurologic symptoms are present
- *Bloody diarrhea, usually from Escherichia coli O157:H7*

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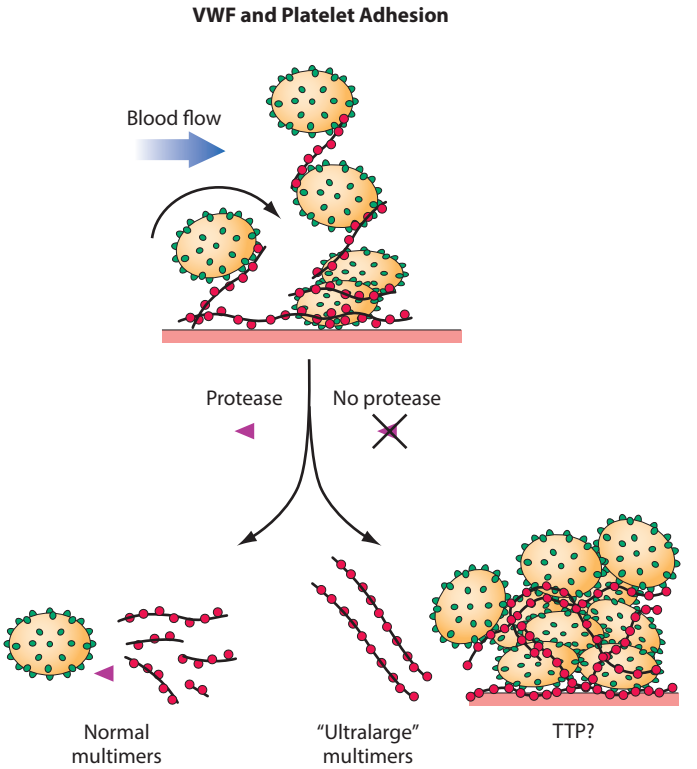

FIGURE 33-4 Pathogenesis of thrombotic thrombocytopenic purpura (TTP). Normally, the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) produced by the endothelial cells are processed into smaller multimers by a plasma metalloproteinase called ADAMTS13. In TTP, the activity of the protease is inhibited, and the ultra-high-molecular-weight multimers of VWF initiate platelet aggregation and thrombosis. (Reproduced with permission from Konkle BA. Disorders of platelets and vessel wall, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Shiga toxin activates the endothelium, leading to activation of VWF, and causes platelet aggregation and thrombocytopenia
    - Bloody diarrhea is not always present
- Atypical HUS is usually due to genetic defects in complement genes or antibodies directed against complementary regulatory proteins that result in chronic complement activation
- Treatment
    - Primarily supportive
    - Dialysis support may be needed (up to 40% of cases in children require dialysis)
    - Can attempt therapeutic plasma exchange at first (especially if TTP is also being considered) until the ADAMTS13 level results, but it does not alter the overall course of HUS or atypical HUS unless antibodies to factor H are present
    - Anticomplement therapy (eculizumab) has efficacy in atypical HUS in the resolution of the condition and in improving or preserving renal function

COMPLICATIONS

- Thrombotic thrombocytopenic purpura (TTP)
    - Patients with persistently low ADAMTS13 in TTP have a greater risk of ongoing sequelae, including stroke
    - There is a significant relapse rate
    - In patients treated with therapeutic plasma exchange, 25–45% of patients relapse within 30 days of initial "remission," and 12–40% of patients have late relapses
    - Relapses are more frequent in patients with severe ADAMTS13 deficiency at presentation

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- Patients with hemolytic-uremic syndrome may require dialysis
- Severe bleeding, including intracranial hemorrhage and spinal cord bleeds
- Increased risk of infections (due to impaired immune function and the inability to form clots properly)
- Complications from invasive procedures
- Death

PROGNOSIS

- Patients with immune thrombocytopenic purpura with platelet counts > 30,000/μL appear not to have increased mortality related to their thrombocytopenia
- The introduction of treatment with plasma exchange for thrombotic thrombocytopenic purpura has markedly improved the prognosis in patients, with a decrease in mortality from 85–100% to 10–30%
- The mortality rate for hemolytic-uremic syndrome (HUS) associated with diarrhea is < 5%, whereas the mortality rate for HUS not associated with diarrhea is ~ 26%

PATHOPHYSIOLOGY

DECREASED PLATELET PRODUCTION (BONE MARROW PROBLEM)

- Bone marrow suppression
  - Direct toxicity to megakaryocytes causes decreased platelet synthesis
  - Causes include
    - Chemotherapy
    - Radiation
    - Alcohol use
    - Use of certain drugs (chloramphenicol, linezolid)
    - Exposure to environmental toxins (benzene)
- Bone marrow infiltration or replacement
  - The normal hematopoietic tissue is replaced by malignant or fibrotic cells
  - Causes include leukemia, lymphoma, myelofibrosis, and metastatic tumors
  - Results in pancytopenia
- Nutritional deficiencies
  - Vitamin B_{12} or folate deficiency leads to impaired DNA synthesis and ineffective megakaryopoiesis
  - Produces megaloblastic marrow changes with concurrent anemia
- Viral infections
  - Direct suppression of the bone marrow (by HIV, hepatitis C, parvovirus B19, COVID-19)
  - Immune-mediated suppression of progenitor cells

INCREASED PLATELET DESTRUCTION & CLEARANCE

- Immune-mediated
  - Autoimmune
    - Immune thrombocytopenic purpura: autoantibodies (usually IgG) against platelet surface glycoproteins (e.g., GPIIb/IIIa, GPIb/IX) lead to splenic macrophage clearance of platelets
    - Can be caused by systemic autoimmune diseases (e.g., SLE, chronic lymphocytic leukemia)
  - Alloimmune
    - Posttransfusion purpura: antibodies against transfused platelets lead to rapid destruction of platelets
  - Drug-induced antibodies
    - Drugs act as haptens, binding to the platelet surface, leading to immune recognition
    - Heparin-induced thrombocytopenia: antibodies against platelet factor 4–heparin complex lead to platelet activation and paradoxical thrombosis
    - Other drugs: quinine, sulfonamides, gold salts
- Non–immune-mediated
  - Microangiopathic processes (platelet consumption within small vessel thrombi)
    - Thrombotic thrombocytopenic purpura: ADAMTS13 deficiency leaves VWF multimers uncleaved, leading platelet-rich microthrombi to form
    - Hemolytic-uremic syndrome: endothelial damage (often from Shiga toxin) leads to platelet activation and microthrombi
    - Disseminated intravascular coagulation: systemic activation of the coagulation cascade leads to widespread fibrin deposition and platelet consumption
    - Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: hemolysis, elevated liver enzymes, and low platelets in pregnancy linked to endothelial dysfunction and placental abnormalities

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- Mechanical destruction
  - Physical trauma to platelets from shear stress or artificial surfaces
  - Prosthetic heart valves and extracorporeal circuits (ECMO, dialysis) can cause this

INCREASED SPLENIC SEQUESTRATION

- Normally, ~30–40% of the total platelets are transiently sequestered into the spleen
- Splenomegaly (e.g., cirrhosis with portal hypertension, hematologic malignancy, storage diseases) can cause up to 90% of the total body platelets to be trapped in the spleen, leading to a low circulating platelet count
- Contributes both to sequestration and accelerated destruction

OTHER CONTRIBUTING MECHANISMS

- Systemic infections/sepsis
  - Inflammatory cytokines are increased and endothelial injury occurs, leading to platelet activation, consumption, and sometimes disseminated intravascular coagulation
- Chronic diseases (liver disease, alcohol use disorder, aplastic anemia) lead to thrombocytopenia through multiple mechanisms

RISK FACTORS

- Any of the underlying etiologies listed in the Etiology section
- Alcohol use
- Nutritional deficiencies
- Autoimmune disorders
- Liver disease with splenomegaly
- Major surgery
- Pregnancy
- Immune thrombocytopenic purpura is more common in women
- Older age
- History of previous thrombocytopenia
- Recent travel to areas with high rates of infectious diseases
- Exposure to certain chemicals (e.g., benzenes, pesticides)

ADMITTING ORDERS

- Admit to floor or ICU if severe thrombocytopenia and bleeding
- Diagnosis: thrombocytopenia
- Condition: guarded
- Vital signs: on admit and q4h, call for signs of bleeding or change in neurologic status
- Nursing: frequent neurologic exams
- Diet: per patient comorbidities
- Diagnostic tests
  - CBC (possibly in a sodium citrate [blue top] or heparin [green top] tube for CBC collection if concerned for pseudothrombocytopenia on peripheral smear)
  - Peripheral smear
  - CMP
  - Blood cultures if septic
  - Indirect bilirubin
  - LDH
  - Haptoglobin
  - PT/PTT/INR
  - Fibrinogen
  - D-dimer
  - Other potential tests to order based on history
    - Coombs test
    - ANA: screens for SLE
    - HIV test
    - Hepatitis C RNA
    - If concerned about heparin-induced thrombocytopenia (HIT), order anti–heparin/platelet factor 4–heparin complex antibody assay with ELISA and serotonin release assay
    - If concerned about thrombotic thrombocytopenic purpura (TTP), order ADAMTS13 levels

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- Medications
  - Platelet transfusion if platelets < 50,000/μL and bleeding, or if platelets < 10,000/μL
    - Other specific transfusion thresholds are listed in the Management section
  - If TTP: consult hematology for therapeutic plasma exchange and IV methylprednisolone, 1000 mg/d
  - If HIT: stop heparin product, and start argatroban, 2 μg/kg/min IV
  - Other medications depend on the underlying etiology

DISCHARGE INFORMATION

- Repeat CBC for platelet count 1 week after discharge
- Education to avoid medications that caused the thrombocytopenia, if applicable
- Prescribe antibiotic treatment if thrombocytopenia was from sepsis
- Education about comorbidities and their treatment that may contribute to thrombocytopenia
- Follow up with primary care clinician and a hematologist (if indicated) after discharge

CASE ANSWERS

1. Pseudothrombocytopenia is an in vitro artifact resulting from platelet agglutination via antibodies when the calcium content is decreased by blood collection in EDTA tubes (purple top) for CBC analysis. A peripheral smear should be reviewed, which will reveal clumped platelets in pseudothrombocytopenia. In this scenario, obtaining a CBC with a sodium citrate (blue top) or heparin (green top) tube eliminates this potential lab analysis artifact.
2. This patient is presenting with concerns of sepsis secondary to a skin and soft tissue infection. The finding of thrombocytopenia in this older patient with an acute illness can stem from many etiologies. Infection-induced thrombocytopenia can be caused by gram-negative rod pathogens (which may be present in skin and soft tissue infections). This patient also has sepsis, which increases inflammatory cytokines, causing endothelial injury and platelet activation, consumption, and sometimes disseminated intravascular coagulation (DIC). The finding of blood oozing from the patient's IV site also supports DIC may be present. Drug-induced thrombocytopenia and heparin-induced thrombocytopenia are both unlikely given the patient takes no medications and has not had recent heparin exposure. Immune thrombocytopenic purpura (ITP) is also less likely, as you would expect the platelet count to be even lower.
3. Labs to evaluate for hemolysis, including LDH, haptoglobin, and indirect bilirubin should be obtained. Whether or not schistocytes are observed on the peripheral smear, a PT, PTT, INR, fibrinogen, and D-dimer should be measured to evaluate for the presence of DIC, given the presence of blood oozing from the IV site. Blood cultures should be obtained in this patient with sepsis.

LANDMARK TRIALS

[1] Lewis BE et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 163:1849, 2003. [PMID: 12912723]
- *Summary:* Argatroban therapy, compared with historic control, improves outcomes, particularly new thrombosis and death due to thrombosis, in patients with heparin-induced thrombocytopenia.

[2] Soulard M et al. Efficacy and safety of TPO receptor agonists in treatment of ITP associated with predominantly antibody deficiencies. Blood Adv 8:6171, 2024. [PMID: 39348667]
- *Summary:* TPO-Ras seemed to be an effective and safe option for patients with immune thrombocytopenic purpura (ITP) and antibody deficiencies. Results suggest that eltrombopag or romiplostim should be considered as second-line therapy for ITP related to predominantly antibody deficiencies.

[3] Ghanima W et al. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet 385:1653, 2015. [PMID: 25662413]
- *Summary:* Despite no reduction in the rate of long-term treatment failure with rituximab, a small benefit cannot be ruled out, as suggested by an apparently longer duration of response and numerically higher response rates with rituximab.

[4] Scully M et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med 380:335, 2019. [PMID: 30625070]
- *Summary:* Among patients with thrombotic thrombocytopenic purpura (TTP), treatment with caplacizumab was associated with faster normalization of the platelet count; a lower incidence of a composite of TTP-related death, recurrent TTP, or a thromboembolic event during the treatment period; and a lower rate of recurrence of TTP during the trial than placebo.

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[5] Scully M et al. Recombinant ADAMTS13 in congenital thrombotic thrombocytopenic purpura. N Engl J Med 390:1594, 2024. [PMID: 38692292]
    - *Summary:* Patients receiving weekly or every 2-week prophylaxis with recombinant ADAMTS13 experienced no episodes of TTP in a 12-month period.

FURTHER READING

- Konkle BA. Disorders of platelets and vessel wall, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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35 Delirium

KEY POINTS

1. Delirium is an illness of mental and behavioral states with reduced comprehension and capacity to reason. Delirium fluctuates over time and has the hallmark of a deficit in attention. A wide variety of clinical etiologies can cause delirium; hence, it is one of the most common problems encountered in medicine.
2. The history is the most important part in assessing a patient with delirium; however, it can be extremely difficult to obtain, given the condition. In most instances, additional history from family members, friends, or caregivers is needed, and special attention should be placed on the following: (1) the patient's baseline cognitive function, (2) the time course of present illness, and (3) current medications. Physical exam (including a full neurologic and mental status exam for attention deficits) should be thorough, seeking clues for an underlying etiology (e.g., jaundice with asterixis supports hepatic encephalopathy). Screen for signs of infection and perform a volume status exam. Delirium can be either hypo- or hyperactive.
3. Delirium is a clinical diagnosis. The Confusion Assessment Method is a valuable tool for screening patients for delirium. No specific blood test or imaging study can diagnose delirium, but diagnostic testing is valuable to identify the underlying cause. Initial tests to obtain in all patients include a CBC and CMP. Further tests (e.g., UA and culture, CXR, blood cultures, ECG, ABG, toxicology screen, TSH, B_{12}/folate/thiamine, brain imaging) are guided by the history, physical, and initial lab data.
4. Always treat the underlying etiology of delirium. Avoid anticholinergic agents and sedating medications (e.g., benzodiazepines). Supportive therapy with frequent orientation, sensory equipment (e.g., glasses, hearing aids), placing the patient near a window, and promotion of a typical sleep-wake cycle is recommended. Melatonin may be used to prevent at-risk patients from developing delirium in the hospital. Avoid antipsychotics (especially in older adults due to increased mortality risk) if possible, but low doses may be necessary for patients who are agitated and violent.
5. Delirium leads to longer hospital stays, higher readmission rates, subsequent episodes of delirium, and further cognitive decline. Patients with delirium have an in-hospital 25–35% mortality rate and a fivefold higher mortality rate in the months after illness.

EPIDEMIOLOGY & DEFINITIONS

Delirium is among the most common problems encountered in medicine, accounting for a large number of ED visits, hospital admissions, and inpatient consultations. Delirium costs billions of dollars annually in the United States alone. Despite increased efforts to raise awareness of delirium, and despite the fact that delirium is often the cognitive manifestation of a serious underlying medical or neurologic illness, it often goes unrecognized.

Estimates of delirium in hospitalized patients range from 10% to > 50%, with higher rates reported for older patients and patients undergoing hip surgery. Older patients in the ICU especially have high rates (~ 75%) of delirium. Detecting delirium in the ICU can be especially difficult at times, and clinicians should view it as a manifestation of organ dysfunction. Outside the hospital, delirium occurs in ~ 25% of patients in nursing homes and in 50–80% of those at the end of life.

Delirium is a relatively acute decline in cognition that fluctuates over hours to days. The hallmark is a deficit of attention, although all cognitive domains—including memory, executive function, visuospatial tasks, and language—are invariably involved. Patients can have either hypo- or hyperactive delirium (patients often fall somewhere along a spectrum, sometimes fluctuating between one and the other).

CLINICAL VIGNETTE

An 80-year-old woman with confusion is transported from her assisted living facility to the ED via ambulance. She is currently unable to engage meaningfully with the history. You notice she occasionally coughs as you try to interview her. She has a list of medications that include metoprolol tartrate, apixaban, donepezil, hydrochlorothiazide, metformin, and prn lorazepam. It is unclear from the paperwork whether any of these medications are new, or if she has been taking them. On physical exam, you determine the following:

- Temperature: 37.8°C (100.1°F)
- Heart rate: 100 beats/min

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- Respiratory rate: 18 breaths/min
- BP: 110/78 mm Hg
- Spo_2: 94% on room air

The heart rate is irregularly irregular, and there are no murmurs. The right lower lobe has dullness to percussion and bronchial breath sounds, and there is decreased chest wall expansion on the right. She has no suprapubic tenderness. She is unable to repeat more than two numbers in a row on the digit span test and cannot spell "world" backward.

GUIDING QUESTIONS

1. What diagnostic tests (labs and imaging) would you order for this patient?
2. When you call the patient's assisted living facility for more information, what questions would you ask them?
3. What risk factors does this patient have that make her susceptible to delirium?

HISTORY

The history is the most important part in evaluating a patient with delirium. Because gaining a reliable history from the patient may be difficult due to the nature of delirium, it is invaluable to have a collateral source available to discuss the patient's current state and how it compares with a baseline. Some patients may present with a family member because of confusion, but the family has not seen the patient in years, and you may need to determine if the patient has underlying cognitive impairment or dementia. In the hospital, many patients will develop delirium, especially if they have underlying cognitive impairment and acute illness. There are three important details to know in this patient population:

(1) Baseline cognitive function
(2) Time course of present illness
(3) Current medications (e.g., new medications, dose changes, over-the-counter medications and herbal supplements, illicit drug use)

While delirium can be easily reversible (e.g., by treating an infection), some episodes may last weeks, months, or even years, and can even lead to long-term cognitive decline and dementia.

Screening tools can aid physicians and nurses in identifying patients with delirium. The Confusion Assessment Method (CAM) score is widely used (there is also a CAM-ICU version), and delirium can be diagnosed if there is

(1) An acute onset and fluctuating course
and
(2) Inattention
accompanied by either
(3) Disorganized thinking
or
(4) An altered level of consciousness

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - An older patient with cognitive impairment who over several days has had worsening attention deficits, has had confusion that fluctuates over time, and may have features of hypo- or hyperactivity
- What is the patient's baseline cognitive function?
  - Need to determine the patient's baseline cognitive function and compare it with the current presentation, as someone with dementia may be at baseline
- Time course of present illness
  - Acute is more likely to be delirium
  - Ongoing over a longer period is more likely to be dementia
- Hyper- or hypoactive features?
  - Agitation, hyperarousal, and hallucinations are seen in hyperactive delirium (e.g., delirium tremens in alcohol withdrawal)
  - Quiet, apathetic, and psychomotor slowing is seen in hypoactive delirium (e.g., benzodiazepine intoxication)
- Review outpatient records if available
  - Important to review their past medical history and medications
- Any recent illness?
  - Infection can be a cause of acute encephalopathy or delirium

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- Illicit drug use?
  - Drugs can be a cause of psychosis, delirium, etc.
- Toxin exposures?
  - Alcohol, carbon monoxide, ethylene glycol, inhalants, pesticides, etc.
- Head trauma?
  - Subdural hematoma, epidural hematoma, etc.
- Hydration status
  - Dehydration can cause delirium; electrolyte abnormalities can occur with dehydration or fluid overload (Na^+ and Ca^{2+} abnormalities)
- Sleep-wake disturbances?
  - Some patients may present with difficulty sleeping at night and sleeping through the day
- Hallucinations or delusions?
  - Common symptom of encephalopathy and delirium
- Attention deficits?
  - Tangential speech, fragmentary flow of ideas, or inability to follow complex commands is a hallmark of delirium

PAST MEDICAL HISTORY

- *It is vital to review the full past medical history*
- History of organ failure?
  - Cirrhosis can cause hepatic encephalopathy
  - CKD can cause uremia
  - HF can lead to decreased perfusion to the brain
- History of long-term alcohol use?
  - Acute alcohol toxicity
  - Alcohol withdrawal
  - Wernicke-Korsakoff syndrome
- History of depression?
  - Can lead to substance use disorder and overdose, or may masquerade as hypoactive delirium
- History of malignancy?
  - Metastases to the brain can cause encephalopathy and personality changes
- History of dementia? What type?
  - Delirium frequently occurs in the hospital in patients with baseline cognitive impairment and dementia
  - Lewy body dementia has a natural fluctuating course with
    - Visual hallucinations
    - Parkinsonism
    - Attention deficits that clinically resemble hyperactive delirium

SOCIAL HISTORY

- Use of alcohol or recreational drugs, smoking
- Occupation
- Living situation
- Sexual history

MEDICATIONS

- *It is vital to review all medications and their doses*
- Many medications can cause delirium (and should mostly be avoided in older patients)
  - Anticholinergics (can also lead to urinary retention causing delirium)
  - Opiates
  - Benzodiazepines
- New medications or changes to prior medications?
- Cefepime: can induce neurotoxicity that presents as encephalopathy, delirium; can lead to myoclonus
- Ask about over-the-counter and herbal medications

PHYSICAL EXAM

Vital signs are the most important aspect of the physical exam in a patient with delirium. A full physical exam should be performed to look for any clues about what may be causing the patient's current state. Screen for signs of infection (e.g., fever, tachycardia, tachypnea, pulmonary consolidation, heart murmur, signs of meningitis). Assess volume status and perform a full skin examination. A distended bladder may reveal urinary retention as a cause of delirium.

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- Vital signs
  - Look for fever, hypotension, hypertension, tachycardia, hypoxemia
- Respiratory exam
  - Consolidation, crackles
- Cardiac exam
  - New murmur? In the right setting, may be a sign of endocarditis.
  - Fluid status assessment
    - JVP, skin turgor, mucous membranes, edema, dry axilla
- Skin
  - Jaundice (hepatic encephalopathy)?
  - Cyanosis (hypoxemia)?
  - Needle tracks (injection drug use)?
  - New skin lesions to suggest infection or systemic illness?
- Neurologic and mental status exam
  - Assess for focal neurologic deficits that may indicate a stroke or brain mass lesion, making the person susceptible to delirium
  - Stiff neck?
    - Brudzinski's and Kernig's signs of meningitis
  - Screen for Parkinson's on exam (e.g., pill-rolling tremor, masked facies, cogwheel rigidity)
  - Assess for asterixis and myoclonus
  - Assess for attention deficits
    - Digit span test
      - Repeat numbers, adding a number each time
      - Patients without delirium can repeat five to seven numbers in a row until they fail
      - Patients with delirium typically can repeat fewer than four numbers
    - Spell "world" backwards
  - Assess Glasgow Coma Scale (GCS), Mini-Mental State Examination (MMSE), and/or Confusion Assessment Method (CAM) scores

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL

- A simple mnemonic to remember common etiologies: *HE STOPS TIPS AEIOU*
  - Hypertension/hepatic
    - Hypertensive emergency and hepatic encephalopathy or acute liver failure
  - Electrolytes
    - Disturbances in sodium, calcium, magnesium, or glucose
  - Stroke
    - Focal strokes in right parietal and medial dorsal thalamus (or a new stroke in a patient with a prior stroke)
  - Trauma
    - Especially trauma to the head, causing intracranial bleeding
  - Opiates
    - Cause sedation and delirium
  - Psychiatric
    - Decompensation of psychiatric disease may have delirium-like states
  - Seizure
    - Intermittent seizures may present like delirium with fluctuations in mental status
  - Temperature
    - Hypo- and hyperthermia (including fever)
  - Infection
    - Systemic infections, especially in older patients, can cause delirium
  - Porphyria
    - Can cause delirium
  - Sepsis
    - "Sepsis encephalopathy" and delirium are common in sepsis
  - Acidosis
    - Either respiratory or metabolic acidosis can cause delirium
  - Endocrine
    - Hyper- and hypothyroidism, hyperparathyroidism, and adrenal insufficiency

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- Intoxication (and medications)
  - Drugs of abuse (e.g., alcohol, ketamine)
  - Ethylene glycol
  - Carbon monoxide poisoning
  - Benzodiazepines
  - Anticholinergic agents
- Oxygen
  - Hypoxemia and hypercapnia
- Uremia/urinary retention
  - AKI and/or severe CKD; acute bladder obstruction

- A more thorough review of the differential diagnosis of delirium is listed in Table 35-1

DIAGNOSTIC TESTS

LABS

- Lab testing is usually guided by the history and physical exam
- Table 35-2 describes a stepwise approach to delirium workup (therefore, not all tests are listed here in the text)
- Consider the following in all patients for the initial assessment
  - CBC
    - Evaluate for anemia (cause of hypoxemia and tissue hypoxia)
    - Presence of leukocytosis may indicate infection
  - CMP
    - Evaluate for electrolyte abnormalities that can cause delirium
    - Hypo- and hyperglycemia (diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome)
    - Abnormal liver function tests (for hepatic encephalopathy or liver failure)
    - Elevated BUN and SCr (for uremia)
  - TSH can be considered initially
    - Hypo- and hyperthyroidism (especially thyroid storm and myxedema coma) can cause delirium
- Other tests can additionally be ordered guided by the history and exam (Table 35-3)

IMAGING

- In all patients, consider
  - ECG
    - In the case of decreased perfusion to the brain occurring from decreased cardiac output from myocardial ischemia
  - CXR for
    - Pneumonia
    - Pneumothorax
    - Aortic dissection (however, CXR is neither sensitive nor specific for aortic dissection evaluation)
- Brain MRI or noncontrast CT
  - Evaluates for stroke, encephalitis, brain abscess, or mass
  - MRI is preferred imaging method
- Electroencephalography is performed if seizures are suspected

MANAGEMENT

GENERAL PRINCIPLES OF DELIRIUM MANAGEMENT

- *Treat the underlying cause once found*
  - For example, correct electrolyte disturbances, treat systemic infections with appropriate antibiotics, and discontinue offending medications
  - It is important to understand that more than one etiology may contribute to delirium, and all need to be managed appropriately
- Use medications judiciously and avoid restraints unless the patient is combative
  - Avoid benzodiazepines, anticholinergics, antipsychotics, and other sedating medications
  - Dexmedetomidine
    - Can be used if severe hyperactive delirium is present
    - Needs monitoring in an ICU setting

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TABLE 35-1 Differential Diagnosis of Delirium
Toxins
Prescription medications: especially those with anticholinergic properties, opiates, and benzodiazepines
Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, "bath salts," marijuana and its synthetic forms
Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic Conditions
Electrolyte disturbances: hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia
Hypothermia and hyperthermia
Respiratory failure: hypoxemia and hypercapnia
Liver failure/hepatic encephalopathy
AKI and/or uremia; urinary retention
HF
Vitamin deficiencies: B_{12}, thiamine, folate, niacin
Dehydration and malnutrition
Anemia
Infections
Systemic infections: UTIs, pneumonia and other respiratory infections, skin and soft tissue infections, sepsis
CNS infections: meningitis, encephalitis, brain abscess
Endocrine Conditions
Hypo-, hyperglycemia
Hyper-, hypothyroidism
Hyperparathyroidism
Adrenal insufficiency
Cerebrovascular Disorders
Global hypoperfusion states
Hypertensive encephalopathy
Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions
Autoimmune Disorders
CNS vasculitis
SLE causing neuropsychiatric lupus
Neurologic paraneoplastic and autoimmune encephalitis
Seizure-Related Disorders
Nonconvulsive status epilepticus
Intermittent seizures with prolonged postictal states
Neoplastic Disorders
Diffuse metastases to the brain
Diffuse glioma
Carcinomatous meningitis
CNS lymphoma
Hospitalization
Terminal end-of-life delirium

GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; PCP, phencyclidine.
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- Empirical treatment, if necessary, for patients with severe encephalopathy (mnemonic: TONG)
  - Thiamine 100 mg IV prior to dextrose (if Wernicke-Korsakoff suspected)
  - Oxygen supplementation for hypoxemia
  - Naloxone 0.2–1.0 mg IV if suspect opiate overdose and the patient has apnea or impending respiratory arrest
  - Glucose: dextrose 50 g IV push if hypoglycemic

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TABLE 35-2 Stepwise Evaluation of a Patient with Delirium
Initial Evaluation
History with special attention to medications (including over-the-counter and herbals)
General physical exam and neurologic exam
CBC
Electrolyte panel, including calcium, magnesium, phosphorus
Liver function tests, including albumin
Renal function tests
First-Tier Further Evaluation Guided by Initial Evaluation
Systemic infection screen
UA and culture
Chest x-ray and tests for respiratory pathogens
Blood cultures
ECG
ABG
Serum and/or urine toxicology screen (perform earlier in young persons)
Brain imaging with MRI with diffusion and gadolinium (preferred) or CT
Suspected CNS infection or other inflammatory disorder: lumbar puncture after brain imaging
Suspected seizure-related etiology: EEG (if high suspicion, should be performed immediately)
Second-Tier Further Evaluation
Vitamin levels: B_{12}, folate, thiamine
Endocrinologic laboratories: TSH and free T_4; cortisol
Serum ammonia
Sedimentation rate
Autoimmune serologies: ANA, complement levels; p-ANCA, c-ANCA, consider paraneoplastic/autoimmune encephalitis testing in the serum and CSF
Infectious serologies: RPR; fungal and viral serologies if high suspicion; HIV antibody
Lumbar puncture (if not already performed)
Brain MRI with and without gadolinium (if not already performed)

c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; EEG, electroencephalogram; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; RPR, rapid plasmin reagin.
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DELIRIUM MANAGEMENT & PREVENTION WITH SUPPORTIVE CARE

- *Provide supportive care to the patient* (Fig. 35-1)
  - Frequent reorientation from nursing and family
  - Have clocks visible
  - Move patient to a bed with an outside-facing window
  - Provide patient with sensory aids if they are needed, including glasses and hearing aids
  - Promote a regular sleep-wake cycle (dark room at night with limited interruptions and lights on during the day)
  - Have family and friends visit during the day
  - Attempt to mimic the home environment (bring in photographs, blankets from home, nightstand objects, etc.)
  - Ensure adequate nutrition and hydration
  - Move patient out of bed for meals and promote regular walking/physical therapy if feasible
  - Remove indwelling lines (e.g., IVs, Foleys, central lines) and other medical equipment (e.g., telemetry) if feasible
- Provide melatonin before bed, to promote sleep
  - Dose
    - 3 mg can help prevent delirium in those at risk
    - Up to 9 mg if the patient already has delirium
  - Findings
    - Melatonin can reduce the rate of delirium in medical patients, and the role of melatonin in reducing the incidence of delirium in surgical patients and critical care unit patients requires further study [1]

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TABLE 35-3 Other Tests Guided by History and Exam

TEST	PURPOSE
Blood cultures	If concerned about a systemic infection
UA with culture	If concerned about UTI as the cause Patients should have symptoms of UTI, such as dysuria, suprapubic tenderness, and/or flank pain
Sputum culture, Gram stain, and respiratory viral panel	Evaluate when concerned about bacterial and viral pneumonia
Serum and/or urine toxicology screen	If concerned about drug use as the cause
ABG or VBG	ABG if concerned about hypoxemia specifically (this is an invasive test) VBG can be helpful in evaluating the $Paco_2$ and pH for hypercapnia and acidosis, respectively
Ammonia level	While hyperammonemia can point toward hepatic encephalopathy, most experts state an ammonia level is not necessary Hepatic encephalopathy is a clinical diagnosis
B_{12}, folate, and thiamine	Test these vitamin levels in the presence of malnutrition, severe alcohol use disorder, or prior gastric bypass surgery
ESR and CRP	If infection or an inflammatory process is suspected
Autoimmune serologies (ANA, complement, perinuclear or cytoplasmic antineutrophil cytoplasmic antibodies)	If autoimmune conditions are suspected
Rapid plasma reagin	If syphilis is on the differential
HIV antibody testing	If HIV is suspected
Lumbar puncture (after brain imaging) Tests from the CSF: Gram stain and culture Cell count and differential Glucose Protein Opening pressure Paraneoplastic/autoimmune encephalitis and cytology testing may be necessary	If meningitis is suspected

        - When nocturnal sleep quantity is severely compromised, melatonin use was associated with increased nocturnal sleep efficiency [2]
        - Although these promising findings need to be confirmed by a larger randomized clinical trial, they do suggest a possible future role for melatonin in the routine care of critically ill patients
- Medications to treat delirium are generally *not* advised unless the patient is combative and/or harming staff
    - Use bed alarms (to prevent falls) and personal sitters, if needed
        - *Avoid physical restraints*, as they can make patients more delirious
    - If medications are needed (Table 35-4) for severe agitation and potential harm to staff, use cautiously
        - Use as needed (not scheduled) and at low doses, as multiple clinical trials have consistently shown these medications are ineffective in preventing or treating delirium [3]
        - The choice of medication is complicated; attempt PO medications first if possible
    - There is increased mortality in older patients who receive antipsychotics [4]
    - Benzodiazepines
        - Often worsen confusion through their sedative properties
        - *Should* be used in alcohol or benzodiazepine withdrawal, however

COMPLICATIONS

- Longer lengths of hospital stay
- Higher likelihood of being discharged to a nursing home
- Higher frequency of readmissions

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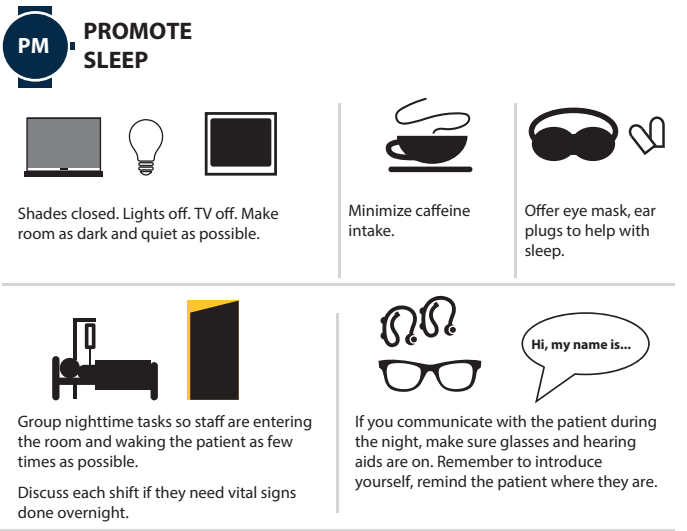
A



B

FIGURE 35-1 Delirium management and prevention: a checklist for hospitalized patients. Effective management of delirium relies on broad efforts to promote wakefulness (*A*) and sleep (*B*). CPO, continuous pulse oximetry. (Reproduced with permission from Josephson S, Miller BL. Confusion and delirium, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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TABLE 35-4 Medications for the Management of Delirium	
INTERVENTIONS	**DOSE**
Neuroleptics	
Haloperidol	0.5–5 mg q2–12h, PO/IV/SC/IM
Thioridazine	10–75 mg q4–8h, PO
Chlorpromazine	12.5–50 mg q4–12h, PO/IV/IM
Atypical Neuroleptics	
Olanzapine	2.5–5 mg qd or bid, PO
Risperidone	1–3 mg q12h, PO
Anxiolytics	
Lorazepam	0.5–2 mg q1–4h, PO/IV/IM
Midazolam	1–5 mg/h continuous infusion, IV/SC
Anesthetics	
Propofol	0.3–2.0 mg/h continuous infusion, IV

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- Subsequent episodes of delirium and cognitive decline
- General decline in health
- Poor recovery from surgery
- Permanent neurologic sequalae and dementia

PROGNOSIS

- Morbidity and mortality are substantial
- In-hospital mortality is 25–35% (similar mortality rates to sepsis)
- Patients with in-hospital delirium have a fivefold higher mortality rate in the months after their illness than those without delirium

PATHOPHYSIOLOGY

- The pathophysiology of delirium is incompletely understood
- Attention deficit
  - Hallmark of delirium
  - Has a diffuse localization within the brainstem, thalamus, prefrontal cortex, and parietal lobes
  - Electroencephalogram shows symmetric slowing, a nonspecific finding that supports diffuse cerebral dysfunction
  - Rarely, focal lesions such as ischemic strokes lead to delirium in otherwise healthy persons
- Multiple neurotransmitter abnormalities, proinflammatory factors, and specific genes likely play a role in the pathogenesis of delirium
  - Deficiency of acetylcholine: Medications with anticholinergic properties can commonly precipitate delirium
    - Alzheimer's disease, dementia with Lewy bodies, and Parkinson's disease are all associated with cholinergic deficiency due to degeneration of acetylcholine-producing neurons in the basal forebrain, and all are associated with higher rates of delirium
  - Increase in dopamine (visual hallucinations)
    - Patients with Parkinson's who are treated with dopaminergic agents can develop a delirium-like state that features visual hallucinations, fluctuations, and confusion
- Not all individuals exposed to the same insult will develop delirium
  - A low dose of an anticholinergic agent may have no cognitive effects on a healthy young adult but produce florid delirium in an older person with known underlying dementia
  - The concept of delirium developing as the result of an insult in predisposed individuals is currently the most widely accepted pathogenic construct
    - Therefore, if a previously healthy adult with no known cognitive illness develops delirium in the setting of a relatively minor insult (e.g., elective surgery, UTI, hospitalization), an unrecognized underlying neurologic illness (e.g., neurodegenerative disease, multiple previous strokes) should be considered
    - Delirium can be viewed as a "stress test" for the brain

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RISK FACTORS

- General
  - Age > 65 years
  - Baseline cognitive dysfunction (those who have low scores on standardized tests of cognition)
  - Pre-existing hearing and/or visual impairments
  - Baseline immobility
  - Malnutrition
  - Administration of medications that are deliriogenic
  - Underlying medical or neurologic illnesses
- If dementia at baseline
  - Difficult to distinguish between dementia and delirium due to significant overlap
  - At least two-thirds of cases of delirium occur in patients with coexisting underlying dementia
  - Lewy body dementia has a natural fluctuating course with visual hallucinations, parkinsonism, and attention deficits that clinically resembles hyperactive delirium
- In-hospital risks
  - Bladder catheterization
  - Physical restraints
  - Sleep and sensory deprivation
  - Addition of ≥ 3 new medications
  - Cardiopulmonary bypass
  - Inadequate or excessive treatment of pain
  - Some inhaled anesthetics or benzodiazepines

ADMITTING ORDERS

- Admit to floor or ICU if severe delirium (e.g., delirium tremens)
- Diagnosis: delirium
- Condition: stable-guarded
- Vital signs: every 4 h until stable, then routine
- Activity: as tolerated with assistance (if needed for risk of falls)
- Nursing: frequent reorientation of the patient, keep room light during day and dark at night, avoid sleep interruptions if possible, may need a personal sitter, strict *I*s/*O*s, frequent neurochecks
- Diet: regular or tailored to comorbidities
- Fluids: if dehydrated, may need fluids; if hypervolemic (e.g., from HF) may need fluid restriction (if HF with hyponatremia)
- Diagnostic tests
  - For all patients initially
    - CBC
    - CMP, including calcium, magnesium, phosphorus, albumin, and TSH
  - CXR and ECG; further testing may be necessary depending on the history and physical exam (see Diagnostic Tests section)
- Medications
  - Depends on the underlying cause of the encephalopathy and delirium
  - Avoid sedating medications (e.g., benzodiazepines) unless in alcohol or benzodiazepine withdrawal, and anticholinergic agents
  - Melatonin, 3–9 mg prior to bed
  - Antipsychotics only if the patient is agitated and at risk of harming staff

DISCHARGE INFORMATION

- Patient and family education
  - What precipitated the delirium, if known, and how to avoid offending triggers
  - Prevention strategies and management of delirium at home (if the patient has a baseline cognitive impairment or neurologic illness putting them at risk for delirium in the future)
- Medications
  - Cessation and avoidance of deliriogenic medications, such as anticholinergics and benzodiazepines
  - If antipsychotic medications were needed in the hospital for agitated delirium
    - Ideally, these medications are stopped before discharge
    - Patient is not sent home with them (increased mortality risk in older adults)
- Follow up with primary care

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CASE ANSWERS

1. This patient is presenting with confusion and delirium. A thoughtful history and exam compose the first step in diagnostic evaluation. Initial diagnostic tests for patients with delirium include a CBC, CMP, TSH, ECG, and CXR. Further testing may be indicated depending on the initial evaluation. For this patient, the additional findings of cough, low-grade fever, tachycardia, and right lower lobe dullness to percussion and bronchial breath sounds make community-acquired pneumonia an initial leading diagnosis. Therefore, a sputum culture and Gram stain, viral respiratory panel, and blood cultures are indicated.
2. While the physical exam and diagnostic tests are helpful in patients with delirium, a thorough history is extremely valuable. Events leading up to the presentation should be thoroughly questioned. An evaluation of the patient's baseline cognitive status (i.e., are they confused at baseline?) and how that compares to now is important. Understanding why the patient lives at an assisted living facility will also help you understand the patient's baseline cognitive and functonal status. A thorough medical history should be elicited. While a list of medications from the patient's assisted living facility is helpful, more information about the medications, how they are administered (e.g., scheduled or as needed), and if any are new or have been changed recently is valuable.
3. Understanding risk factors for delirium is important when evaluating a patient being admitted to the hospital. Age > 65 years and baseline cognitive dysfunction are the two most prevalent risk factors for delirium. Donepezil, which usually is administered to treat Alzheimer's dementia, is on her medication list. Patients with dementia are at very high risk for delirium. This patient also has lorazepam, which is a deliriogenic medication, on her medication list.

LANDMARK TRIALS

[1] You W et al. Melatonin intervention to prevent delirium in hospitalized patients: A meta-analysis. World J Clin Cases 10:3773, 2022. [PMID: 35647160]
- *Summary:* Melatonin can reduce the rate of delirium in medical patients, and the role of melatonin in reducing the incidence of delirium in surgical patients and critical care unit patients requires further study.

[2] Bourne RS et al. Melatonin therapy to improve nocturnal sleep in critically ill patients: Encouraging results from a small randomised controlled trial. Crit Care 12:R52, 2008. [PMID: 18423009]
- *Summary:* In this study, nocturnal sleep quantity was severely compromised and melatonin use was associated with increased nocturnal sleep efficiency. Although these promising findings need to be confirmed by a larger randomized clinical trial, they do suggest a possible future role for melatonin in the routine care of critically ill patients.

[3] Girard TD et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med 379:2506, 2018. [PMID: 30346242]
- *Summary:* The MIND-USA trial showed that use of haloperidol or ziprasidone, compared with placebo, in patients with acute respiratory failure or shock and hypoactive or hyperactive delirium in the ICU did not significantly alter the duration of delirium.

[4] Kheirbek RE et al. Association between antipsychotics and all-cause mortality among community-dwelling older adults. J Gerontol A Biol Sci Med Sci 74:1916, 2019. [PMID: 30753301]
- *Summary:* In a large cohort of older adults, antipsychotics were associated with an increased risk of all-cause mortality. While significant increase in mortality was attributable to the diagnosis of dementia, the addition of antipsychotics resulted in added mortality risk among all patients.

FURTHER READING

- Emanuel EJ, Urwin JW. Palliative and end-of-life care, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- Josephson S, Miller BL. Confusion and delirium, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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36 Sepsis

KEY POINTS

1. Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Any local infection can progress to systemic involvement causing sepsis.
2. Symptoms of sepsis can be localized to the site of infection (e.g., pain, erythema, and warmth in cellulitis) and/or nonspecific (e.g., fever, tachycardia, lethargy, myalgias). The general appearance of the patient (sick or not sick) can help form an initial impression of how ill the patient is. A thorough history, review of systems, and physical exam are necessary in all patients, with special focus on symptom progression, recent travel or sick contacts, recent hospitalizations or surgeries, immunocompromising conditions, vital signs, and skin and neurologic examination.
3. Sepsis remains a clinical diagnosis, as there is no specific test that can identify septic patients. Screening tools for early identification of sepsis (e.g., SIRS, qSOFA, NEWS) all have advantages and limitations. A broad workup, including blood cultures, CBC with differential, CMP, ESR/CRP, lactic acid, peripheral blood smear, D-dimer, lipase, and TSH should be initiated early. Other studies are directed toward the individual presentation.
4. After blood cultures are obtained, empirical antibiotic therapy and IV fluid resuscitation (at least 30 mL/kg in 3 h) should be administered. The earlier antibiotics are administered, the better the outcomes. Further fluids should be guided by dynamic measures and lactic acid levels. Identification of a source of infection is crucial, as some infections require source control via surgical intervention. Once a source has been identified, antibiotics should be tailored to the typical pathogens responsible for infection while also taking into account patient factors affecting the risk of certain pathogens (*Pseudomonas* and methicillin-resistant *Staphylococcus aureus* [MRSA]).
5. End-organ damage from sepsis is common and can include cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), AKI, and GI, hematologic, and neurologic complications. Septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities increase the mortality risk of sepsis alone. Mortality from sepsis (~ 15% overall in adults hospitalized in the United States) increases with age, the presence of existing comorbidities, and if end-organ damage occurs. Sepsis is responsible for one in five total global deaths yearly.

EPIDEMIOLOGY & DEFINITIONS

This chapter focuses on sepsis that is sufficiently hemodynamically stable to be admitted to the general medical floor. The complications section will also discuss end-organ dysfunction of sepsis that may require an ICU level of care.

Each year, ~ 48.9 million sepsis cases occur globally, and 1.7 million cases occur in the United States. Data from > 400 U.S. academic, community, and federal hospitals indicate that sepsis occurs in ~ 6% of hospitalized adults, with stable incidence over time. About 11 million sepsis deaths occur globally each year, accounting for 1 in 5 total global deaths, with 85% occurring in low- and middle-income countries. An estimated 350,000 sepsis deaths or discharges to hospice occur annually in the United States, with ~ 15% overall mortality among adults with sepsis. Data from the United States Centers for Medicare and Medicaid Services indicate that the aggregate cost for inpatient hospital and skilled nursing facility sepsis admissions was ~ $13.4 billion in 2018.

The definition of sepsis has changed with evolving consensus guidelines. Although clinicians still often use Systemic Inflammatory Response Syndrome (SIRS) criteria, the 2016 Sepsis-3 guidelines removed the SIRS criteria (which poorly distinguished sepsis from other noninfectious inflammatory processes) and the term *severe sepsis*. Instead, the 2021 Surviving Sepsis Campaign guidelines recommend that hospitals implement one of the many sepsis screening tools, such as the Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), National Early Warning Score (NEWS), Modified Early Warning Score, or the artificial intelligence–based Targeted Real-Time Early Warning System. Each screening tool has advantages and limitations. Use the scoring tool your hospital uses.

Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection.
Septic shock: a subset of sepsis in which organ dysfunction results from an imbalance between cellular oxygen supply and demand, resulting in cellular and tissue hypoxia.
qSOFA score: a scoring tool used outside the ICU setting. Presence of ≥ 2 of the following criteria shows a poorer prognosis from sepsis (this is one of many sepsis screening tools; use the tool your hospital system uses).

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1) Respiratory rate ≥ 22 respirations/min
2) Altered mentation
3) Systolic BP ≤ 100 mm Hg

SIRS: presence of ≥ 2 of the following conditions suggests sepsis (this is no longer recommended by sepsis guidelines but is still used clinically).

1) Fever (> 38°C) or hypothermia (< 36°C)
2) Tachypnea (> 24 respirations/min)
3) Tachycardia (heart rate > 90 beats/min)
4) Leukocytosis (> 12,000 cells/μL), leukopenia (< 4000 cells/μL), or presence of > 10% bands

CLINICAL VIGNETTE

A 65-year-old man presents to the ED with fever, chills, nausea, lethargy, and abdominal pain. He has diabetes, hypertension, and hyperlipidemia. He states the pain started yesterday, was sudden in onset, and is located in the left lower quadrant. The fever, chills, and vomiting started today, causing him to come to the ED. He denies blood in the stool. A full review of systems is otherwise negative.

On exam, vitals reveal a temperature of 38.6°C (101.6°F), heart rate 108 beats/min, respiratory rate 20 breaths/min, BP 112/68 mm Hg, and SpO_2 96% on room air, and he weighs 80 kg. He appears lethargic and is wincing in pain. Respiratory exam is normal. There is a regular tachycardic rhythm without murmurs. Abdominal exam reveals voluntary guarding with palpation of the left lower quadrant and with normal bowel sounds.

Lab data reveal the following:

- WBC count 12,000 cells/μL
- Hemoglobin 12.8 mg/dL
- Platelets 250,000/μL
- CRP 110 mg/dL
- Lactic acid 3.8 mmol/L
- Normal TSH

A CT of the abdomen and pelvis reveals left-sided localized colonic bowel wall thickening in diverticula with an associated 5-cm abscess with a well-defined wall. Colonic perforation, bowel obstruction, and fistulization are not present on the CT. Blood cultures are obtained.

GUIDING QUESTIONS

1. What two categories of microorganisms would you consider when selecting empirical antibiotics?
2. What empirical antibiotics would you start for this patient?
3. How much fluids would you order initially?
4. Does this patient need source control?

HISTORY

There is wide variation in presentations of sepsis. Nonspecific signs and symptoms may be present, including fever, lethargy, and myalgias with or without localizing organ findings such as cough, pyuria, abdominal pain, or evidence of end-organ dysfunction (e.g., oliguria, altered mental status). Patients can be very ill yet afebrile or even hypothermic. Absence of fever is common in neonates, older persons, patients with uremia or alcohol use disorder, as well as those with immunocompromising conditions or therapies. Hyperventilation producing respiratory alkalosis is a common early manifestation. Some patients will be encephalopathic and will not be able to meaningfully provide a history. In these patients, physical exam and correspondence with someone who knows the patient are vital.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/*s*ymptoms—or use your preferred mnemonic)
  - May present with focal infectious symptoms (e.g., a red, warm, and painful cellulitis), while others may present with nonspecific symptoms including fever, tachycardia, lethargy, and myalgias
- Fever and/or chills?
  - Common findings in patients with sepsis

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- Altered mental status?
  - May be a clue to a specific cause (e.g., meningitis, encephalitis) or be part of the sepsis syndrome
- Shortness of breath?
  - May point to a specific cause (e.g., pneumonia) or herald a severe infection at another site, causing acute lung injury
- Skin changes?
  - Possible cellulitis, osteomyelitis, gangrene, necrotizing fasciitis, or rashes of various infections
- Cough?
  - Bacterial or viral pneumonia may be present
- Abdominal pain/swelling?
  - Spontaneous bacterial peritonitis, cholangitis, cholecystitis, colitis, and pancreatitis should be considered
- Nausea and vomiting?
  - Able to tolerate oral meds?
  - Could be a sign of a GI infection (e.g., diverticulitis) or part of the sepsis syndrome
- Pain with urination? Flank pain?
  - Points toward the urinary tract and kidney (e.g., UTI, pyelonephritis) as potential sepsis sources
- Diarrhea?
  - Sign of GI infection, and possible hypovolemia
- Jaundice?
  - Sign of biliary infection, underlying cirrhosis, or part of the sepsis syndrome
- Recent exposure to a sick contact?
  - What was their infection? How were they treated? What type of exposure and for how long?

REVIEW OF SYSTEMS

- *A full review of systems is required, especially focusing on the following*
  - Neurologic symptoms?
    - Possible meningitis, encephalitis, brain abscess
  - Rashes?
    - Skin and soft tissue infections or potential systemic infections
  - Focal pain?
    - Skin, soft tissue and muscle infections; osteomyelitis and abscesses should be considered
  - Respiratory/GI/genitourinary complaints
    - Pneumonia, GI illness, UTI/pyelonephritis

PAST MEDICAL HISTORY

- History of diabetes?
  - More susceptible to *Pseudomonas* infections and infections in general
  - Glycemic control will be important in management
- History of cirrhosis?
  - Possible spontaneous bacterial peritonitis and susceptible to most types of infections
- History of HIV/AIDS?
  - Susceptible to certain types of infections, including *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, cytomegalovirus, toxoplasmosis, cryptococcus, cryptosporidiosis, coccidioidomycosis, *Histoplasma*, *Mycobacterium avium* complex, tuberculosis, herpes simplex virus
- History of cancer?
  - Immunocompromised state, especially if on chemotherapy
- Any other underlying medical conditions?
  - Two-thirds of sepsis cases occur in patients with significant medical comorbidities

SURGICAL HISTORY

- Any recent surgical procedures?
  - Makes the patient prone to surgical site infections
- Any prior surgeries with hardware placed?
  - Hardware in the body may be a nidus of infection
- History of splenectomy?
  - These patients are susceptible to encapsulated organisms and have worse outcomes compared to other patients
    - *Haemophilus influenza* type b
    - *Streptococcus pneumoniae*
    - *Neisseria meningitidis*

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- Group B *Streptococcus*
- *Klebsiella*
- *Salmonella typhi*
- *Capnocytophaga canimorsus*

SOCIAL HISTORY

- Use of alcohol or recreational drugs (especially injection drug use), smoking
- Occupation
- Living situation
- Sexual history
- Recent travel?
  - Especially in areas endemic to specific pathogens
- Vaccine history

MEDICATIONS

- Ask about any recent or new medications
- Chemotherapy makes patients susceptible to severe infections

PHYSICAL EXAM

A full exam to look for any signs of infection is warranted. It is important to assess vital signs early, as sepsis and septic shock need emergent interventions to improve outcomes. Areas that may be overlooked, including general appearance and a detailed skin, soft tissue, and neurologic exam, should receive special attention. All central catheters and tubes (e.g., Foley catheters, G-tubes) should be evaluated for signs of infection. The physical findings of the sepsis syndrome are too diverse to fully list here.

- Vital signs
  - Evaluate for fever (or hypothermia), hypotension, tachycardia, tachypnea, and hypoxemia
  - Older and immunocompromised persons may not mount a fever response in sepsis
- General appearance
  - Sick or not sick?
- HEENT
  - Cranial nerve exam
    - Evaluates for neurologic infections that may have focal neurologic signs, like intracranial abscess and encephalitis
  - Oral mucosa exam
    - Evaluates hydration status and for infectious sources
- Cardiac
  - New murmurs can be seen in endocarditis
  - Evaluate JVP
  - Capillary refill testing
    - Capillary refill times can help titrate fluid resuscitation in sepsis [1]
- Respiratory
  - Auscultate and percuss to evaluate for pneumonia, loculated pleural effusions, and empyema
- Abdominal
  - Listen for bowel sounds
  - Evaluate for areas of tenderness (e.g., suprapubic tenderness)
  - Examine for abdominal distention and fluid wave for presence of ascites
- Genital
  - Evaluate genitalia for signs of infection
  - Presence of Foley catheter may be a nidus for infection
- Skin and musculoskeletal
  - Evaluate for possible sources of infection
    - Open wounds, abscesses, rashes, and wet gangrene
  - Neck stiffness
    - Possible meningitis or intracranial abscess
  - Petechial rashes may be seen in meningococcemia or Rocky Mountain spotted fever
  - Erythroderma is associated with toxic shock syndrome
  - Examine joints and vertebrae to look for signs of septic arthritis and spinal epidural abscesses, respectively
  - Lymphadenopathy can be a sign of infection

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- Neurologic
  - Evaluate for any focal neurologic findings
    - Possible encephalitis or brain abscess
  - Papilledema?
    - Papilledema suggests increased intracranial pressure

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Sepsis mimics include but are not limited to
  - Noninfectious inflammatory febrile syndromes such as
    - Connective tissue diseases
    - Vasculitides
    - Thyroid storm
  - HF, MI, and other noninfectious causes of pneumonitis or lung injury
  - Noninfectious abdominal syndromes including
    - Mesenteric ischemia
    - Inflammatory bowel disease
    - Pancreatitis
  - Hypotension due to noninfectious causes, including
    - Hypovolemia
    - Autonomic dysfunction
    - Adrenal insufficiency

ETIOLOGY

- About 88% of sepsis cases are community-acquired (defined as being detected within 48 h of hospitalization)
- The other ~ 12% are hospital-acquired, detected after 48 h of hospitalization
- While viruses, fungi, and other pathogens may induce sepsis, the role of bacterial infection is best described
- An estimated 53% of sepsis cases in the United States are bacterial culture–positive, with a relatively even split between gram-positive and gram-negative pathogens
- Community-acquired infections
  - *Staphylococcus aureus*, *Streptococcus*, and *Enterococcus* species are the most prevalent gram-positive organisms isolated
    - 13.6% are antibiotic-resistant, including
      - Methicillin-resistant *S. aureus* (MRSA)
      - Vancomycin-resistant enterococci (VRE)
  - *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* were the most frequently isolated gram-negative organisms
    - 13.2% were resistant to ceftriaxone, extended-spectrum β-lactams, or carbapenems
  - The most frequently reported anatomic site of primary infection is
    - Urinary tract (48.9%)
    - Respiratory tract (32.9%)
    - Intraabdominal site (13.6%)
    - Skin or soft tissue (10.3%)
- Hospital-acquired infections
  - Differ from community-onset sepsis in that patients more often have comorbidities and experience intraabdominal infections and bacteremia with *Enterococcus*, *Candida*, and *Pseudomonas* more frequently

DIAGNOSTIC TESTS

- Sepsis remains a clinical diagnosis
- There is no gold standard diagnostic test for sepsis
- Therefore, epidemiologic, demographic, clinical, laboratory, radiologic, and microbiologic parameters must be considered in diagnosing sepsis

LABS

- Blood cultures × 2 before antibiotics (or 3 sets if concerned about endocarditis)
- CBC with differential
  - Leukocytosis with left shift, thrombocytopenia, and leukopenia may develop
  - Also assess neutrophil count

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- CMP
  - Hyperbilirubinemia and elevated LFTs may point toward a specific etiology
  - Evaluate electrolytes and glucose
  - Metabolic acidosis is a common finding in severe infection
- Lactic acid
  - Lactic acidosis is suggestive of infection and may define the severity of tissue hypoxia
  - Repeat a lactic acid after antibiotics and fluids are initiated to ensure it has returned to normal
  - Serial lactic acid levels can be used to guide fluid resuscitation in patients whose initial level was elevated
- Lipase
  - Pancreatitis mimicking sepsis
  - An infected necrosis of the pancreas also can occur
- Coagulation studies (PT/PTT/INR) and D-dimer
  - Some infections may lead to disseminated intravascular coagulopathy
- TSH
  - Thyroid storm and myxedema coma may mimic an acute febrile infection
- ABG or VBG
  - In the early stages of sepsis, may see a respiratory alkalosis from tachypnea
  - With respiratory fatigue and accumulation of lactate, metabolic acidosis (with increased anion gap) typically supervenes
- Cosyntropin test
  - Can help rule out adrenal insufficiency as a mimic
  - However, many experts feel this test is not useful for detecting less profound degrees of corticosteroid deficiency in patients who are critically ill
- UA with culture
  - If suspecting UTI or pyelonephritis
- Sputum culture, Gram stain, and respiratory viral panels
  - If suspecting pneumonia from bacterial or viral sources (COVID-19 or influenza)
- Wound cultures
  - Do not delay antibiotics to obtain a wound culture if it will take longer than a few minutes
  - Wound cultures are often not accurate in identifying a specific pathogen causing the wound
- Procalcitonin
  - Can help differentiate a bacterial infection (procalcitonin will be high) from a viral infection

IMAGING

- ECG
  - May show only sinus tachycardia, may have ST–T wave abnormalities
  - However, myocardial ischemia can present similar to sepsis
- CXR
  - Evaluates for pneumonia or other sources of infection, dyspnea, or hypoxemia in the chest (such as HF or COPD)
- Head CT and/or brain MRI if encephalopathic
  - Evaluates for meningitis, encephalitis, brain abscesses, and head bleeds
- Other imaging studies depend on the patient's presentation
  - Abdominal CT
  - MRI of bones/soft tissues
  - Transthoracic and/or transesophageal echocardiogram if suspecting endocarditis

PROCEDURES

- Lumbar puncture to obtain CSF studies before antibiotics if suspecting meningitis
  - Include opening pressure, cell count and differential, culture, glucose, protein, and bacterial and viral PCRs
  - Obtain brain imaging prior to lumbar puncture if there are focal neurologic findings, depressed mental status, or papilledema
    - These findings are suggestive of increased intracranial pressure, where a lumbar puncture could cause brain herniation
- Paracentesis if concerned about spontaneous bacterial peritonitis in a patient with cirrhosis
  - Order serum albumin, ascitic albumin, ascitic protein, and cell count and culture, and potentially other studies based on clinical presentation

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MANAGEMENT

Patients with suspected sepsis must be managed urgently. This includes measures to treat the infection (*antibiotics*), to provide hemodynamic stability (*fluids*), and to remove or drain infected tissues (*source control*). These measures should be initiated within 1 h of the patient's presentation. It is now a strong recommendation that hospitals and health systems use a performance improvement program for sepsis in order to improve timeliness in the recognition and management of sepsis.

CORE PRINCIPLES (FROM SURVIVING SEPSIS CAMPAIGN: INTERNATIONAL GUIDELINES FOR MANAGEMENT OF SEPSIS AND SEPTIC SHOCK 2021)

- Administer *broad-spectrum antibiotics* as soon as possible [2]
  - Early appropriate antibiotics have been most clearly associated with improved survival in septic shock
    - Empirical antibiotics are recommended within ≤ 1 h of presentation in septic shock
  - In patients with suspected or confirmed sepsis without shock, the time to antibiotics to improve mortality has not been clearly established
    - If an alternative diagnosis is not identified within 3 h of clinical presentation, empirical antibiotic administration is recommended
- *Aggressive early fluid resuscitation: administer at least 30 mL/kg IV crystalloid fluid in the first 3 h* [3]
  - Most patients require continued administration of IV fluids following initial resuscitation
  - After initial resuscitation, administer additional fluids guided by a frequent reassessment of status of dynamic measures like heart rate, BP, Pao_2, respiratory rate, temperature, urinary output, noninvasive cardiac output monitoring, and capillary refill time [1]
    - *Use dynamic measures to guide fluid resuscitation over static parameters and physical exam alone* (see Complications section for more information)
  - Guide resuscitation *to normalize the lactic acid* in those with an initial elevated lactate
  - May need to administer less fluids if the patient has decompensated HF or ESRD
- *Source control*
  - An important step that can often be overlooked
  - Always attempt to find the source of infection, as some infections require surgical intervention to adequately manage the infection

ANTIBIOTICS

- Start antibiotics as soon as blood and other relevant sites have been obtained for culture if sepsis is confirmed
- Initial empirical antibiotic selection should consider
  - The site of infection and potential etiologic organisms
  - Community versus health care exposure
  - Known prior infections
  - Recent antibiotic usage
  - Local antimicrobial resistance profiles
  - The patient's immune status, comorbidities, and illness severity
- In patients with a *suspected site of infection*
  - Take into account patient factors in addition to likely pathogens when deciding initial empirical antibiotics (**Table 36-1**)
  - In patients with suspected sepsis but unconfirmed infection, it is recommended to
    - Continuously re-evaluate and search for alternative diagnoses
    - Discontinue empirical antibiotics if an alternative cause of illness is demonstrated or strongly suspected
- In *undifferentiated sepsis*
  - The primary site of infection is unclear
  - Use broad-spectrum antibiotics with a high likelihood of activity against all organisms likely causing the infection
    - Broad coverage for both gram-positive and gram-negative organisms is recommended
  - If *Pseudomonas* is a likely pathogen, administer one of the following agents
    - Cefepime
    - Piperacillin-tazobactam
    - A carbapenem (imipenem or meropenem)
  - If *Pseudomonas* is *not* a likely pathogen, use a third-generation cephalosporin
    - Ceftriaxone or cefotaxime are commonly used antimicrobials

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TABLE 36-1 Site-Specific Empirical Antibiotic Recommendations

SITE OF INFECTION	INITIAL EMPIRIC THERAPY	OTHER CONSIDERATIONS
Pulmonary		
CAP	Multidrug therapy with a β-lactam (ampicillin + sulbactam, ceftriaxone, or ceftaroline) and a macrolide (azithromycin or clarithromycin) Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin)	Risk factors for MRSA and/or *Pseudomonas aeruginosa*: add vancomycin or linezolid for MRSA coverage; replace standard CAP therapy with antipseudomonal coverage such as piperacillin-tazobactam, cefepime, meropenem, or imipenem. Recommendation based on "local validation" of risk factors for community-onset MRSA or *P. aeruginosa* or prior isolation of these organisms in the previous year, particularly from respiratory specimens.
HAP/VAP	Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam	Two antipseudomonal antibiotics from different classes (addition of fluoroquinolones, aminoglycosides, or polymyxins) if prior IV antibiotic use within 90 days for HAP/VAP and septic shock at time of VAP, ARDS preceding VAP, 5 or more days of hospitalization prior to VAP, or acute renal replacement therapy prior to VAP. If prior colonization with carbapenem-resistant Enterobacterales or KPC-producing organism, ceftazidime-avibactam and meropenem-vaborbactam should be considered, but further efficacy data are needed. Empiric regimens should be informed by local distribution of pathogens and their antimicrobial susceptibilities.
Central Nervous System		
Health care–associated ventriculitis and meningitis	Vancomycin and cefepime, ceftazidime, or meropenem	β-Lactam choice based on local in vitro susceptibility patterns. If carbapenem-resistant *Acinetobacter* is suspected, addition of meropenem and colistin or polymyxin B.
Meningitis	Vancomycin and ceftriaxone	Age > 50, alcohol abuse, or immunocompromised: add ampicillin. Penetrating head trauma, CSF shunt, or postneurosurgery, vancomycin and cefepime, ceftazidime, or meropenem. Clinical presentation suggestive of *Rickettsia* or *Ehrlichia*, add doxycycline.
Skin and Soft Tissue		
Necrotizing fasciitis including Fournier gangrene	Multidrug therapy with vancomycin or daptomycin, piperacillin-tazobactam or a carbapenem, plus clindamycin or linezolid	Prompt surgical consultation is recommended for patients with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene.
Nonpurulent cellulitis/erysipelas (severe)	Vancomycin and piperacillin-tazobactam	Emergent surgical inspection to rule out necrotizing process.
Purulent furuncle/carbuncle/abscess (severe)	Vancomycin, daptomycin, linezolid, telavancin, or ceftaroline	Incision and drainage as indicated.
Intraabdominal		
Community-onset extrabiliary (mild)	Cefoxitin, ertapenem, moxifloxacin, or tigecycline	Health care setting with high prevalence of ESBL-producing Enterobacterales or > 20% of *Pseudomonas* resistant to ceftazidime, consider carbapenem or piperacillin-tazobactam.

(*Continued*)

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TABLE 36-1 Site-Specific Empirical Antibiotic Recommendations (*Continued*)

SITE OF INFECTION	INITIAL EMPIRIC THERAPY	OTHER CONSIDERATIONS
Community-onset extrabiliary (severe)	Imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam	Health care associated: imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin, or cefepime each along with metronidazole, vancomycin added to each regimen.
Community-onset biliary (mild to moderate)	Cefazolin, cefuroxime, or ceftriaxone	Empiric therapy should be driven by local microbiologic data and source control performed as indicated.
Community-onset biliary (severe) or cholangitis	Imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin, or cefepime each in combination with metronidazole	
Genitourinary		
Acute pyelonephritis (IDSA archived)	Ceftriaxone, trimethoprim-sulfamethoxazole, or ciprofloxacin	Requiring hospitalization: IV fluoroquinolone, aminoglycoside, extended-spectrum cephalosporin, extended-spectrum penicillin, or carbapenem with choice of agents based on local resistance data. Do not use fluoroquinolone if > 10% resistance prevalence or trimethoprim-sulfamethoxazole in areas of high resistance.

ARDS, acute respiratory distress syndrome; CAP, community acquired pneumonia; ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; IDSA, Infectious Diseases Society of America; KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.
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    - In patients at risk for highly resistant gram-negative infections (e.g., patients with prior known highly resistant infections or colonization)
        - Administration of two empirical gram-negative–covering antibiotics is recommended
    - If methicillin-resistant *Staphylococcus aureus* (MRSA) is a likely pathogen (e.g., frequent health care exposure or hospital-onset sepsis)
        - Administer vancomycin or linezolid
    - Empirical antifungal coverage is *not* recommended in patients with undifferentiated sepsis unless the patient is at risk of fungal infections
        - Scenarios in which antifungal coverage may be considered, such as
            - Recent abdominal surgery
            - Parenteral nutrition
            - Liver failure
            - Colonization of multiple anatomic sites with *Candida*
        - Use an echinocandin (micafungin or caspofungin) if concern for fungal infection
- Antivirals should be used only in viral-specific etiologies
    - Remdesivir for COVID-19
    - Oseltamivir for influenza
- Consult with a pharmacist to optimize antibiotic delivery methods
    - For example, administering β-lactams prior to vancomycin and prolonged infusions of β-lactam antibiotics after the initial infusion
- Tailor and de-escalate antibiotics according to type of infection and microbiologic data
- Treatment duration depends on type of infection
- For details of the management of specific infections, refer to the following chapters
    - UTI (**Chap. 38**)
    - Pneumonia (**Chap. 39**)
    - *Clostridioides difficile* infection (**Chap. 40**)
    - Endocarditis (**Chap. 41**)
    - Meningitis
    - Cellulitis (**Chap. 43**)
    - Osteomyelitis

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SOURCE CONTROL

- Identifying sources of infection amenable to control is imperative and should occur as rapidly as possible
- Examples include (with accompanying diagnostic imaging tests), but are not limited to
  - Intraabdominal abscess: ultrasound or CT of the abdomen
  - Bowel perforation: CT of the abdomen
  - Pyelonephritis with perinephric abscess: CT of the abdomen
  - Cholangitis: clinical picture guided by ultrasound and/or CT of the abdomen
  - Necrotizing skin and soft tissue infections: clinical diagnosis, but CT can help support diagnosis
- Management based on those additional studies
  - Surgery
  - Percutaneous drainage
- *Removal of indwelling catheters* should occur if
  - The catheter appears infected (e.g., erythema or purulence at the catheter insertion site)
  - Endovascular infection (e.g., endocarditis) is suspected or documented
  - In critically ill patients without a clear alternate source of infection
- Foley and drainage catheters should be cultured, then replaced

GENERAL SUPPORT

- Nutritional supplementation if the patient is not meeting goals
- Use insulin only if needed to maintain glucose concentration at 140–180 mg/dL
- Can do an insulin drip to maintain levels in the appropriate range if needed

DE-ESCALATING CARE

- While hospitalized, care should focus on limiting complications and optimizing long-term outcomes
- Remove indwelling catheters (including Foley catheters) when no longer needed
- Ensure early mobilization with physical therapy, DVT prophylaxis, discontinuing unnecessary fluids, and judicious use of diuretics for patients with significant fluid overload

COMPLICATIONS

The following sections describe sepsis complications and their characteristics. When managing a patient with sepsis, these complications should be monitored frequently with exams and labs. Table 36-2 provides information on the management of sepsis complications.

NEUROLOGIC COMPLICATIONS

- Encephalopathy and delirium are often early manifestations of sepsis
  - Occur in > 50% of patients at some point during the hospital stay
  - Increased mortality and long-term functional and neuropsychiatric sequelae can develop among survivors
- Seizure, stroke, CNS infections, or coma also can occur
  - These can also develop not directly from sepsis
  - Therefore, further investigation is needed in understanding how these complications develop
- If sepsis lasts for weeks to months, "critical illness polyneuropathy" may prevent weaning from ventilatory support and produce distal muscle weakness
- Long-term cognitive loss has been documented in survivors of sepsis
- Management
  - Early recognition of sepsis-associated encephalopathy
  - Treatment of the underlying infection appropriately
  - Supportive care, including correction of metabolic or electrolyte abnormalities
  - Limiting of exposure to neurotoxic medications (e.g., cefepime) and CNS depressants (e.g., opiates, benzodiazepines)

CARDIOVASCULAR DYSFUNCTION

- Cardiovascular compromise, manifested as hypotension or shock, occurs in ~ 25% of septic patients
- Hypotension
  - Results initially from maldistribution of blood flow and blood volume from hypovolemia from diffuse capillary leakage of intravascular fluid
  - Dehydration, vomiting, diarrhea, hemorrhage, and polyuria may contribute
  - Initially, the heart rate and cardiac output are increased to compensate for vasodilation
  - As sepsis progresses, loss of vascular smooth muscle contractility, despite endogenous neurohormonal stimuli and exogenous catecholamine administration, result in progressive or refractory shock

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TABLE 36-2 Organ-Specific Clinical Findings and Management

	CLINICAL FINDINGS	DIAGNOSIS	TREATMENT
Neurologic	Altered consciousness, cognition, or attention; seizure, stroke, or meningism	Brain imaging (MRI or CT), EEG, lumbar puncture	Early recognition and supportive care; treat underlying cause; correct metabolic and electrolyte abnormalities; limit neurotoxic agents and sedatives
Cardiovascular	Tachycardia, hypotension, skin mottling, prolonged capillary refill, oliguria, altered mental status	Invasive BP monitoring, dynamic assessment of volume status, echocardiogram	Intravenous fluid resuscitation with balanced crystalloid, ~30 mL/kg; vasopressors for persistent hypotension, norepinephrine (first agent), vasopressin (second agent), epinephrine (third agent); hydrocortisone 50 mg q6h if ongoing vasopressor requirement; consider adding dobutamine to norepinephrine or switch to epinephrine in septic shock patients with decreased LVEF; consider use of pulmonary artery catheter in patients with mixed septic and cardiogenic shock
Respiratory	Tachypnea, hypoxemia, increased work of breathing	CXR or ultrasound with noncardiogenic bilateral infiltrates and Pao_2/Fio_2 < 300 mm Hg or $Spo_2/Fio_2 \leq 315$	Maintain Spo_2 90–96%; use high-flow nasal canula in patients with adequate neurologic status; target plateau pressure < 30 cm H_2O and tidal volume of 6–8 mL; consider rescue therapies in patients with refractory hypoxia
Genitourinary	Oligura or anuria	Elevated serum creatinine and blood urea nitrogen, acidemia, hyperkalemia	Treat underlying infection, maintain renal perfusion, avoid nephrotoxic agents; start renal replacement therapy for progressive acidemia, hyperkalemia, uremia, or volume overload; infuse sodium bicarbonate if renal failure and pH ≤ 7.2
GI	Right upper quadrant pain, asterixis, jaundice	Elevated bilirubin, alkaline phosphatase, and transaminases; right upper quadrant ultrasound	Treat underlying infection, avoid hypotension and hepatoxic agents; stress ulcer prophylaxis for high-risk patients; enteral feeding if shock controlled within 48 h; parenteral feeding if nutrition goal not met within 7 days; insulin if blood glucose ≥ 180 mg/dL
Hematologic	Clinical or subclinical thrombosis or hemorrhage	Thrombocytopenia, increased fibrin split products, decreased fibrinogen, prolonged PT/INR	Administer cryoprecipitate for fibrinogen < 150 mg/dL, platelets for platelet count ≤ 50×10^9/L and evidence of bleeding, and fresh frozen plasma for prolongated PT/INR and evidence of bleeding; transfuse packed RBCs for hemoglobin < 7.0 g/dL

ARDS, acute respiratory distress syndrome; EEG, electroencephalogram; LVEF, left ventricular ejection fraction.
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- Depression of myocardial function
  - Up to half of patients with septic shock also have myocardial dysfunction (associated with increased mortality)
  - Sepsis-induced cardiomyopathy manifests as decreased LV ejection fraction (LVEF), increased end-diastolic volume index, and RV impairment
- Management of hypotension
  - *IV fluids, multiple boluses of crystalloid fluid, then maintenance fluids*
    - For sepsis-induced hypotension, give ≥ 30 mL/kg IV crystalloid fluid in the first 3 h
      - LR may be recommended over NS in some studies to prevent acidosis and AKI [4]
    - Most patients require continued administration of IV fluids following initial resuscitation
    - After initial resuscitation, administer additional fluids guided by a frequent reassessment of status of dynamic measures, such as
      - Capillary refill time [1]

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        - Passive leg raise maneuver
        - POCUS exam
      - Target a mean arterial pressure of ≥ 65 mm Hg
      - Guide resuscitation to normalize lactate in those with elevated lactate
  - Vasopressors
    - Indicated when the mean arterial pressure is < 65 mm Hg with end-organ dysfunction after adequate fluid resuscitation
    - Norepinephrine is the first-line vasopressor
    - Vasopressin is second line, used as an adjunct to norepinephrine to down-titrate norepinephrine dose
    - Epinephrine is a third-line agent in refractory septic shock
  - Glucocorticoids
    - When septic shock is refractory to fluids and ongoing vasopressor use, glucocorticoids are recommended [5]
      - Improves secondary outcomes and time to reversal of shock
      - Does not improve mortality rates
    - Hydrocortisone, 50 mg IV q6h
  - If myocardial dysfunction occurs, produces mixed septic and cardiogenic shock
    - Dobutamine may be added to norepinephrine in septic shock patients with decreased LVEF
    - Consider the use of a pulmonary artery catheter for hemodynamic monitoring in patients with mixed septic and cardiogenic shock
  - Albumin has not shown any mortality benefit

ACUTE LUNG INJURY

- Ventilation-perfusion mismatching produces a fall in arterial PO_2 early in the disease course
- Increasing alveolar epithelial injury and permeability results in increased pulmonary water content and decreased compliance, and interferes with oxygen exchange
- *Acute respiratory distress syndrome* (ARDS) develops in ~ 7% of sepsis cases
  - In the absence of pneumonia or HF, progressive diffuse pulmonary infiltrates and arterial hypoxemia occurring within 1 week of a known insult indicate the development of ARDS
    - The Pao_2/Fio_2 is < 300 mm Hg
  - Occurs in ~ 50% of patients with severe sepsis or septic shock
- An elevated post-capillary wedge pressure (> 18 mm Hg) suggests fluid volume overload or cardiac failure rather than ARDS
- Management
  - Administer adequate oxygen supplementation for hypoxemia while limiting cellular injury from oxidative stress
  - Target Spo_2 of 90–96%
  - High-flow nasal cannula is preferred to noninvasive ventilation when patients have adequate neurologic function without hypercapnia
  - Mechanical ventilation with low tidal ventilation strategy in ARDS

AKI

- Occurs in up to 67% of patients with sepsis or septic shock
  - Associated with increased mortality and risk of CKD and disability among sepsis survivors
- Sepsis-induced AKI, which accounts for all AKI cases occurring within 7 days of sepsis onset, presents with
  - Oliguria or anuria
  - Elevated BUN and SCr
- Many patients are inappropriately polyuric, which may be exacerbated by hyperglycemia
- Most AKI in sepsis is due to *acute tubular necrosis* induced by
  - Hypovolemia
  - Abdominal compartment syndrome
  - Arterial hypotension, or
  - Toxic agents (e.g., antibiotics and contrast dye)
- Management
  - Treat the underlying infection
  - Maintain renal perfusion with fluid resuscitation and vasopressors to achieve mean arterial pressure ≥ 65 mm Hg

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- Avoid nephrotoxic agents when possible
- Identify and treat reversible causes
- Initiation of early renal replacement therapy (RRT) during sepsis-associated AKI is not associated with improved outcomes
  - Start RRT for standard definitive indications (e.g., progressive acidemia, hyperkalemia, uremia, volume overload)
- Consider sodium bicarbonate infusion only in patients with AKI and severe metabolic acidosis (pH ≤ 7.2)
  - Maintains vasopressor effectiveness and mitigates fatal ventricular dysrhythmia risk

- Refer to Chap. 26 for further details on AKI

GI COMPLICATIONS

- About 50% of patients with septic shock develop liver dysfunction (associated with increased mortality)
  - May develop right upper quadrant pain, jaundice, and asterixis depending on the severity
  - Elevated bilirubin, alkaline phosphatase, and transaminases are observed with marked hypotension
  - Sepsis-induced cholelithiasis is attributed to impaired bile formation and decreased flow in a nonobstructive pattern
- Sepsis has been associated with alteration of the intestinal mucosa, including increased epithelial permeability, changes in gut microbiota, and translocation of enteric microbes into circulation
  - GI bleeding and impaired intestinal absorption can occur
- Management
  - Treat the underlying infection
  - Avoid hypotension and hepatotoxic medications
  - Stress ulcer prophylaxis (IV proton pump inhibitor therapy) for patients with
    - Mechanical ventilation requirements
    - Coagulopathy
    - Pre-existing liver disease (e.g., cirrhosis)
    - High organ failure score
    - Renal replacement therapy requirements
  - Supplemental nutrition within 48 h of shock onset

HEMATOLOGIC COMPLICATIONS

- Thrombocytopenia (10–30% of patients), anemia, and disseminated intravascular coagulopathy (DIC) can develop
  - Increased mortality when DIC develops
- Clinical or subclinical thrombosis and hemorrhage may develop
- Management
  - DIC management
    - Goals focus on mitigating bleeding risk
    - Administer cryoprecipitate when fibrinogen levels are < 150 mg/dL
    - Administer fresh frozen plasma to patients with prolonged PT/INR and evidence of bleeding
    - Administer platelets when counts are ≤ 50,000/μL and there is evidence of bleeding
  - DVT prophylaxis with low-molecular-weight heparin is recommended over unfractionated heparin
  - Transfuse packed RBCs when hemoglobin is < 7 g/dL

IMMUNOSUPPRESSION

- Loss of delayed-type hypersensitivity reactions, failure to control the primary infection, and increased risk for secondary infection (e.g., from opportunistic infections) can occur as sepsis impairs the immune system
- Approximately one-third of patients experience reactivation of herpes simplex virus, varicella, or cytomegalovirus
- Manage the underlying infection

PROGNOSIS

- Figure 36-1 describes sepsis incidence and mortality rates
- Sepsis mortality is estimated at 15% among U.S. hospitalized adults with sepsis
- Sepsis mortality increases with age and is higher among men than women in all age groups
- Sepsis mortality risk is increased by preexisting medical conditions, including
  - Diabetes and obesity
  - Neurologic, respiratory, or cardiac conditions
  - Renal or hepatic insufficiency
  - Cancer or other immunosuppressing conditions

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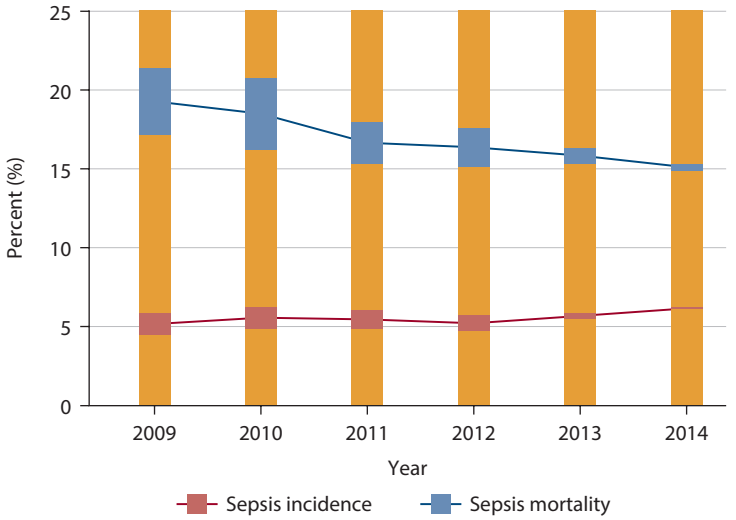

FIGURE 36-1 Sepsis incidence and mortality. Sepsis incidence is expressed as a proportion of sepsis cases among 7,801,624 adult hospitalizations across 409 U.S. hospitals from 2009 to 2014. Mortality is the proportion of sepsis deaths among sepsis cases. (Reproduced with permission from Strich JR, Chertow DS. Sepsis and septic shock, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Elevated Sequential Organ Failure Assessment (SOFA) scores are associated with increased sepsis mortality at the population level but cannot accurately predict outcomes of individual patients
- If any of the complications listed above occur, mortality and disability among survivors increases

PATHOPHYSIOLOGY

GENERAL OVERVIEW

- There are many mechanisms in the pathophysiology of sepsis
- Sepsis starts with an infectious source that triggers the patient's immune defenses
- The pathophysiology and molecular pathogenesis of sepsis vary across patients and pathogens and depend on patient demographics, clinical factors, and pathogen type/virulence
- During sepsis, pathogen components and exuberant cellular and soluble immune responses contribute to systemic illness, resulting in end-organ injury and dysfunction (Fig. 36-2)
- All the mechanisms of sepsis pathophysiology are not worked out or understood

PATHOPHYSIOLOGY OF SEPSIS

- Mediators of the pathologic response
  - Myeloid cells (neutrophils, monocytes, macrophages, dendritic cells)
  - Lymphoid cells (natural killer cell and T/B lymphocytes)
  - Parenchymal cells (endothelial and epithelial cells)
  - Soluble mediators (cytokines, chemokines, NO, histamine, prostaglandin, and bradykinin)
- Effects
  - Leukocyte activation and migration into tissues generate reactive oxygen species → tissue injury
- Endothelial/platelet/clotting activation → thrombosis and hemorrhage risk increases
- Core features
  - Systemic vasodilation, capillary leak, and microthrombosis → impaired oxygen delivery/utilization → cellular injury and end-organ dysfunction

TRIGGERS OF IMMUNE RESPONSES

- Immune responses in sepsis are initiated by pathogen components termed *pathogen-associated molecular patterns* (PAMPs)
  - Lipopolysaccharide
  - Bacterial wall/membrane
  - Nucleic acids

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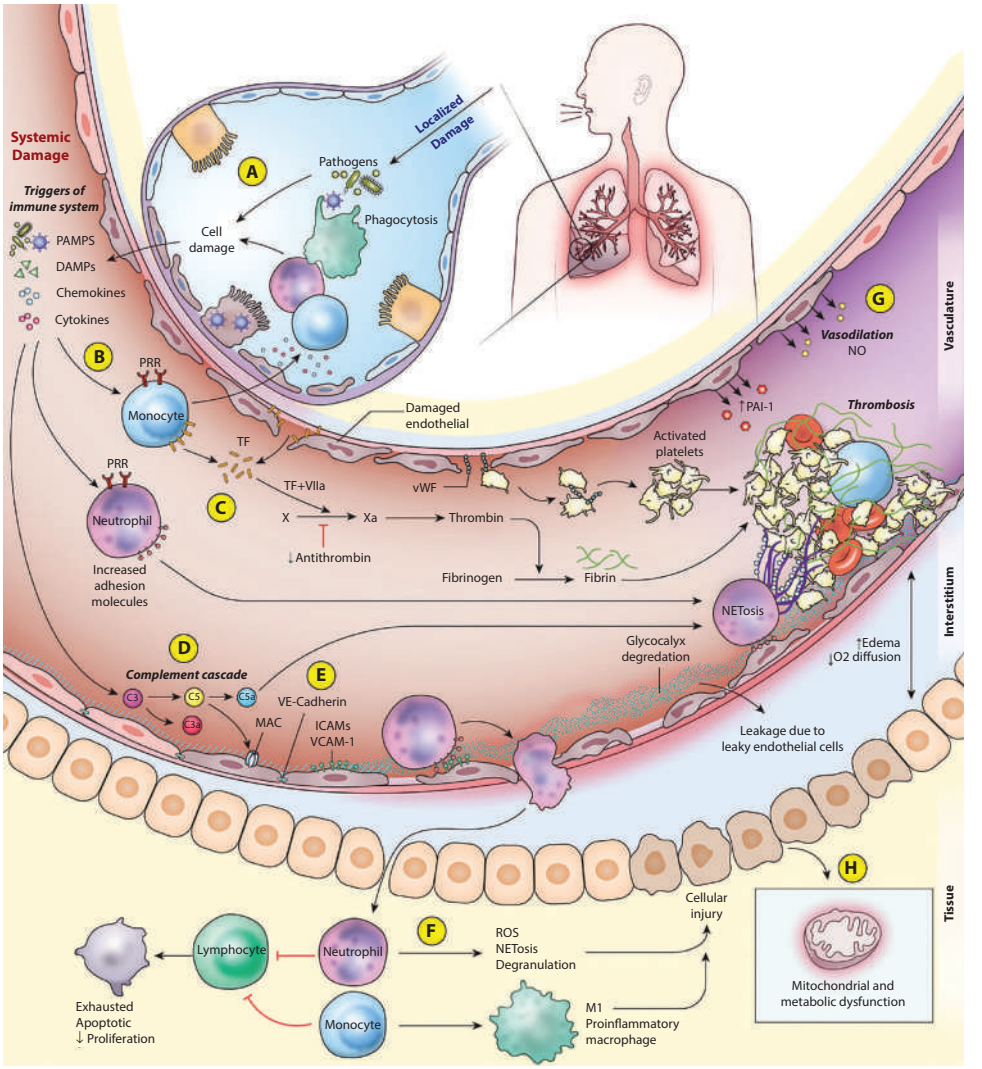

FIGURE 36-2 Sepsis pathogenesis. (*A*) Invading pathogens and tissue-resident and recruited leukocyte responses induce localized cell damage. (*B*) Systemic damage is mediated by pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cytokines, and chemokines that activate pattern recognition receptors (PRRs) on circulating monocytes and neutrophils. (*C*) Increasing tissue factor (TF) on endothelium and leukocytes triggers the clotting cascade and fibrin generation. Adherent neutrophils release extracellular traps (NETs) and microthrombi form, composed of leukocytes, fibrin, and platelet aggregates, bound together by von Willebrand factor (vWF). Antithrombin levels are decreased, promoting clot formation, and plasminogen activator inhibitor-1 (PAI-1) levels are increased, impairing clot breakdown. (*D*) Complement activation generates C3a and C5a, which activate platelets and myeloid cells. The C5b-9 membrane attack complex (MAC) promotes endothelial injury. (*E*) Activated and injured endothelium increase intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecule (VCAM)-1 expression, glycocalyx breakdown, apoptosis, and loss of intercellular vascular endothelial (VE)-cadherin and tight junctions contributing to interstitial edema, decreased oxygen diffusion, and leukocyte migration. (*F*) Activated neutrophils degranulate and release reactive oxygen species (ROS) and NETs, and monocytes differentiate into proinflammatory (M1) macrophages, contributing to cellular injury and dysfunction. Activated myeloid cells also suppress lymphocyte function through exhaustion, apoptosis, and decreased proliferation. (*G*) Arterial vasodilation, partially mediated by excess nitric oxide, contributes to tissue hypoperfusion and ischemia. (*H*) With or without adequate oxygen delivery, cellular mitochondrial and metabolic functions are disrupted during sepsis. (Reproduced with permission from Strich JR, Chertow DS. Sepsis and septic shock, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- PAMP signaling is propagated by patient factors called *damage-associated molecular patterns* (DAMPs)
  - Histones, high mobility group box 1 proteins, S100 proteins, oxidized phospholipids, dsDNA, and ATP
- PAMPs and DAMPs interact with innate and adaptive immune cells and parenchymal cells during sepsis, amplifying immune responses
- PAMPs and DAMPs are recognized by *pattern recognition receptors* (PRRs)
  - Toll-like receptors (TLRs), C-type lectin receptors (CLRs), receptors for advanced glycation end products (RAGE), retinoic acid–inducible gene-I–like receptors (RIG-I), and nucleotide-binding oligomerization domain-like (NOD) receptors
- Recognition of PAMPs and DAMPs by PRRs on innate immune cells such as neutrophils, monocytes, and macrophages
  - *Activates inflammatory pathways*
  - *Triggers release of proinflammatory cytokines and chemokines*
  - *Increases surface expression of vascular adhesion molecules*

MYELOID RESPONSES

- Neutrophils, monocytes, and macrophages provide early innate immune defenses against invading pathogens but also contribute to sepsis pathogenesis by promoting
  - Inflammation
  - Cellular injury
  - In some cases, limiting adaptive immunity
- Neutrophils
  - Most abundant leukocyte; activated by sepsis → adhesion molecule upregulation (CD11b)
  - Functions: phagocytosis, degranulation, reactive oxygen species (ROS) generation, neutrophil extracellular trap (NET) formation, cytokine release
  - NETs trap pathogens but promote microvascular thrombosis via activated platelets on endothelial cells from CD11b upregulation
  - ROS and proteases cause cellular injury
  - Soluble inflammatory markers further recruit immune cells to sites of infection, exacerbating inflammation and cellular injury
  - Cytokines (interleukin [IL]-6, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor) trigger emergency granulopoiesis (release of immature neutrophils from the bone marrow)
    - Poor prognostic sign in septic patients
- Monocytes
  - Types
    - Classic (CD14+CD16–)
    - Intermediate (CD14+CD16+)
    - Nonclassic ($CD14^{low}CD16+$)
  - Classic monocytes (~ 85% of circulating monocytes) during sepsis migrate to infected tissues → transient monocytopenia and a resulting increase in the proportion of circulating nonclassic and intermediate monocytes
    - Classic monocytes differentiate into macrophages or dendritic cells upon exposure to PAMPs/DAMPs in the tissues
    - Dendritic cells act as antigen-presenting cells with broad PRR and cytokine secretion function, contributing to pathogen clearance, inflammation, and bridging the innate to adaptive immune response
    - The macrophages formed from monocytes either become proinflammatory (M1 macrophages) or anti-inflammatory (M2 macrophages)
      - M1 macrophages contribute to pathogen clearance but also generate ROS and release inflammatory cytokines, which additionally cause tissue damage
    - The macrophages process and present antigens on surface major histocompatibility complex (MHC) II molecules, linking myeloid and lymphoid cells
      - Sepsis pathogens can downregulate MHC surface expression, impairing the immune response
- Myeloid cells
  - Myeloid cells typically contribute to inflammation in sepsis
  - A subset of pathologically activated myeloid cells in tissues, termed *myeloid-derived suppressor cells*, functionally suppress natural killer (NK) cell, T cell, and B cell function, contributing to immunosuppression in sepsis

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LYMPHOID RESPONSES

- NK cells
  - Innate lymphocytes that migrate to sites of infection and recognize PAMPs/DAMPs and cytokines (interferon [IFN], IL-12)
  - Functions
    - Release IFN-γ, IL-32 (proinflammatory, activates myeloid cells), and cytotoxic granules (perforin, granzyme) that mediate the inflammatory response in sepsis
    - Produce IL-10, which suppresses myeloid cell–mediated inflammatory response → anti-inflammatory role
- T cells
  - CD8+
    - Kill infected cells via MHC surface antigen recognition and lysis
    - Also form memory cells
  - CD4+ subsets
    - T_H1: activate CD8+ T cells and support memory T cell formation
    - T_H2: support B cell class switching
    - T_H17: protect against extracellular bacteria/fungal infections
- B cells
  - Produce antibodies against foreign antigens
  - Form antigen-specific memory cells
- Adaptive immune dysfunction in sepsis
  - Lymphocyte death, exhaustion, decreased proliferation, and apoptosis-refractory regulatory T cells result in impaired anti-inflammatory mechanisms
  - T cell exhaustion includes impaired cytokine production and diminished cytotoxic activity, while diminished antibody generation is observed in exhausted B cells

ENDOTHELIAL ACTIVATION

- Normal role
  - Endothelial cells line blood vessels and regulate vascular tone, exchange of cells, fluid, and molecules between the bloodstream and surrounding tissue
  - The endothelial glycocalyx lines the luminal endothelium and maintains homeostatic functions
- In sepsis
  - PAMPs and DAMPs activate endothelial cells, altering their structure and function
  - Glycocalyx breakdown disrupts blood flow → proadhesive, procoagulant, and proinflammatory endothelial state
  - ↑ adhesion molecules (intracellular adhesion molecules and vascular adhesion molecules) → leukocyte adhesion, rolling, and diapedesis
  - ↑ TF expression, platelet adhesion, impaired fibrinolysis (↑ plasminogen activator inhibitor 1 [PAI-1] release)
  - Cytokine production (IL-1β, IL-6, IFN-α) → inflammation
  - Barrier dysfunction
    - Endothelial cell apoptosis, loss of intracellular adherence (VE-cadherin, tight junctions) → interstitial fluid accumulation, increased interstitial pressure, and tissue hypoperfusion
  - Altered NO metabolism → systemic vasodilation and cellular injury

COAGULOPATHY

- PAMPs/DAMPs activate clotting, platelets, the endothelium, and complement → thrombus formation
- Increased tissue factor (TF) on activated leukocytes activates the extrinsic cascade → thrombin-mediated fibrinogen conversion to fibrin
- Endothelial injury exposes vWF on subendothelial surfaces → platelets bind glycoprotein 1b and fibrinogen via glycoprotein IIb/IIIa receptors
- Activated platelets and endothelial cells release more vWF (from Weibel-Palade bodies) forming platelet-rich microthrombi
- Neutrophils add NETs, forming a fibrin meshwork of fibrin-rich microthrombi
- *Complement activation* (classic, alternative, and lectin pathways)
  - Release of C3a/C5a further activates platelets, myeloid cells, and assembly of the membrane attack complex (MAC) promoting endothelial injury
- Anticoagulant molecules (antithrombin, TF pathway inhibitor, activated protein C) are impaired in sepsis
- Antifibrinolysis molecules (PAI, thrombin-activatable fibrinolysis inhibitor) limit clot breakdown
- When clotting factors and platelets are consumed, spontaneous and provoked hemorrhage can occur

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CELLULAR INJURY AND DYSFUNCTION

- A hallmark of sepsis is multiorgan cellular injury and dysfunction
- Causes
  - Arterial hypotension (vasodilation, myocardial depression, hypovolemia)
  - Vascular leakage → interstitial edema and impaired oxygen diffusion distance
  - Microcirculatory dysfunction from endothelial activation, injury, and microvascular thrombosis
- Mediators of injury
  - PAMPs, DAMPs, leukocytes, cytokines, ROS, reactive nitrogen species (RNS) (peroxynitrite, nitrogen dioxide, dinitrogen trioxide)
- RNS and ROS contribute to protein/lipid oxidation and DNA damage of proximate cells
- Mitochondrial dysfunction causes
  - Impaired ATP generation (glycolysis oxidative phosphorylation dysfunction)
  - Ion homeostasis disruption (Na^+, K^+, Ca^{2+})
  - Dysregulated cell death

RISK FACTORS

- Infection of any source
- Extremes of ages
- Diabetes and obesity
- Chronic neurologic, respiratory, cardiac, renal, or liver disease
- Cancer, chemotherapy use, or other immunosuppressing conditions
- Recent hospital admission for any reason has also been associated with a threefold increased risk of developing sepsis in the following 90 days
- Asplenia
- Injection drug and chronic alcohol use
- Recent surgery

ADMITTING ORDERS

- Admit to floor or ICU
- Diagnosis: sepsis
- Condition: critical
- Vital signs: every 4 h or more frequently if worsening; call for BP < 90/60 mm Hg, heart rate > 120 beats/min, worsening oxygenation, or urinary output < 30 mL/h
- Activity: early mobilization with physical therapy when able
- Nursing: strict *I*s/*O*s and daily weights; call for worsening neurologic status
- Diet: tailor to patient comorbidities
- Fluids: at least 30 mL/kg bolus of fluids over the first 3 h, then fluids guided by dynamic measures and lactic acid levels (if elevated)
- Diagnostic tests
  - Blood cultures × 2 (or 3 sets if concerned about endocarditis)
  - UA with culture (if indicated)
  - Sputum culture and Gram stain; respiratory viral panel (if indicated)
  - CBC with diff
  - CMP
  - Lactic acid
  - ESR/CRP
  - Lipase
  - TSH
  - PT/PTT/INR and D-dimer
  - ABG or VBG
  - CSF studies if meningitis is suspected
  - ECG
  - CXR
  - CT or MRI of specific anatomical locations when necessary
  - Transthoracic and/or transesophageal echocardiogram if endocarditis is suspected
- Medications
  - Antibiotics depend on the potential site of infection (see Table 36-1) and patient factors
  - Insulin to maintain blood glucose 140–180 mg/dL
  - DVT prophylaxis with unfractionated heparin or low-molecular-weight heparin

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DISCHARGE INFORMATION

- Patients with mild sepsis may be discharged when vital signs and any end-organ dysfunction have improved
- Patients with prolonged hospitalization may have significant functional impairment and may need physical rehabilitation within an acute or subacute rehab facility before returning home
- Always ensure patients are educated on
    1. The cause of infection
    2. Symptoms that may show worsening or recurrence of infection
    3. When to call their primary care clinician or return to the ED
- Prescribe adequate antibiotic coverage and duration for discharge
- Follow up with primary care in 1–2 weeks

CASE ANSWERS

1. This patient is presenting with signs, symptoms, and CT evidence of sepsis secondary to complicated diverticulitis. Patients with acute diverticulitis should be initiated on broad-spectrum antibiotics that cover both gram-negative rods and anaerobic organisms.
2. In the treatment of complicated diverticulitis, a strategy of a single agent or a combination regimen with metronidazole to cover gram-negative rods and anaerobic organisms can be chosen.
    a. Single-agent regimen
        i. Piperacillin-tazobactam
        ii. Meropenem
        iii. Doripenem
        iv. Imipenem
    b. Combination regimen: metronidazole plus one of the following agents
        i. Ceftriaxone
        ii. Cefazolin
        iii. Cefuroxime
        iv. Ciprofloxacin
        v. Levofloxacin
3. Early aggressive fluid resuscitation (≥ 30 mL/kg IV crystalloid in the first 3 h) is recommended for sepsis. This patient weighs 80 kg; therefore, he should receive 2.4 L of IV crystalloid in the first 3 h.
4. This patient with a large abscess (≥ 4 cm) has an indication for source control. The initial strategy would be to perform percutaneous drainage if feasible.

LANDMARK TRIALS

[1] ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN) et al. Personalized hemodynamic resuscitation targeting capillary refill time in early septic shock: The ANDROMEDA-SHOCK-2 randomized clinical trial. JAMA 334:1988, 2025. [PMID: 41159835]
    - *Summary:* The ANDROMEDA-SHOCK 2 trial showed that among patients with early septic shock, a personalized hemodynamic resuscitation protocol targeting capillary refill time was superior to usual care for the primary composite outcome, primarily due to a lower duration of vital support.

[2] Ferrer R et al. Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. Am J Respir Crit Care Med 180:861, 2009. [PMID: 19696442]
    - *Summary:* In severe sepsis, early administration (within 1 hour) of broad-spectrum antibiotics in all patients and administration of drotrecogin alfa (activated) in the most severe patients reduce mortality.

[3] Kuttab HI et al. Evaluation and predictors of fluid resuscitation in patients with severe sepsis and septic shock. Crit Care Med 47:1582, 2019. [PMID: 31393324]
    - *Summary:* Failure to reach 30 mL/kg crystalloid bolus within 3 h of sepsis onset was associated with increased odds of in-hospital mortality, irrespective of comorbidities.

[4] Semler MW et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med 378:829, 2018. [PMID: 29485925]

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- *Summary:* Among critically ill adults, the use of balanced crystalloids (LR) for IV fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal replacement therapy, or persistent renal dysfunction than the use of NS.

[5] Venkatesh B et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 378:797, 2018. [PMID: 29347874]

- *Summary:* Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo, but it did reduce some secondary outcomes.

FURTHER READING

- Evans L et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med 49:e1063, 2021. [PMID: 34599691]
- Strich JR, Chertow DS. Sepsis and septic shock, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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38 Urinary Tract Infections

KEY POINTS

1. Urinary tract infections (UTIs) describe an infection anywhere along the urinary tract that produces clinical symptoms. UTIs comprise cystitis, pyelonephritis, and prostatitis. Uncomplicated UTIs are infections confined to the bladder in an afebrile woman or man without a urinary catheter. Infections that extend beyond the bladder (including bacteremia), are associated with fever, or in a patient with a catheter (catheter-associated UTI [CAUTI]) are termed complicated UTIs. Asymptomatic bacteriuria is the presence of bacteria on urine culture not associated with symptoms of UTI.
2. Uncomplicated UTIs confined to the bladder have symptoms of suprapubic pain, dysuria, hematuria, frequency, hesitancy, and new nocturia. Complicated UTIs additionally can have symptoms of flank pain and costovertebral angle tenderness, fever, nausea and vomiting, encephalopathy, and rigors. Acute bacterial prostatitis will present with pain in the prostatic pelvis or perineal area accompanied by fever, rigors, and/or bladder outlet obstruction. The most common uropathogen across all UTIs is *Escherichia coli*.
3. UTIs are a clinical syndrome with symptoms as above, and will have accompanying UA findings of pyuria, nitrites (in infections from the *Enterobacterales* family), leukocyte esterase, and the presence of bacteriuria. Imaging is not necessary for a diagnosis but may be necessary in critically ill patients, patients with suspected or documented urinary obstruction, or patients with pyelonephritis and continued fever or worsening symptoms despite appropriate antibiotic therapy.
4. Because of the increasing prevalence of drug-resistant uropathogens, empirical antibiotics should be carefully chosen based on patient-specific factors and local antibiograms. Previous urine cultures in patients with prior UTIs can be helpful in making antibiotic choices. First-line therapies for cystitis include trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, fosfomycin, and pivmecillinam. For hospitalized patients with a complicated UTI, third- and fourth-generation cephalosporins are first-line therapy. For critically ill patients, a carbapenem plus methicillin-resistant *Staphylococcus aureus* (MRSA) coverage (e.g., vancomycin) is indicated. Culture results and susceptibilities guide de-escalating broad-spectrum antibiotics, and patients can be switched to oral antibiotics when they are clinically improving. Acute bacterial prostatitis requires antibiotics that penetrate the prostate tissues adequately, including fluoroquinolones or TMP-SMX.
5. With modern antibiotics, UTIs are favorably managed without long-term sequelae. Emphysematous (especially in patients with diabetes) and xanthogranulomatous pyelonephritis can be life-threatening infections and require consultation with urology. Pyelonephritis may also be complicated by acute papillary necrosis causing urinary obstruction.

EPIDEMIOLOGY & DEFINITIONS

The term *urinary tract infection (UTI)* refers to an infection somewhere along the urinary tract that produces clinical symptoms. The urinary tract is colonized with bacteria that are in dynamic equilibrium. When a new pathogen invades the bladder, or there is a shift in the existing bacterial equilibrium, local tissue injury and inflammation can occur. Importantly, while UTI encompasses a broad range of clinical presentations (from cystitis to bacteremic emphysematous pyelonephritis), the presence of bacteria alone in the urinary tract in a patient *without* related symptoms does *not* constitute a UTI (termed *asymptomatic bacteriuria*). Unless otherwise mentioned in this chapter, the term *UTI* denotes symptomatic disease.

In neonates, the incidence of UTI is slightly higher in males because male infants more commonly have congenital urinary tract abnormalities. Between the ages of 1 and ~ 50 years, UTI and recurrent UTI are predominantly conditions of women, with most true male UTIs occurring in the context of urinary catheterization or anatomic abnormalities. After 50 years of age, obstruction from benign prostatic hyperplasia becomes common in men, and the incidence of UTI is almost as high as that in women. Up to 80% of women develop at least one UTI during their lifetime. The lifetime prevalence in men in the United States is ~ 14%. UTIs are the number one cause of hospitalization from sepsis (48.9% of sepsis admissions).

Cystitis: symptomatic infection of the bladder.

Prostatitis: symptomatic infection of the prostate (literature is sparse for prostatitis, and clinical guidelines for complicated UTI cannot be assumed to be generalizable for patients with prostatitis).

Pyelonephritis: symptomatic infection of the kidneys.

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Uncomplicated UTI: an infection confined to the bladder in an afebrile woman or man without a urinary catheter.

Complicated UTI: infection that extends beyond the bladder (e.g., prostatitis, pyelonephritis, bacteremia, or UTI in the setting of intermittent or indwelling urinary catheterization, termed *catheter-associated UTI [CAUTI])* or in the setting of fever

- This is an updated definition of "complicated UTI" that more closely reflects actual clinical practice
- While prostatitis is a complicated UTI, it differs in treatment compared with other complicated UTIs

UTI relapse: early recurrence (within 2 weeks) of UTI (might indicate the need to evaluate a sequestered focus of ongoing infection).

Recurrent UTI: repeat UTI after 2 weeks from original. (It is not uncommon for multiple recurrences to follow an initial infection, resulting in clustering of episodes.) Recurrent UTIs are not necessarily complicated UTIs. (Individual episodes can be uncomplicated and treated as such.) Clustering infections may be related to the presence of a new risk factor, sloughing of the protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis, or possibly antibiotic-related alteration of the normal bacterial flora.

CLINICAL VIGNETTE

A 54-year-old woman with poorly controlled diabetes mellitus, hypertension, and multiple sclerosis presents to the ED with fever and chills. One week ago, she started developing dysuria, urinary frequency, suprapubic tenderness, and occasional urinary incontinence. In the past 2 days, she noticed left-sided flank pain. She had a UTI 10 years ago and was treated successfully with nitrofurantoin. She resides at her house, has not traveled internationally in the past 5 years, and has not received antibiotics in 10 years. She has no known drug allergies. She is not sexually active.

Her temperature is 38.4°C (101.2°F), heart rate 110 beats/min, respiratory rate 20 breaths/min, BP 102/68 mm Hg, and Spo_2 96% on room air. She appears anxious and has rigors. Cardiovascular and pulmonary examinations are normal except for a regular tachycardic heart rate. She has a normal mental status examination. There is suprapubic and left costovertebral angle tenderness on palpation. There is no vaginal discharge. Laboratory data reveal:

- WBC count: 18,200 cells/μL
- Lactic acid: 3.4 mmol/L
- Sodium: 132 mEq/L
- Glucose: 300 mg/dL
- SCr: 2.3 mg/dL
- BUN: 48 mg/dL

Her most recent SCr and BUN 6 months ago were 1.1 mg/dL and 22 mg/dL, respectively. A UA reveals the presence of leukocyte esterase and nitrites, > 500 WBC per high-powered field, hematuria, and bacteria. A postvoid residual demonstrates 720 mL of urine in the bladder. You do not have the results of her prior UTI culture for review.

GUIDING QUESTIONS

1. What antibiotic(s) would you initiate for this patient?
2. Would you order any imaging?
3. Would you insert an indwelling Foley catheter for this patient?

HISTORY

Because UTIs are the most common infection to cause sepsis requiring hospitalization, clinical suspicion and urine testing should be on the clinician's mind. However, a UA showing bacteriuria needs to be interpreted in the right clinical setting, as asymptomatic bacteriuria is common, and isolated bacteriuria does not mean the patient has a UTI.

Symptoms of cystitis include:

- Dysuria
- Urinary frequency and urgency
- Suprapubic discomfort or tenderness
- New nocturia
- Hesitancy
- Gross hematuria

Fever, rigors, and unilateral flank pain are all inconsistent with uncomplicated cystitis and should provoke suspicion of infection beyond the bladder (i.e., the kidneys, prostate, or bloodstream).

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A meta-analysis of the diagnostic utility of history and physical findings for UTI concluded that, in women presenting with at least one localizing urinary symptom (dysuria, frequency, hematuria, or back pain) and no complicating factors, the probability of acute cystitis or pyelonephritis is 50%. If vaginal discharge and complicating factors are absent and risk factors for UTI are present, then the probability of UTI is close to 90%. In men, the diagnostic utility of history and physical alone are less predictive than in women.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Cystitis
    - Urgency
    - Frequency
    - Dysuria
    - Suprapubic pain
    - Hematuria
  - Pyelonephritis
    - Signs of cystitis, plus
    - Nausea and vomiting
    - Costovertebral angle (CVA) tenderness
    - Fever/chills
  - Perinephric abscess
    - Pyelonephritis that is not improving
    - High fever and toxic appearance
  - Acute bacterial prostatitis
    - Pain in the prostatic pelvic or perineal area accompanied by
      - Fevers
      - Rigors, and/or
      - Bladder outlet obstruction
- Fever/chills?
  - Sign of potential sepsis; fever indicates a complicated UTI
- Dysuria? Urinary frequency? Hematuria?
  - Sign of any type of UTI
- Urinary urgency?
  - Sign of any type of UTI or sexually transmitted infection (STI)
- Suprapubic tenderness?
  - Sign of cystitis
- Flank and CVA tenderness?
  - Raises suspicion for pyelonephritis and/or nephrolithiasis
- Confusion?
  - Encephalopathy and delirium can make obtaining an accurate history difficult, especially to establish whether localized UTI symptoms are present
- Nausea/vomiting?
  - May not be able to swallow oral antibiotics; sign of potential complicated UTI
- Vaginal discharge?
  - Sign of any type of UTI or STI (STI should be higher on the differential)
- Recurrent or relapse?
  - May be able to look up old culture data (guiding empirical therapies) and may need to use preventative strategies for the future
- Catheter?
  - More susceptible to both UTIs (and asymptomatic bacteriuria), and makes it complicated UTI (specifically catheter-associated UTI)
  - The current catheter needs to be replaced with a new one prior to obtaining a UA/urine culture
- Sexual activity?
  - Does the sexual partner have symptoms?
  - STI screening might be necessary
- Last menses?
  - May explain blood in the urine if present

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PAST MEDICAL HISTORY

- Prior UTIs?
  - Can help with the initial antibiotic choice based on previous cultures
  - Resistant organisms may be more common in recurrent UTIs
- Recent hospitalizations or stay at long-term health care facilities in the last three months?
  - Potential risk factors for multidrug-resistant organisms
- History of sexually transmitted infections?
  - Are the symptoms similar to the prior episode(s)?
- History of diabetes? How well controlled is it?
  - May be prone to *Pseudomonas* and emphysematous pyelonephritis (especially in the setting of uncontrolled diabetes)
- History of neurologic diseases → incontinence/urinary retention
  - A full bladder and incomplete emptying can predispose to UTIs

SURGICAL HISTORY

- Urogenital surgeries, ureteral stents, and/or nephrostomy tubes?
  - If present, it is a complicated UTI
  - Multidrug-resistant organisms may be more common when urogenital devices are in place

SOCIAL HISTORY

- Use of alcohol
- Smoking
- Recreational drugs
- Occupation
- Living situation
- Sexual history
  - Recent sexual intercourse?
  - New partner?
  - Use of spermicide (risk factor for UTI)?

MEDICATIONS

- SGLT-2Is make patients more prone to UTIs

PHYSICAL EXAM

The physical exam should focus on vital signs, mental status, and signs of dehydration, and it should include abdominal and genital exams. Also evaluate for other signs of infection on exam, as UTI should not be assumed on initial examination. It is important to determine whether this is a simple cystitis or a complicated UTI (costovertebral angle tenderness), as well as if signs of sepsis are present.

- Vitals signs
  - Fever indicates a complicated UTI
    - Younger women with pyelonephritis tend to have fever for longer than older women due to a more vigorous immune response
  - Hypotension and tachycardia can indicate severe infection
- Abdominal
  - Evaluate for suprapubic tenderness (can be present in both uncomplicated and complicated UTIs)
  - Costovertebral angle tenderness is present in complicated UTI but may also be from noninfected kidney stones
  - Examine nephrostomy tube, if present, for signs of infection
- Genital
  - Presence of Foley or suprapubic catheter?
  - Exam for lesions suggestive of sexually transmitted infection (STI)
    - Is there vaginal discharge (may point more toward an STI)?
  - Bimanual exam if indicated
    - Anterior vaginal pain with palpation suggests cystitis/urethritis
- Mental status
  - Encephalopathy and delirium can make the diagnosis of UTI difficult
  - Do they have baseline cognitive impairment? If so, are they more confused than normal?

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DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Cystitis
  - Suprapubic pain
  - Dysuria
  - Possible hematuria
  - Frequency
  - Hesitancy
  - New nocturia
  - Typically absence of costovertebral angle (CVA) tenderness
- Pyelonephritis
  - CVA tenderness with *fever* (a key feature distinguishing pyelonephritis from cystitis) and other common UTI symptoms (dysuria, frequency, hematuria)
  - Severe pyelonephritis is characterized by
    - High fever
    - Rigors
    - Nausea
    - Vomiting
    - Flank pain
  - *Emphysematous pyelonephritis*
    - A severe form of pyelonephritis with the production of gas in the renal and perinephric tissues occurring in a patient with poorly controlled diabetes
  - *Xanthogranulomatous pyelonephritis* (Fig. 38-1)
    - Occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, lead to suppurative destruction of renal tissue

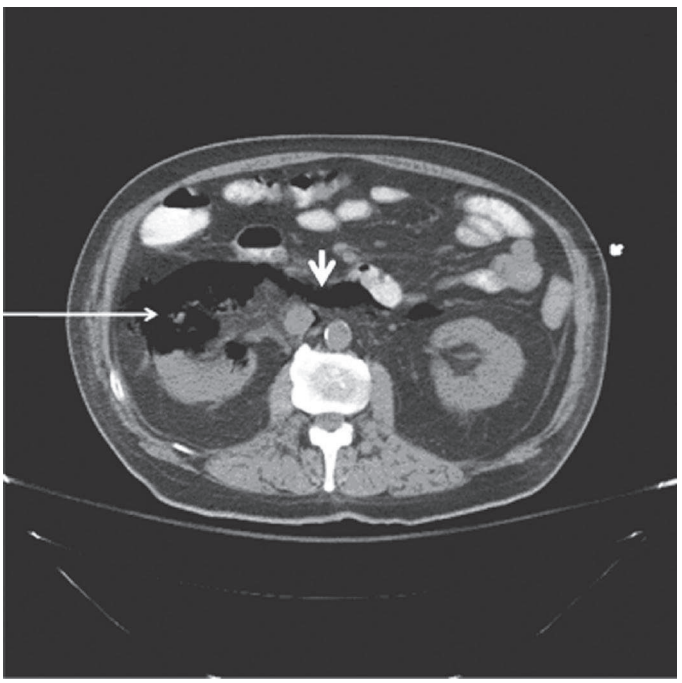

FIGURE 38-1 Emphysematous pyelonephritis. Infection of the right kidney of a diabetic man by *Escherichia coli*, a gas-forming, facultative anaerobic uropathogen, has led to destruction of the renal parenchyma (*arrow*) and tracking of gas through the retroperitoneal space (*arrowhead*). (Used with permission from Trautner BW et al. Urinary tract infections: Cystitis, prostatitis, and pyelonephritis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- *Intraparenchymal abscesses* can form in pyelonephritis
  - Should be suspected when a patient has a continued fever and/or bacteremia despite antibacterial therapy
- Prostatitis
  - Prostatitis can be noninfectious (chronic pelvic pain syndrome) or infectious (acute or chronic)
  - *Acute* bacterial prostatitis presents as
    - Dysuria
    - Frequency
    - Pain in the prostatic pelvic or perineal area accompanied by
      - Fever
      - Rigors, and/or
      - Bladder outlet obstruction
  - *Chronic* bacterial prostatitis presents more insidiously as
    - Recurrent episodes of cystitis, sometimes with pelvic and perineal pain, with
    - Absence of systemic signs
- Sexually transmitted infections (STIs)
  - Have dysuria, urethral or vaginal discharge, and typical lesions of STIs in the setting of recent sexual activity
- Epididymitis
  - Gradual onset (days) of
    - Unilateral scrotal pain and swelling
    - Dysuria
    - Frequency
    - Fever
    - Chills
  - Urethral discharge preceding pain occurs in some cases
- Pelvic inflammatory disease
  - Young woman with recent sexual intercourse
  - Symptoms
    - Fever
    - Nausea
    - Vomiting
    - Lower abdominal pain that is dull, achy, or crampy and constant bilaterally, exacerbated by movement
    - Vaginal discharge
- Ectopic pregnancy
  - Lower abdominal pain
  - Amenorrhea
  - Vaginal bleeding
  - Fever
  - Possibly abdominal rigidity, involuntary guarding
  - Evidence of hypovolemia and hypotension
- Nephrolithiasis
  - Severe flank pain (patient is writhing on the exam table) radiating to the inguinal area
  - Dysuria, hematuria, with absence of fever (unless infection is also present)
- Asymptomatic bacteriuria (ASB)
  - A UA with bacteriuria without the clinical syndrome of UTI
  - In the setting of pyuria (presence of WBCs in the urine) and bacteriuria in a patient without symptoms localizing to the urinary tract, systemic signs such as fever, altered mental status, and leukocytosis could be features of UTI but do not on their own merit a diagnosis unless other potential etiologic causes of such findings have been adequately explored and ruled out
- Figure 38-2 describes an approach to the clinical presentation, patient characteristics, and next diagnostic and management considerations for patients who may have a UTI
  - Some patients in the ED have had a UA already done; therefore, it is crucial to differentiate UTI from ASB

ETIOLOGY

- *Escherichia coli is the predominant pathogen across the spectrum of UTI clinical syndromes and patient populations*
- Acute cystitis and pyelonephritis
  - Etiologies between acute cystitis and pyelonephritis are similar since pyelonephritis usually develops as an ascending infection from the bladder
  - *E. coli* (75–90% of isolates)

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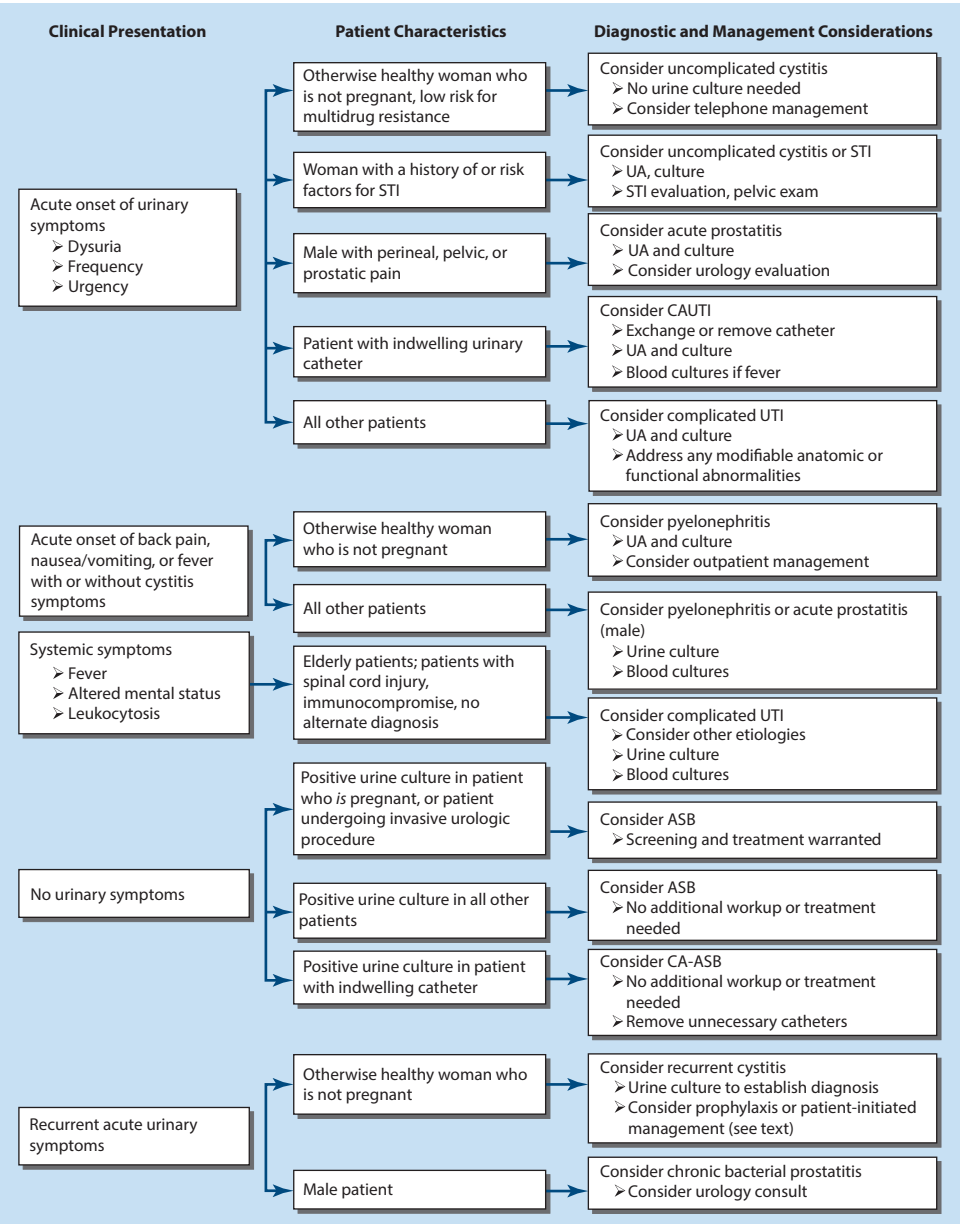

FIGURE 38-2 Diagnostic Approach to UTI. ASB, asymptomatic bacteriuria; NTF, nitrofurantoin; STI, sexually transmitted infection; TMP-SMX, trimethoprim-sulfamethoxazole. (Reproduced with permission from Trautner BW et al. Urinary tract infections: Cystitis, prostatitis, and pyelonephritis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- *Staphylococcus saprophyticus* (5–15%, more frequent in younger women)
- *Klebsiella*, *Proteus* (increased urine pH), *Enterobacter*, and *Citrobacter* are responsible for most of the remainder
- Other rarer causes include *Pseudomonas*, *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant *S. aureus*), *Salmonella*, *Acinetobacter*, *Morganella*, and *Candida*
  - If a patient has either *Salmonella* or *S. aureus*, consider concomitant bacteremia, as these organisms are highly virulent and may have caused hematogenous spread to the urinary tract

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    - *Candida*
        - The presence of *Candida* in the urine of a noninstrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination
        - In contrast, candiduria is common in catheterized patients, particularly following antimicrobial therapy for catheter-associated UTI (CAUTI) or inappropriate treatment of asymptomatic bacteriuria
- CAUTI
    - *E. coli* (predominant organism, although the etiology is more diverse in CAUTI)
    - *P. aeruginosa*
    - Enterococci
    - *S. aureus*
    - *Candida*
- Antimicrobial-resistant organisms
    - Antimicrobial resistance among *Enterobacterales* species that cause UTI is increasing
        - A surveillance study showed resistance rates of > 20% to trimethoprim-sulfamethoxazole, fluoroquinolones, and nitrofurantoin among ambulatory patients
        - 6% of isolates were resistant to ≥ 3 antibiotic classes
        - 9% of isolates had production of extended-spectrum β-lactamase (ESBL)

DIAGNOSTIC TESTS

LABS

- CBC with differential
    - Evaluates for leukocytosis
- BMP
    - Evaluates electrolyte abnormalities, kidney function, and hyperglycemia
- β-human chorionic gonadotropin if female
    - To rule out pregnancy with possible ectopic pregnancy
- Blood cultures × 2 before antibiotics if sepsis is present
- Lactic acid
    - To assess the severity of tissue hypoxia if sepsis is present
- UA with urine culture and Gram stain
    - Gram stain can more quickly differentiate gram-positive and gram-negative infections than the urine culture, which can more quickly narrow your differential diagnosis and antibiotic selection
    - If the patient has a urinary catheter, obtain UA/cultures after the old catheter has been replaced with a new one
    - Leukocyte esterase
        - Detects this enzyme in neutrophils present in the patient's urine, whether the cells are intact or lysed
        - It is a less sensitive and specific surrogate for pyuria
    - Nitrites
        - Only members of the *Enterobacterales* family convert nitrate to nitrite
        - Nitrites can be positive in *Enterobacterales* asymptomatic bacteriuria
        - Nitrites are negative in UTI due to non-*Enterobacterales* organisms
        - Nitrites may also be falsely negative in a woman with acute cystitis who is voiding frequently because of significant oral fluid intake
    - WBCs (pyuria) → the most important test
        - Urine microscopy reveals pyuria in nearly all cases of cystitis
        - The cutoff of > 10 WBCs per high-powered field (HPF) has poor specificity (36%) for UTI; a cutoff closer to 250 WBCs/HPF better correlates with the presence of urinary symptoms
            - However, at present, > 10 WBCs/HPF remains the generally accepted standard for pyuria
    - Leukocyte casts
        - Present in pyelonephritis
    - If squamous epithelial cells are present, it is a *contaminated* sample
        - Another sample is needed
    - Hematuria
        - Urine microscopy reveals hematuria in ~ 30% of cases of UTI
    - Presence of bacteriuria
        - Culture results take at least 24 h
        - Susceptibility testing takes another 24–48 h

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        - Studies of women with symptoms of cystitis have found that a colony count threshold of $> 10^2$ bacteria/mL is more sensitive (95%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women
            - Fewer data are available in men about the threshold of bacteriuria to establish cystitis
        - A culture that yields mixed bacterial species is contaminated except in settings of
            - Long-term catheterization
            - Chronic urinary retention
            - The presence of a fistula between the urinary tract and the GI or genital tract
        - Again, the presence of bacteriuria in isolate does *not* diagnose a UTI
    - Patients with a catheter will almost always have both pyuria and bacteriuria
        - *Therefore, the presence of pyuria and bacteriuria in the absence of symptoms does not diagnose a UTI*
- *Review previous urine cultures if available*
    - Helps in the choice of initial empirical antibiotic treatment
- Nucleic acid testing if considering chlamydia or gonorrhea

IMAGING

- The main objective of imaging is
    - To evaluate for processes that may delay response to therapy or warrant intervention, such as a calculus or obstruction
    - To diagnose a complication of infection, such as emphysematous or xanthogranulomatous pyelonephritis, or intraparenchymal abscess
- It is reasonable to get a postvoid residual measurement for all patients in the hospital to rule out urinary obstruction
- For cystitis, no specific imaging is needed
- Consider a CT abdomen/pelvis without contrast if
    - Complicated UTI
    - Sepsis/septic shock, or
    - If not improving in 48–72 h
- Ultrasound can be considered for patients for whom exposure to contrast or radiation is not appropriate
- Indications for renal imaging in patients with presumed pyelonephritis
    - Uncertain diagnosis
    - Severe illness
    - Immunocompromised state
    - Worsening renal function
    - Failure to improve after 72 h of antibiotics
    - Suspected kidney stone or urinary tract obstruction
    - Relapsing or recurrent pyelonephritis
    - Male sex

MANAGEMENT

Before initiating antibiotics for a suspected UTI, it is essential to answer three key questions.

1. Does the patient actually have a UTI (rather than asymptomatic bacteriuria or urinary symptoms not related to infection)?
2. If the patient does have a UTI, is it confined to the bladder (uncomplicated UTI), or is there evidence that infection might be present beyond the bladder (complicated UTI)?
3. If the diagnosis is uncertain, would it be safe to delay empirical antimicrobial therapy while attempting to achieve more diagnostic clarity?

EVALUATION OF ASYMPTOMATIC BACTERIURIA (ASB)

- In practice, one of the most challenging clinical scenarios is to differentiate ASB from UTI
- Especially difficult when an older patient presents with isolated altered mentation often superimposed on chronic cognitive deficits
    - Accurately diagnosing the cause of such a patient's acute encephalopathy is challenging both because
        - The patient might not be able to reliably report localizing urinary symptoms
        - True UTI is an important diagnostic consideration on a long list of possible causes of the patient's symptoms

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- In situations of encephalopathy with possible UTI or ASB, establish whether the patient has *sepsis*
  - *If sepsis is present or withholding antibiotics is not feasible*, then begin empirical antibiotics
  - If sepsis is *absent*, decide if empirical antibiotics can be safely withheld while the diagnostic process is ongoing and symptomatic treatment for other noninfectious causes of delirium is trialed
    - Seek collateral history from caregivers or family to elicit information about what occurred prior to the patient's acute encephalopathy
    - The clinician should rule out other potential causes of encephalopathy and delirium (see **Chap. 35**)
- Catheter-associated UTIs (CAUTIs) also are difficult to diagnose accurately in the setting of bacteriuria
  - The accepted threshold for bacteriuria to meet the definition of CAUTI is $\geq 10^3$ colony-forming units per milliliter of urine
  - Always remove the old catheter and replace with a new one prior to performing a UA with culture
  - The central diagnostic difficulty of CAUTI is that, because catheters provide a conduit for bacteria to enter the bladder, bacteriuria is inevitable with urinary catheterization
  - The typical signs and symptoms of UTI, including pain, urgency, dysuria, fever, and peripheral leukocytosis, also have less predictive value for diagnosis of UTI in catheterized patients
  - To make a diagnosis of CAUTI, first, signs and symptoms of UTI (localizing and/or systemic) should be present along with pyuria and bacteriuria
  - Rule out other infectious and noninfectious causes of the patient's symptoms before settling on the diagnosis of CAUTI
- ASB should *not* be treated *unless*
  - The patient is pregnant
  - Prior to urologic procedures
  - The patient is a preschool child with vesicoureteral reflux

WHEN TO ADMIT A PATIENT FOR UTI

- Admit patients if they have any of the following
  - Sepsis
  - Complicated UTI
  - Altered mental status
  - Persistently high fever or pain
  - Marked debility
  - Unreliable follow-up
  - Inability to maintain oral hydration or take oral medications

PRINCIPLES OF INPATIENT MANAGEMENT OF UTI

- If prior urine cultures are available, tailor initial therapy based on those susceptibilities unless other data suggest otherwise
- Assess risk factors for multidrug-resistant organisms (MDROs) when choosing antibiotics
  - Risk factors for MDROs include a history of any of the following in the prior 3 months
    - An MDR urinary isolate (i.e., nonsusceptible to at least one agent in three or more antimicrobial classes) including
      - An extended-spectrum β-lactamase–producing isolate
      - A fluoroquinolone-resistant *Pseudomonas* urinary isolate
    - Inpatient stay at health care facility (e.g., hospital, nursing home, long-term acute care facility)
    - Use of a broad-spectrum antimicrobial (e.g., fluoroquinolone, trimethoprim-sulfamethoxazole, third- or later-generation cephalosporin)
    - Travel to parts of the world with high rates of MDROs (India, Spain, Mexico)
- Use your local hospital antibiogram
- If the patient has significant urinary obstruction (e.g., a large postvoid residual) associated with a UTI, temporary relief of the obstruction with insertion of a Foley catheter may be indicated
  - It is reasonable to initially perform an "in-and-out" catheter to avoid an indwelling Foley
    - If urinary retention recurs, a temporary indwelling Foley would need to be inserted
  - Remove Foley catheters as early as possible
- Tailor antibiotics as soon as culture susceptibilities come back
- IV antibiotics can be switched to oral once the patient has improvement in symptoms if culture and susceptibility allow
- Pyelonephritis due to drug-resistant uropathogens requiring nonpreferred antibiotics should be treated in consultation with infectious disease specialists
- Total treatment duration is 5–14 days based on response rate and the antibiotic selection
  - Fluoroquinolones: 5–7 days

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- Trimethoprim-sulfamethoxazole: 7–10 days
- β-Lactams: 10–14 days

PYELONEPHRITIS

- If the patient is hospitalized with sepsis or is unable to tolerate outpatient therapy
  - Fluid resuscitation per sepsis guidelines (at least 30 mL/kg in the first 3 h)
  - Assess risk factors for multidrug-resistant organisms (MDROs)
  - If no MDRO risk factors are present
    - A third-generation cephalosporin is first-line therapy
      - IV ceftriaxone, 1–2 g daily
    - If the patient has a β-lactam allergy use either
      - Levofloxacin, 750 mg IV daily, or
      - Ciprofloxacin, 400 mg IV q12h
  - If the patient has risk factors for MDROs, choose one of the following
    - Cefepime, 1–2 g IV q8–12h
    - Piperacillin-tazobactam, 3.375 g IV q6h
    - Meropenem, 1–2 g IV q8h
    - Imipenem, 500 mg IV q6h
- If the patient is *critically ill requiring ICU admission* or has *suspected or documented urinary tract obstruction*
  - Obtain abdominal imaging if not already performed
  - Treat with broad-spectrum antibiotics, with extended-spectrum β-lactamase and methicillin-resistant *Staphylococcus aureus* (MRSA) coverage
    - Select one of the following
      - Imipenem, 500 mg IV q6h
      - Meropenem, 1–2 g IV q8h
      - Doripenem, 500 mg IV q8h
    - Plus, add one of the following
      - Vancomycin
      - Daptomycin, 6 mg/kg IV daily
      - Linezolid, 600 mg IV q12h
- If the *patient is not responding or is having worsening symptoms at 48–72 h of starting antibiotics,* additional evaluation with imaging or other factors should be assessed that may be compromising clinical response
  - Pyelonephritis may be complicated by *acute papillary necrosis*, causing urinary obstruction
    - This requires intervention to relieve the obstruction, overcome the infection, and preserve renal function
  - *Perinephric and renal cortical abscesses* may require percutaneous drainage
  - Percutaneous drainage can also be used as the initial therapy in *emphysematous pyelonephritis*
    - This can be followed by elective nephrectomy as needed depending upon the patient's clinical status in consultation with urologic specialists
  - *Xanthogranulomatous pyelonephritis* is treated in close collaboration with urologic colleagues and often requires nephrectomy
    - Antibiotic treatment duration should be individualized
- Indications for considering urologic consultation in pyelonephritis
  - Urinary tract obstruction and/or high urinary postvoid residual volume
  - Nephrolithiasis with pyelonephritis
  - Intraparenchymal abscess
  - Emphysematous pyelonephritis
  - Xanthogranulomatous pyelonephritis
  - Gross hematuria
  - Prostatic abscess

CATHETER-ASSOCIATED UTI (CAUTI)

- Urine cultures are essential to guide treatment given the diversity of organisms that can cause a CAUTI
- Replace the old catheter with a new one (preferably before the UA/culture is sent)
- Empirical antibiotics are as above for pyelonephritis treatment, but prior cultures, if available, may change empirical therapy
- Duration of therapy is typically 7–14 days based on clinical response
- The best strategy for prevention of CAUTI is to
  - Avoid the insertion of unnecessary catheters
  - Remove catheters once they are no longer necessary

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ACUTE BACTERIAL PROSTATITIS (ABP)

- ABP should specifically be suspected in men presenting with UTI with systemic symptoms without another clear anatomic location of UTI, such as pyelonephritis
- Antimicrobial therapy should be promptly initiated after urine and blood cultures are obtained
  - Appropriate empirical IV antibiotics are
    - Ceftriaxone, 1–2 g daily
    - Piperacillin-tazobactam, 3.375 g IV q6h, or
    - Ciprofloxacin, 400 mg q12h
- Treatment duration
  - At least 2 weeks and potentially up to 4 weeks with a fluoroquinolone or trimethoprim-sulfamethoxazole is recommended for susceptible uropathogens
- Identification of a prostatic abscess should prompt consultation with urologic specialists
- Prescribe tamsulosin or finasteride for chronic prostatitis/pelvic pain syndrome, if present

OUTPATIENT MANAGEMENT OF UTI

- The increased prevalence of multidrug-resistant uropathogens has left few oral options for therapy in some cases
  - No single agent or agents can confidently be recommended for empirical ambulatory treatment of UTI without regard to geographic region
  - Always use a local antibiogram and prior urine cultures, if available, to tailor empirical antibiotic selection

CYSTITIS

- If the patient does not have any risk factors for multidrug-resistant organisms (MDROs), then choose from the agents in Table 38-1
  - Preferred agents include trimethoprim-sulfamethoxazole, nitrofurantoin, fosfomycin, and pivmecillinam
    - Pivmecillinam often retains activity against multidrug-resistant *Escherichia coli*, including some expressing extended-spectrum β-lactamases [1]
- If the patient does have MDRO risk factors
  - Obtain a urine culture and susceptibility testing, and
  - If possible, defer treatment until a regimen can be chosen based on susceptibilities
- Alternative agents for cystitis include fluoroquinolones and β-lactams
  - β-Lactams are favored over fluoroquinolones as an alternative agent for treatment of uncomplicated cystitis because of the bacterial resistance and side effects associated with fluoroquinolones
  - In men
    - If there is concern for prostatic involvement, fluoroquinolones or TMP-SMX are preferred over β-lactams because of their superior penetration into the prostate
- Treatment duration depends on the antibiotic chosen (Table 38-1)

PYELONEPHRITIS

- Choose between one of the following
  - TMP-SMX, one double-strength table PO bid × 7–14 days
  - Ciprofloxacin, 500 mg PO daily × 7–14 days
  - Levofloxacin, 750 mg PO × 7–14 days
- Nitrofurantoin is *not* used in pyelonephritis

TABLE 38-1 Treatment Strategies for Acute Uncomplicated Cystitis

DRUG	DOSE	DURATION	COMMON SIDE EFFECTS
Nitrofurantoin	100 mg bid	Women or men: 5–7 days	Nausea, headache
TMP-SMX	1 double-strength tablet bid	Women: 3 days Men: 7 days	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin	3-g sachet	Women: 1 day Men: Every other day × 3 doses	Diarrhea, nausea, headache
Pivmecillinam	400 mg bid	Women: 3–7 days	Nausea, vomiting, diarrhea
Fluoroquinolones	Dose varies by agent	Women: 3 days Men: 7 days	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams	Dose varies by agent	Women or men: 5–7 days	Diarrhea, nausea, vomiting, rash, urticaria

TMP-SMX, trimethoprim-sulfamethoxazole.

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CHRONIC BACTERIAL PROSTATITIS (CBP)

- A 4- to 6-week course of antibiotics (fluoroquinolones or TMP-SMX)
- Recurrences may warrant up to a 12-week course of therapy

CANDIDURIA

- Treat in patients who have symptomatic cystitis or pyelonephritis or those who are asymptomatic but are at high risk for disseminated disease
  - For example, patients with neutropenia, patients who will undergo urologic manipulation, and low-birth-weight infants
- Fluconazole, 200–400 mg PO daily for 7–14 days, reaches high levels in the urine and is the first-line agent

UTI IN PREGNANCY

- Aminopenicillins (ampicillin and amoxicillin) and cephalosporins are the drugs of choice in pregnancy
- Avoid sulfonamides and fluoroquinolones due to teratogenic effects
- Patients with asymptomatic bacteriuria during pregnancy also should receive treatment
- Duration is 5–7 days in cystitis
- For pregnant patients with pyelonephritis
  - Guidelines recommend parenteral β-lactam therapy with or without aminoglycosides based on limited observational data and historic norms of practice

PREVENTION OF UTIS IN WOMEN

- The threshold of ≥ 3 symptomatic episodes per year to intervene or develop a specific preventive strategy is not absolute
  - Clinicians are recommended to engage in shared decision-making with each individual patient to make determinations about a UTI preventive strategy
- Initial evaluation of a patient with recurrent cystitis should include
  - Confirmation of the diagnosis of recurrent UTI
  - Imaging to identify renal calculi or another potential nidus of infection
  - Assessment for urinary retention
- Nonantimicrobial prophylactic interventions
  - Increase fluid intake
  - Methenamine hippurate (might reduce recurrent UTIs as much as antibiotic prophylaxis) [2]
  - Cranberry product use [3]
  - Topical estrogen reduces recurrent UTIs in postmenopausal women (without systemic hormone effects) [4]
    - Oral estrogen is not recommended
  - Postcoital voiding
- Antibiotic prophylactic strategies
  - Continuous (daily or thrice-weekly dosing of low-dose trimethoprim-sulfamethoxazole [TMP-SMX] or nitrofurantoin)
  - Postcoital single-dose TMP-SMX or nitrofurantoin
  - Patient-initiated therapy
    - Supply the patient with materials for urine culture and a course of antibiotics (TMP-SMX or nitrofurantoin) for self-medication at the first sign of symptoms

COMPLICATIONS

- Cystitis leading to pyelonephritis
- Emphysematous pyelonephritis (especially in patients with diabetes—can be life-threatening)
- Xanthogranulomatous pyelonephritis
- Intraparenchymal or perinephric abscess
- Chronic pyelonephritis with scarring
- Sepsis and septic shock
- Papillary necrosis and urinary obstruction

PROGNOSIS

- Patients typically respond favorably and quickly to appropriately chosen modern antimicrobials
- In the absence of anatomic abnormalities such as reflux, recurrent infections in children and adults do not lead to chronic pyelonephritis or renal failure
- In the presence of underlying renal abnormalities (particularly obstructing stones), infection as a secondary factor can accelerate renal parenchymal damage

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PATHOPHYSIOLOGY

- The urinary tract is an anatomic unit linked by a continuous column of urine extending from the kidneys to the urethra
- Ascending bacteria from the urethra migrating to the bladder is the primary mechanism of UTI
  - Bacteria can then ascend to the kidneys through the ureters
- The other major route of entry into the genitourinary tract is hematogenous, where bacteremia precedes UTI (hematogenous spread accounts for < 2% of documented UTIs)
  - Consider concomitant bacteremia when a patient has either *Salmonella* or *Staphylococcus aureus* on urine culture, as these organisms are highly virulent and may cause hematogenous spread to the urinary tract
  - Hematogenous spread can also produce focal renal abscesses or pyelonephritis
  - The pathogenesis of candiduria is distinct because hematogenous spread is more common
    - The presence of *Candida* in the urine of a noninstrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination
    - In contrast, candiduria is common in catheterized patients, particularly following antimicrobial therapy for catheter-associated UTI or inappropriate treatment of asymptomatic bacteriuria
- Importantly, introduction of bacteria into the bladder does not inevitably lead to sustained and symptomatic infection
  - The interplay of environment, hygiene, bacteria, and a patient's individual immune status determines whether tissue invasion or symptomatic infection will arise (Fig. 38-3)
  - For example, bacteria enter the bladder after sexual intercourse, but normal voiding and innate defense mechanisms eliminate these organisms
  - Any foreign body in the urinary tract, such as a urinary catheter, ureteral stent, or kidney stone, provides an inert surface for bacterial colonization
  - Abnormal micturition and/or significant residual urine volume promote infection
  - Anything that increases the likelihood of bacteria entering the bladder and staying there increases the risk of UTI
- Environmental factors
  - Vaginal ecology
    - Colonization of the vaginal/periurethral area with intestinal flora (especially *Escherichia coli*) is the critical step in UTI pathogenesis
    - Sexual intercourse increases the risk of vaginal *E. coli* colonization → higher UTI risk
    - Spermicides with nonoxynol-9 kill normal lactobacilli → increased *E. coli* colonization and bacteriuria

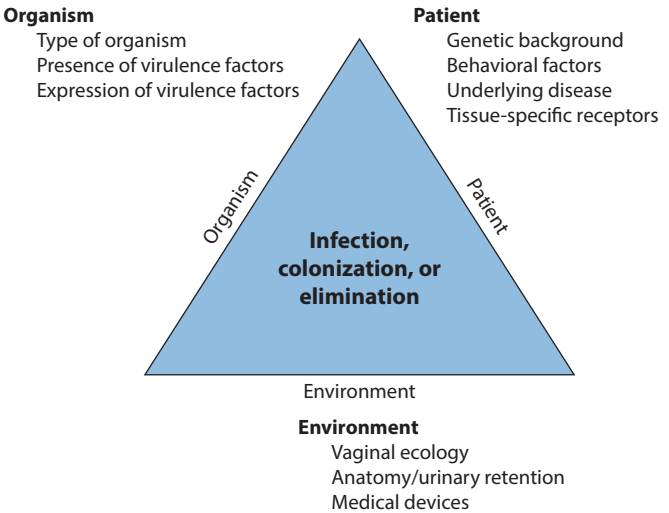

FIGURE 38-3 Pathogenesis of UTI. The relationship among specific patient, pathogen, and environmental factors determines the clinical outcome. (Reproduced with permission from Trautner BW et al. Urinary tract infections: Cystitis, prostatitis, and pyelonephritis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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        - Postmenopausal atrophy → lactobacilli are replaced by gram-negative bacteria
            - Topical estrogen reduces recurrent UTIs in postmenopausal women (without systemic hormone effects)
    - Anatomical and functional abnormalities
        - Urinary stasis/obstruction predisposes to UTI
        - Foreign bodies (stones, stents, and catheters) allow biofilm formation and persistent colonization
        - Thus, vesicoureteral reflux, prostatic hypertrophy, neurogenic bladder, and urinary diversion surgery all create an environment that can lead to UTI
        - Pregnancy: decreased ureteral tone and peristalsis → reflux → pyelonephritis
        - The shorter female urethra explains the higher incidence of UTI in young women compared with young men
- Patient factors
    - Genetic susceptibility influences recurrent UTI risk
        - Familial predisposition (maternal history and first UTI at age < 15)
    - Persistent asymptomatic *E. coli* colonization may underlie recurrence, even during asymptomatic bacteriuria
    - Vaginal/periurethral mucosa in recurrent UTI binds bacteria 3 × more than controls
        - Related to the absence of certain blood group antigens and facilitating enhanced *E. coli* adherence to the urothelium
    - Innate immune genetic variations (e.g., Toll-like receptors, IL-interleukin 8 receptor) are linked to recurrent UTI and pyelonephritis
- Microbial factors
    - Pathogenic *E. coli* strains that cause invasive symptomatic infection in otherwise healthy patients often possess and express genetic virulence factors, including bacterial surface adhesins that mediate microbial binding to specific receptors on the surface of uroepithelial cells
    - Adhesins
        - P fimbriae: hair-like proteins that bind blood-group antigen P on renal epithelial cells
            - Important in the pathogenesis of pyelonephritis and subsequent bacteremia
        - Type 1 pili (fimbria): play a key role in *E. coli* strains by mediating binding to mannose on bladder cells
    - Other virulence mechanisms can contribute to the ability of pathogenic *E. coli* to thrive in the bladder; they include
        - Toxins
        - Iron-acquisition systems
        - Biofilm formation
        - Bacterial capsules

RISK FACTORS

- *Sexual intercourse and the use of spermicide are the most consistently documented risk factors*
- Risk factors can be grouped broadly into three categories
    - Factors that impede the normal outflow of urine
        - Infant males (from congenital anatomic urinary tract abnormalities)
        - Bladder dysfunction leading to overflow urinary incontinence
        - Benign prostatic hyperplasia
        - Cystoceles
        - Pelvic organ prolapse
    - Factors that introduce new bacteria into the genitourinary tract or serve as a nidus of infection
        - Frequent sexual intercourse
        - For men: insertive rectal intercourse and lack of circumcision
        - Urinary instrumentation (e.g., intermittent or chronic catheterization or the existence of a draining nephrostomy tube)
        - Foreign bodies in the urinary tract (e.g., stents and kidney stones)
    - Factors that disrupt or impair local mucosal defenses
        - Recent use of diaphragms or spermicide and menopause in females
        - Women with diabetes (especially those prescribed SGLT-2Is)
- Other risk factors
    - A new sexual partner
    - First UTI before 15 years of age
    - Family and maternal history of UTI
    - Pregnancy

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- Vaginal infection
- Obesity

ADMITTING ORDERS

- Admit to floor or ICU if septic shock
- Diagnosis: complicated UTI (and state the specific etiology that makes it complicated)
- Condition: stable/guarded
- Vital signs: routine
- Nursing: routine vital signs, call for temperature > 38.5°C (101.4°F), systolic BP < 100 mm Hg, or heart rate > 110 beats/min
- Fluids: administer sepsis resuscitation if indicated
- Diagnostic tests
  - CBC with differential
  - UA with culture and Gram stain
  - BMP
  - Blood cultures if septic
  - β-human chorionic gonadotropin if female and premenopausal
  - If suspected pyelonephritis → ultrasound of kidneys
  - CT abdomen/pelvis if sepsis, complicated UTI, or UTI not improving after 48–72 h
- Medications
  - Ceftriaxone, 1 g IV daily, or any of the empirical antibiotics listed in the Management section depending on patient-specific factors and risk of multidrug-resistant organisms

DISCHARGE INFORMATION

- Can discharge when able to tolerate food and medications by mouth
- Ensure the patient is prescribed the correct antibiotic and duration based on culture and sensitivity data
- Educate about postcoital voiding and avoidance of spermicides
- Schedule a follow-up urine culture if the patient is pregnant or if a urinary tract obstruction is present
- Educate on preventive nonantimicrobial or antimicrobial preventive measures if indicated for recurrent UTI

CASE ANSWERS

1. This patient's constellation of symptoms and UA findings are typical of pyelonephritis. She is septic but is not so critically ill as to require ICU care. She has no risk factors for multidrug-resistant organisms. Because she has no known drug allergies, first-line therapy is with a β-lactam (e.g., IV ceftriaxone 1–2 g daily).
2. Imaging is not required in all patients with pyelonephritis on initial presentation. However, this patient is presenting with AKI and signs of urinary retention (postvoid residual of 720 mL). Because of this, imaging with a CT abdomen/pelvis to rule out urinary obstruction is reasonable, as acute papillary necrosis can cause urinary obstruction in patients with pyelonephritis.
3. In the setting of known multiple sclerosis, an elevated postvoid residual, and pyelonephritis, urinary catheterization to relieve pressure in the bladder is indicated. Initially, an in-and-out catheter can be performed with repeat postvoid residual to avoid an indwelling Foley. If a repeat postvoid residual is still elevated, then an indwelling Foley may need to be inserted to relieve the urinary obstruction until the infection and inflammation of the bladder are more controlled.

LANDMARK TRIALS

[1] Lodise TP et al. Pivmecillinam for treatment of uncomplicated urinary tract infection: New efficacy analysis. Clin Infect Dis 81:e285, 2025. [PMID: 40567143]
- *Summary:* This reanalysis of randomized, controlled trial data confirmed the efficacy of oral pivmecillinam in uncomplicated UTI and was used to support its recent approval in the United States.

[2] Heltveit-Olsen SR et al. Methenamine hippurate to prevent recurrent urinary tract infections in older women: Protocol for a randomised, placebo-controlled trial (ImpresU). BMJ Open 12:e065217, 2022. [PMID: 36319057]
- *Summary:* Methenamine hippurate reduces the frequency of recurrent UTIs in older women with a point estimate of a 25% reduction, suggesting advantages over low-dose antibiotic prophylaxis because of its low potential for selection for antimicrobial resistance and mild side effects.

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[3] Williams G et al. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 4:CD001321, 2023. [PMID: 37068952]
    - *Summary:* Cranberry products may help to prevent UTIs that cause symptoms in women with frequent UTIs, in children with UTIs, and in people who have undergone an intervention involving the bladder.
[4] Tan-Kim J et al. Efficacy of vaginal estrogen for recurrent urinary tract infection prevention in hypoestrogenic women. Am J Obstet Gynecol 229:143.e1, 2023. [PMID: 37178856]
    - *Summary:* In this retrospective review of 5600 women with hypoestrogenism who were prescribed vaginal estrogen for the prevention of recurrent UTIs, the frequency of UTI decreased by > 50% in the following year.

FURTHER READING

- Borgert BJ et al. Prostatitis: A review. JAMA 334:1003, 2025. [PMID: 40788632]
- Gupta K. Acute complicated urinary tract infection (including pyelonephritis) in adults. UpToDate. https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults. Accessed February 5, 2026.
- Trautner BW et al. *Clinical Practice Guideline by Infectious Diseases Society of America (IDSA): 2025 Guideline on Management and Treatment of Complicated Urinary Tract Infections: Executive Summary*. Arlington, Infectious Diseases Society of America, 2025.
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39 Pneumonia

KEY POINTS

1. Pneumonia is an infection of the pulmonary parenchyma and can be classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP).
2. The clinical presentation of pneumonia can vary from indolent to fulminant and from mild to fatal, and includes fever, cough (productive or nonproductive), chills, sweats, dyspnea, and chest pain. Asymmetric chest wall expansion, egophony, dullness to percussion, and bronchial breath sounds on exam make the diagnosis of pneumonia more likely.
3. Pneumonia is a clinical and radiographic diagnosis, with the presence of ≥ 2 signs (e.g., temperature > 38°C or ≤ 36°C; leukocyte count < 4000/μL or > 10,000/μL) or symptoms (e.g., new or increased cough or dyspnea) of pneumonia in conjunction with consistent radiographic findings (e.g., air space density) without an alternative explanation of the findings. Respiratory samples for culture, such as sputum or tracheal aspirate, may help identify a specific organism. Blood cultures may be obtained but have a low yield. Molecular testing can identify viral or intracellular pathogens. Risk factors for multidrug-resistant pathogens also should be considered.
4. Empirical antibiotic selection for inpatients with CAP is based on the severity of illness and whether there are risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and/or *Pseudomonas* (Fig. 39-2 and Table 39-5). For HAP and VAP, multidrug-resistant organisms are more common, but risk factors again should be considered in choosing an empirical antibiotic regimen (Table 39-6). Glucocorticoids should be considered for severe CAP. A negative MRSA nares PCR aids the decision to discontinue MRSA coverage. Oseltamivir should be given in influenza pneumonia. Dexamethasone reduces mortality in patients with hypoxemic COVID-19 pneumonia.
5. Complications of pneumonia include respiratory failure, lung abscess, empyema, necrotizing pneumonia, and sepsis. Mortality rates vary based on the type of pneumonia and the presence of risk factors. Prompt and appropriate treatment can improve outcomes.

EPIDEMIOLOGY & DEFINITIONS

It is estimated that 7 million or more community-acquired pneumonia (CAP) cases occur annually in the United States. The annual incidence in adults ranges from 16 to 23 per 1000 population. The incidence of hospitalization is 650 per 100,000 but rises to 2000 per 100,000 yearly in older persons. About 30% of patients are hospitalized, resulting in 1.5 million admissions. Along with influenza, CAP is the eighth leading cause of death in the United States, resulting in > 60,000 deaths annually; CAP is the leading cause of death from infection among patients > 65 years of age. Moreover, 18% of patients hospitalized with CAP are readmitted within 1 month of discharge. The overall yearly CAP cost is estimated at $17 billion.

In addition to CAP, hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are common in health care settings. VAP prevalence estimates vary between 6 and 52 cases per 100 patients requiring mechanical ventilation, depending on the population studied. Although in recent years the frequency of this infection was declining as a result of effective prevention strategies, with the advent of COVID-19 there has been an increase in its frequency. The frequency of VAP changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~ 2 weeks. While less well studied than VAP, HAP in nonintubated patients—both inside and outside the ICU—is similar to VAP. The main differences are the higher frequency of non–multidrug-resistant pathogens and the generally better underlying immunity in nonintubated patients.

Pneumonia caused by macroaspiration of oropharyngeal or gastric contents, usually referred to as *aspiration pneumonia*, is best thought of as a point on the continuum that includes CAP and HAP.

CAP in immunocompetent patients is the focus of this chapter. This chapter also briefly discusses the etiology and the management of HAP and VAP, along with a brief description of the etiology in patients who are immunocompromised.

CAP: acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community (or the pneumonia occurs within 48 h of hospitalization).

HAP: pneumonia that occurs ≥ 48 h after admission and did not appear to be incubating at the time of admission.

VAP: pneumonia that develops ≥ 48 h after mechanical ventilation initiation.

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CLINICAL VIGNETTE

A 72-year-old man with HF with reduced ejection fraction, COPD, alcohol use disorder, and hypertension presents to the ED with dyspnea that is associated with a productive cough, fever, chills, and body aches. He has no recent travel; however, his daughter, who visited him last weekend, was coughing and had a fever. He has not been hospitalized or received antibiotics in the past 3 months and has no previous pneumonia or methicillin-resistant *Staphylococcus aureus* (MRSA) infection. He has been adherent with all his medications. His temperature is 38.6°C (101.4°F), heart rate 115 beats/min, respiratory rate 24 breaths/min, BP 122/82 mm Hg, and Spo_2 90% on room air. He appears uncomfortable and is under two blankets with visible light shaking. His mental status exam is normal. There is decreased chest wall expansion on the right side with deep inhalation. Dullness to percussion and egophony are heard in the right lower lobe. There is no lower extremity edema, and the JVP is not elevated.

Initial lab data reveal:

- WBC count: 16,000 cells/μL
- Platelets: 220,000/μL
- Sodium: 132 mEq/L
- BUN: 40 mg/dL
- SCr: 1.8 mg/dL
- Lactic acid: 2.6 mmol/L
- Normal BNP and troponin levels
- ABG: Pao_2/Fio_2 ratio of 300 mm Hg

A procalcitonin and CRP, sputum and blood cultures, and respiratory viral panel results are pending. A CXR reveals a lobar consolidation in the right lower lobe.

GUIDING QUESTIONS

1. Does this patient have community- or hospital-acquired pneumonia?
2. Does this patient have nonsevere or severe pneumonia, and to what level of care should they be admitted?
3. What empirical antibiotic regimen would you order for this patient?

HISTORY

Pneumonia is a clinical and radiographic diagnosis, with the presence of ≥ 2 signs (e.g., temperature > 38°C or ≤ 36°C; leukocyte count < 4000/μL or > 10,000/μL) or symptoms (e.g., new or increased cough or dyspnea) of pneumonia in conjunction with consistent radiographic findings (e.g., air space density) without an alternative explanation for the signs, symptoms, or radiographic finding.

The clinical presentation of pneumonia can vary from indolent to fulminant and from mild to fatal, and includes fever, cough (productive or nonproductive), chills, sweats, and shortness of breath. Gross hemoptysis is suggestive of necrotizing pneumonia (e.g., due to community-acquired methicillin-sensitive or methicillin-resistant *Staphylococcus aureus* [MRSA]). Pleural involvement may result in chest pain. Up to 20% of patients may have GI symptoms such as nausea, vomiting, or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias. Atypical pneumonia is often due to intracellular pathogens (e.g., mycoplasma, chlamydia).

It is important to know about comorbidities and prior medical conditions when considering pneumonia. HF and COPD exacerbation may present like pneumonia. Immunocompromised states, such as HIV/AIDS, also have to be considered as treatment changes. There are regional patterns to certain infections, making a recent travel history important.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Typical pneumonia has an acute onset of fever, shaking chills, thick productive cough, pleuritic chest pain, dyspnea
  - Atypical pneumonia has an insidious onset with headache, sore throat, fatigue, myalgias, nonproductive cough; fever and chills are uncommon
  - Ultimately, it does not matter if it is typical or atypical; it does matter if it is community-acquired, hospital-acquired, or ventilator-associated pneumonia
- Dyspnea?
  - Common symptom of pneumonia

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- Fever/chills/rigors?
  - Part of CURB-65 score and common symptoms of pneumonia
  - Chills occur in 40–50% and rigors in 15% of patients with pneumonia
- Cough?
  - Productive? Hemoptysis?
  - Common symptom, plus the quality of cough helps with possible PE versus an infectious cause
  - Mucopurulent sputum production is most frequently seen in bacterial pneumonia
  - Scant or watery sputum is more suggestive of an atypical pathogen
  - Dry cough can also occur in any type of pneumonia
- Chest pain?
  - Pleuritic?
  - Occurs in ~ 30% of pneumonia cases
  - Pleuritic pain is more likely pneumonia than angina
- Sinus pain?
  - Helps rule out sinusitis
- Recent illness?
  - Recent viral illnesses predispose to pneumonia, especially influenza followed by *Staphylococcus aureus*
- Nausea/vomiting?
  - Common symptoms of pneumonia; may not be able to tolerate oral antibiotics
- Edema?
  - Can help in the differential diagnosis if HF is a possibility
- Change in mental status?
  - Part of the CURB-65 score, and may be the initial presentation in older persons
- Recent antibiotic use?
  - Important in terms of what antibiotics you may use as this is a risk factor for multidrug-resistant organisms
- Exposure to a sick contact?
  - May make pneumonia of certain etiologies more likely
- Diarrhea?
  - Common symptom in pneumonia
  - Legionella produces diarrhea with pneumonia and relative bradycardia

PAST MEDICAL HISTORY

- History of HF?
  - HF presenting with dyspnea may present similarly to pneumonia
- History of COPD?
  - It can sometimes be difficult to differentiate pneumonia from COPD exacerbation
  - Patients with COPD are more prone to pneumonia, and pneumonia may coexist with a COPD exacerbation
- History of HIV/AIDS?
  - *Pneumocystis jirovecii* pneumonia should be on the differential, as well as other rare causes of pneumonia in patients who are immunocompromised
- History of cystic fibrosis?
  - More likely to have *Pseudomonas, Burkholderia*, or *Staphylococcus aureus* pneumonia
- History of neurologic disease (e.g., dementia, epilepsy, and cerebrovascular disease)?
  - More prone to pneumonia from aspiration
- Prior radiation?
  - Can have radiation pneumonitis if recently treated
- History of sarcoidosis?
  - Prone to cough and pneumonia

SOCIAL HISTORY

- Use of alcohol (risk of aspiration pneumonia) and recreational drugs, smoking
- Occupation
- Living situation
- Sexual history
- Where is the patient from regionally? Or have they traveled recently? (Keep in mind that the geographic ranges below are gross approximations and that these organisms are appearing more often in more places.)
  - Histoplasmosis in the Mississippi and Ohio River Valleys
  - Blastomycosis in states touching and east of the Mississippi River and in Central America
  - Coccidioidomycosis in Southwestern states, California and Mexico
  - Paracoccidioidomycosis in Latin and South America

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MEDICATIONS

- Antibiotic use within the last 3 months is a risk factor for multidrug-resistant organisms

PHYSICAL EXAM

Findings on physical exam vary with the degree of pulmonary consolidation and the presence or absence of a significant pleural effusion. An increased respiratory rate and use of accessory muscles of respiration are common. Vital signs are important not only in detecting if sepsis is present but also in considering whether the patient can be treated as an outpatient or needs to be admitted to the medical floor or to the ICU.

Certain findings make a diagnosis of pneumonia more likely. The clinical presentation may be less obvious in older persons, who may initially display new-onset or worsening confusion, or decompensation of a chronic illness, with few other manifestations.

A positive likelihood ratio (PLR) for physical exam findings is helpful in supporting a diagnosis of pneumonia. The higher the PLR value, the higher the probability of diagnosis. For example, PLR of 3 = 20% probability patient has condition, a PLR of 4 = 25% probability patient has condition, a PLR of 5 = 30% probability patient has condition, and a PLR of 10 = 45% probability patient has condition.

- Vital signs
  - Tachypnea > 28 breaths/min and the BP are part of CURB-65 (see Management section)
    - A respiratory rate > 24 breaths/min is present in 45–70% of patients and may be the most sensitive sign in older persons
  - Fever
    - Fever is frequently absent in older persons
    - Temperature may be deceptively low in the morning due to normal diurnal variation
  - Tachycardia is often present, especially with severe illness
    - *Legionella* pneumonia may cause a relative bradycardia
  - Oxygen saturation assessment for hypoxemia helps determine the severity of illness
- General exam
  - Cachexia (PLR 4.0)
- HEENT
  - Oral mucosa moist or dry
- Cardiac
  - S_3 can indicate HF in the differential
  - New murmur may indicate endocarditis or MI instead of pneumonia
  - JVD is not associated with pneumonia
- Respiratory
  - Asymmetric chest wall expansion (**PLR 44**) highly suggests unilateral pneumonia
    - This finding can be helpful to rule out other causes of dyspnea (e.g., HF, COPD)
  - Accessory muscle use
  - Percussion dullness (PLR 3.6) and tactile fremitus
  - Diminished breath sounds, bronchial breath sounds (PLR 4.0), egophony (PLR 8.2), crackles, wheezes
- Neurologic
  - Mental status exam
    - Confusion may be the sole presentation in older patients
    - Encephalopathy indicates a more severe illness from pneumonia

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Noninfectious
  - HF
    - Cardiac history, no fever, presence of edema and JVD, elevated BNP
  - PE
    - Less likely to have fever
    - May have pleuritic chest pain and hemoptysis like in pneumonia
    - CXR will not reveal lobar or multifocal pneumonia
  - Radiation pneumonitis
    - History of lung cancer and radiation to the lungs with cough
  - COPD exacerbation
    - Increased dyspnea and sputum production from baseline with expiratory wheezing
    - May have an associated viral or bacterial pneumonia

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- Lung cancer or cancer metastasis to the lungs
  - May coexist with a postobstructive pneumonia
- Sarcoidosis
  - Bilateral hilar lymphadenopathy and erythema nodosum may be present
- Aspiration pneumonitis
  - A patient prone to aspiration (alcohol users, epilepsy, older adults with neurologic disease) that may have fever and cough after an aspiration event not associated with bacterial pathogenesis

- Infectious
  - Acute bronchitis
    - Cough, mild hemoptysis, without leukocytosis and a normal CXR
  - Upper respiratory infection
    - Viral infection with dominant symptoms of nasal congestion, sore throat, and cough
  - Abscess, parapneumonic effusion, and empyema
    - Abscess will have long-standing pneumonia symptoms, giving time for abscess to form
    - Parapneumonic effusion and empyema are infected pleural effusions associated with a pneumonia

ETIOLOGY

- Community-acquired pneumonia (CAP)
  - The causative pathogen is often difficult to predict with certainty; in more than half of cases, a specific etiology is not determined
  - Numerous microbes—including a variety of bacteria, viruses, fungi, and protozoa—may cause CAP
    - ***Streptococcus pneumoniae*** remains the most common cause of CAP
  - Newer viral pathogens include
    - Metapneumoviruses
    - Coronaviruses responsible for
      - Severe acute respiratory syndrome (SARS)
      - Middle East respiratory syndrome (MERS)
      - SARS-CoV-2 coronavirus (COVID-19)
  - *Staphylococcus aureus* pneumonia is known to complicate influenza virus infection
    - Methicillin-resistant *S. aureus* (MRSA) may cause *necrotizing pneumonia* as a primary pneumonia
  - Microbial causes of CAP can be described from
    - The site of care (Table 39-1)
    - From epidemiologic and risk factors suggesting certain pathogens (Table 39-2)
  - Separation of agents into "typical" and "atypical" bacterial pathogens may be useful, although both types of pathogens can lead to similar clinical syndromes
    - The "*typical*" group includes
      - *S. pneumoniae*
      - *Haemophilus influenzae*
      - *S. aureus* and gram-negative bacilli such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in selected patients
    - The "*atypical*" organisms include
      - *Mycoplasma pneumoniae*
      - *Chlamydia pneumoniae*

TABLE 39-1 Microbial Causes of Community-Acquired Pneumonia, by Site of Care

	HOSPITALIZED PATIENTS	
OUTPATIENTS	NON-ICU	ICU
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*Staphylococcus aureus*
Haemophilus influenzae	*C. pneumoniae*	*Legionella* spp.
Chlamydia pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses[a]	*Legionella* spp.	*H. influenzae*
	Respiratory viruses[a]	Respiratory viruses[a]

[a]Influenza A and B viruses, SARS-CoV-2 and other coronaviruses, human metapneumovirus, adenoviruses, respiratory syncytial viruses, parainfluenza viruses.

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TABLE 39-2 Epidemiologic Factors Suggesting Possible Causes of Community-Acquired Pneumonia

FACTOR	POSSIBLE PATHOGEN(S)
Alcohol use disorder	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* spp., *S. pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*
Structural lung disease (e.g., bronchiectasis)	*P. aeruginosa*, *Burkholderia cepacia* complex, *Staphylococcus aureus*
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, *M. tuberculosis*, nontuberculous mycobacteria
Travel to Ohio or St. Lawrence River Valleys	*Histoplasma capsulatum*
Travel to southwestern United States	Hantavirus, *Coccidioides* spp.
Travel to Southeast Asia	*Burkholderia pseudomallei*, avian influenza virus
Stay in hotel or on cruise ship in previous 2 weeks	*Legionella* spp.
Local influenza activity	Influenza virus, *S. pneumoniae*, *S. aureus*
Exposure to infected humans	SARS-CoV-2
Exposure to birds	*H. capsulatum*, *Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to sheep, goats, parturient cats	*Coxiella burnetii*

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
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- *Legionella* species
- Respiratory viruses such as influenza, adenoviruses, human metapneumoviruses, respiratory syncytial virus, and coronaviruses

- Hospital-acquired and ventilator-associated pneumonia (HAP and VAP)
  - Microbiologic causes include both non–multidrug-resistant (non-MDR) organisms and MDR organisms (Table 39-3)
  - The non-MDR group of "core pathogens" is nearly identical to the pathogens found in severe CAP (Table 39-1)
  - If patients have other risk factors (particularly prior antibiotic treatment), MDR pathogens become a higher consideration

TABLE 39-3 Microbiologic Causes of Ventilator-Associated Pneumonia

NON-MDR PATHOGENS (CORE PATHOGENS)	MDR PATHOGENS
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Other *Streptococcus* spp.	Methicillin-resistant *S. aureus*
Haemophilus influenzae	*Acinetobacter* spp.
Methicillin-susceptible *Staphylococcus aureus*	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	ESBL-positive strains
Escherichia coli	Carbapenem-resistant strains
Klebsiella pneumoniae	*Legionella pneumophila*
Proteus spp.	*Burkholderia cepacian* complex
Enterobacter spp.	*Aspergillus* spp.
Serratia marcescens	

ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant.
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- The relative frequency of individual MDR pathogens can vary significantly from hospital to hospital and even between different critical care units within the same institution
- *P. aeruginosa* and MRSA are common etiologies

- Pneumonia in immunocompromised patients
  - Typical organisms of CAP and HAP/VAP are still the most common
  - However, other etiologies are more likely to occur compared with immunocompetent patients
    - *Legionella*
    - Nocardia
    - Fungi (aspergillus, *Pneumocystis jirovecii* pneumonia, *Candida*, *Cryptococcus*)
    - Cytomegalovirus and herpes simplex virus
    - Nontuberculous mycobacteria
- Aspiration pneumonia
  - Chemical from gastric contents causes inflammation and bacterial invasion
  - Earlier literature suggested that aspiration pneumonia was caused primarily by anaerobes, with or without aerobic pathogens
    - A shift, however, has been noted recently
    - If aspiration pneumonia is acquired in a community or hospital setting, the likely pathogens are those usually associated with CAP or HAP
    - Anaerobes may still play a role, especially in patients with poor dentition, lung abscess, necrotizing pneumonia, or empyema

DIAGNOSTIC TESTS

LABS

- CBC with differential
  - Presence of leukocytosis or leukopenia
    - A WBC count < 6000 cells/μL may be seen in overwhelming infection in patients with pneumococcal pneumonia
      - This finding has an associated > 65% mortality rate
  - Thrombocytopenia may indicate a serious infection
- BMP
  - Hyponatremia with diarrhea in a patient with pneumonia and bradycardia should raise concern for *Legionella*
  - A serum sodium < 130 mg/dL, elevated BUN, or serum glucose > 250 mg/dL in a nondiabetic patient is associated with a poor prognosis
- Sputum culture and Gram stain
  - Recommended only for hospitalized patients with pneumonia
    - Particularly those with severe cases or those with risks of methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* infection
  - Since pathogens in severe and mild CAP may differ (Table 39-1), the greatest benefit of staining and culturing respiratory secretions is to alert the physician to unexpected and/or resistant pathogens and to permit appropriate modification of therapy
  - To be suitable, a sputum sample must have > 25 neutrophils and < 10 squamous epithelial cells per low-power field
- Blood cultures before antibiotics
  - If CXR findings of pneumonia and positive blood cultures, the organism in the blood is likely the cause of the pneumonia
  - Blood cultures typically have a low yield toward identifying an etiology
- Respiratory PCR
  - PCR tests amplify a microorganism's DNA or RNA
  - PCR of nasopharyngeal swabs has become the standard for diagnosis of respiratory viral infections
    - Able to test for influenza, coronaviruses (including COVID-19), parainfluenza virus, human metapneumovirus, rhinovirus, adenovirus, and other organisms
  - PCR can also detect the nucleic acid of
    - *Legionella* species
    - *Mycoplasma pneumoniae*
    - *Chlamydia pneumoniae*
    - *Mycobacteria*
- MRSA rapid nares PCR
  - Detects the presence of MRSA colonization in deciding whether MRSA coverage should be included

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- Urinary antigen tests for *Legionella* (only detects *Legionella pneumophila* serogroup 1; other types not detected) and pneumococcus
  - Reserved for severe cases and when relevant epidemiologic factors are present
- BNP and troponin
  - Order if considering myocardial ischemia, HF, and/or PE as a source of symptoms
- Lactic acid
  - To determine the severity of tissue hypoxia, if present
- Procalcitonin
  - Theoretically, procalcitonin levels increase with bacterial infections
  - Procalcitonin is insufficiently accurate for use in the diagnosis of bacterial CAP, and initial serum levels should not be used as a basis for withholding initial antibiotic treatment
- CRP
  - CRP is considered even less sensitive than procalcitonin for detecting bacterial pathogens
  - However, severe elevations can ascertain the severity of illness
  - In patients with severe CAP and elevated CRP levels, the addition of glucocorticoids can improve mortality rates
- LDH
  - Marked elevations in LDH are seen in *Pneumocystis* and *Histoplasma* pneumonia in patients with AIDS
- ABG
  - In patients with severe pneumonia, an ABG can help determine the severity of hypoxemia

IMAGING

- CXR
  - Typical pneumonia
    - Lobar consolidation (Fig. 39-1)
    - Multilobar consolidation may indicate serious illness
  - Atypical pneumonia
    - Diffuse reticulonodular infiltrates
    - Absent or minimal consolidation
  - Sometimes the initial CXR is negative, but then shows an infiltrate after fluid resuscitation, termed *blossoming pneumonia*

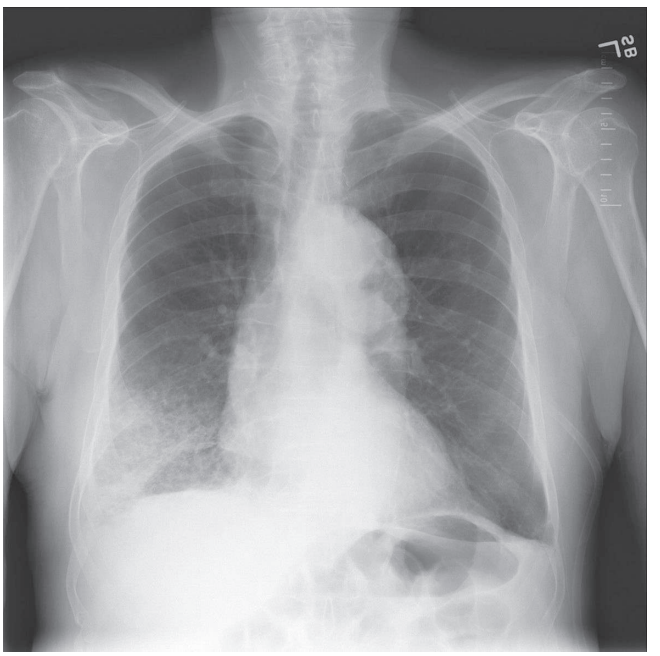

FIGURE 39-1 Pneumococcal lobar pneumonia. (Used with permission from Musher DM. Community-acquired pneumonia, in *Principles and Practices of Hospital Medicine,* 2nd ed, SC McKean et al (eds). New York, McGraw Hill, 2017.)

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- CT may be of value in suspected loculated effusion, cavitary cases, or in postobstructive pneumonia caused by a tumor or foreign body
  - CT can also be performed if there is a high suspicion of pneumonia with an initial normal CXR
- Lung ultrasound and POCUS
  - Findings include consolidation (hypoechoic tissue-like area resembling the liver) and focal B-lines
  - In experienced hands, the sensitivity of diagnosing pneumonia with ultrasound was 80–90% with a specificity of 70–80%
- ECG
  - To rule out a cardiac cause of either chest pain or dyspnea that can be associated with pneumonia

MANAGEMENT

PROGNOSTIC FACTORS & ADMITTING CRITERIA

- Pneumonia Severity Index (PSI)
  - Uses 20 criteria separated into different classes to rate the severity of illness
  - Class 3 and above can be admitted (class 3 either outpatient or brief observational stay in the hospital)
  - Class 4 or 5 should be considered for ICU admission
  - Based on the score, mortality rates were
    - Class 1: 0.1%
    - Class 2: 0.6%
    - Class 3: 2.8%
    - Class 4: 8.2%
    - Class 5: 29.2%
- CURB-65 score
  - 1 point for each
    - Confusion
    - Urea ≥ 20 mg/dL
    - Respiratory rate ≥ 30 breaths/min
    - BP: systolic < 90 mm Hg or diastolic < 60 mmg Hg
    - Age ≥ 65
  - A score of 0 → outpatient management
  - A score of 1 or 2 → admit to general medicine ward
    - A score of 1 can be considered for outpatient management if the patient has stable housing and is able to follow up reliably with their primary care clinician
  - Score ≥ 3 → consider admitting to the ICU
  - Score of 2 = 9.2% mortality; ≥ 3 = 33% mortality
- However, neither the CURB-65 nor the PSI is accurate in determining the need for ICU admission
  - Patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation should be directly admitted to an ICU
  - Those with 3 of the 9 minor criteria in Table 39-4 should also be admitted to an ICU or a high-level monitoring unit

CORE MEASURES IN THE MANAGEMENT OF ALL PATIENTS WITH PNEUMONIA

- Obtain cultures before antibiotics
- Start antibiotics as early as possible (improves mortality)
- Oxygen assessment (Spo_2, ABG) and administer supplemental oxygen for Spo_2 < 92%
- Smoking cessation counseling
- Vaccination to prevent future pneumonia

INPATIENT COMMUNITY-ACQUIRED PNEUMONIA (CAP) MANAGEMENT

- An initial branching point in the choice of empirical antimicrobial therapy while hospitalized is to assess the severity of illness (Table 39-2) and the risk of pneumonia from methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas*
  - Risk factors for MRSA include
    - Colonization or prior infection with MRSA as suggested by gram-positive cocci in clusters on sputum Gram stain
    - A MRSA rapid nares PCR can be used to rule in/out MRSA colonization
  - Risk factors for *P. aeruginosa* include
    - A prior respiratory isolate with *Pseudomonas*
    - Underlying lung disease (e.g., bronchiectasis or very severe COPD)

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TABLE 39-4 Criteria for Severe Community-Acquired Pneumonia

Minor criteria
Respiratory rate ≥ 30 breaths/min
Pao_2/Fio_2 ratio ≤ 250 mm Hg
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level ≥ 20 mg/dL)
Leukopenia (WBC count < 4000 cells/μL)
Thrombocytopenia (platelet count < 100,000 cells/μL)
Hypothermia (core temperature < 36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Respiratory failure requiring invasive mechanical ventilation
Septic shock requiring vasopressors

Pao_2/Fio_2, arterial oxygen pressure/fraction of inspired oxygen.
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    - *However,* to date, there are no prediction rules that reliably identify patients who should be started empirically on treatment for MRSA or *P. aeruginosa*
    - Figure 39-2 describes how to approach whether a patient should be started on MRSA or *Pseudomonas* coverage based on
        - The severity of illness
        - Risks of MRSA or *Pseudomonas*
        - If the patient has recently been hospitalized or received antibiotics
- Table 39-5 describes initial empirical antibiotic selection based on the categorizations from Table 39-2 and Figure 39-2

NONSEVERE CAP WITHOUT *RISK FACTORS FOR* PSEUDOMONAS *OR MRSA*

- β-lactam plus a macrolide
    - IV ceftriaxone, 1–2 g daily
    - Azithromycin, 500 mg daily
- Alternatively, can use a respiratory fluoroquinolone (e.g., levofloxacin, 750 mg daily)

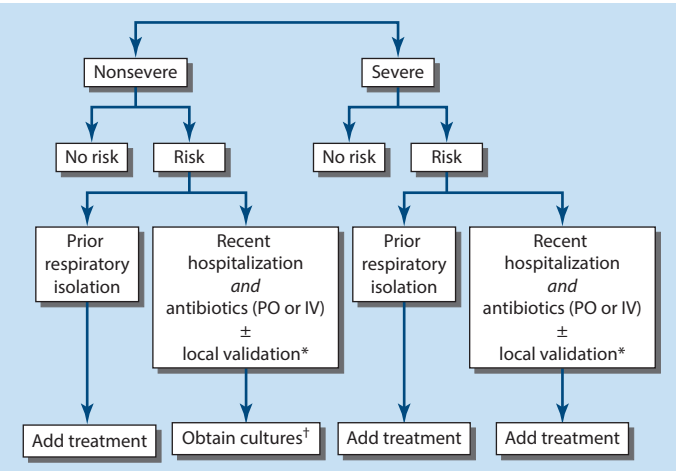

FIGURE 39-2 Algorithm for assessment of inpatient risk of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*. Underlying lung diseases (e.g., bronchiectasis or very severe COPD) are also risks for *P. aeruginosa* infection. *Local validation consists of information on local prevalence, resistance, and risk factors. †Can also use MRSA rapid nasal PCR if available. (Reproduced with permission from Mandell LA, Niederman MS. Pneumonia, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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TABLE 39-5 Initial Treatment for Inpatients with or without Risk Factors for Infection with MRSA or *Pseudomonas aeruginosa*

DISEASE SEVERITY, RISK STATUS	REGIMEN
Nonsevere	
No risk factors	A β-lactam[a] + a macrolide[b] *or* A respiratory fluoroquinolone[c]
Prior respiratory isolation	Add coverage for MRSA[d] or *Pseudomonas aeruginosa*[e]
Recent hospitalization, antibiotic treatment, ± LV[f]	Add coverage for MRSA[d] or *P. aeruginosa*[e] only if cultures are positive
Severe	
No risk factors	A β-lactam[a] + a macrolide[b] *or* A β-lactam[a] + respiratory fluoroquinolone[c]
Prior respiratory isolation	Add coverage for MRSA[d] or *P. aeruginosa*[e]
Recent hospitalization, antibiotic treatment ± LV[f]	Add coverage for MRSA[d] or *P. aeruginosa*[e]

[a]Ampicillin-sulbactam (1.5–3 g q6h), ceftriaxone (1–2 g/d), cefotaxime (1–2 g q8h), ceftaroline (600 mg q12h), or ertapenem (1 g/d). [b]Azithromycin (500 mg/d) or clarithromycin (500 mg bid). [c]Levofloxacin (750 mg/d), moxifloxacin (400 mg/d), or gemifloxacin (320 mg/d). [d]Vancomycin (15 mg/kg q12h, with adjustment based on serum levels) or linezolid (600 mg q12h). [e]Piperacillin-tazobactam (4.5 g q6h), cefepime (2 g q8h), ceftazidime (2 g q8h), imipenem (500 mg q6h), meropenem (1 g q8h), or aztreonam (2 g q8h). [f]Obtain cultures. MRSA rapid PCR also can be used if available.
LV, local validation (local prevalence, resistance, risk factors); MRSA, methicillin-resistant *Staphylococcus aureus*.
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SEVERE CAP WITHOUT *RISK FACTORS FOR* PSEUDOMONAS *OR MRSA*

- β-Lactam plus a macrolide
  - IV ceftriaxone, 1–2 g daily
  - Azithromycin, 500 mg daily
- Alternatively, can use IV ceftriaxone, 1–2 g daily, plus a respiratory fluoroquinolone (e.g., levofloxacin, 750 mg daily)
- Consider glucocorticoids (see Adjunctive Measures section)

NONSEVERE OR SEVERE CAP WITH *RISK FACTORS FOR* PSEUDOMONAS *OR MRSA*

- MRSA prior isolate empirical antibiotic regimen
  - Combination therapy with
    - IV ceftriaxone, 1–2 g daily
    - Azithromycin, 500 mg daily
    - Linezolid, 600 mg bid or vancomycin
      - Linezolid may be preferred because of its inhibition of bacterial exotoxin and better lung penetration
  - Alternative combination regimen with
    - IV ceftriaxone, 1–2 g daily plus
    - Respiratory fluoroquinolone (levofloxacin, 750 mg daily)
    - Linezolid or vancomycin
- *Pseudomonas* prior isolate empirical antibiotic regimen
  - Combination therapy with
    - IV ceftriaxone, 1–2 g daily
    - Azithromycin, 500 mg PO daily
    - Piperacillin-tazobactam, 4.5 g q6h or cefepime, 2 g q8h
  - Alternative regimen
    - IV ceftriaxone, 1–2 g daily plus
    - Respiratory fluoroquinolone (e.g., levofloxacin, 750 mg daily) plus
    - Piperacillin-tazobactam, 4.5 g q6h or cefepime, 2 g q8h
  - Some guidelines suggest double coverage for *Pseudomonas*
    - If this is considered, use agents from different classes
- If the risk factor is a recent hospitalization and antibiotic use within the previous 3 months
  - Obtain adequate sputum samples, and start coverage for MRSA or *Pseudomonas* only if cultures are positive

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DE-ESCALATION OF ANTIBIOTICS AND TREATMENT DURATION

- Tailor specific antibiotics to sputum or blood cultures if available
- A switch from IV to PO antibiotics is appropriate when the patient
  - Can ingest and absorb the drugs
  - Is hemodynamically stable
  - Is showing clinical improvement
- A 5-day course of antibiotics is usually sufficient for uncomplicated CAP
  - A longer treatment may be required for patients who
    - Have not stabilized clinically
    - For those with bacteremia, metastatic infection, or infection with a more virulent pathogen such as *P. aeruginosa* or MRSA (duration is ~ 14 days)
  - Emerging data and guidelines suggest 3-day antibiotic duration for nonsevere CAP is acceptable when the patient is stabilized at 3 days

HOSPITAL-ACQUIRED & VENTILATOR-ASSOCIATED PNEUMONIA (HAP & VAP)

- Microbiologic causes include both non–multidrug-resistant organisms and multidrug-resistant organisms (Table 39-3)
  - MRSA and *Pseudomonas* should be considered in initial antibiotic selection coverage
- Perform an MRSA nares PCR swab
  - If negative, you do not need to treat for MRSA (i.e., stop vancomycin or linezolid)
- Empirical therapy (Table 39-6)
  - Double coverage for *Pseudomonas* is recommended if risk factors are present
- A 7- or 8-day course of therapy is just as effective as a 2-week course and is associated with less frequent emergence of antibiotic-resistant strains
- Deescalate therapy based on respiratory cultures if available
- The most important preventive intervention is to avoid intubation or minimize its duration
- Strategies that minimize the duration of ventilation through daily holding of sedation and formal weaning protocols have also been highly effective in preventing VAP
- Elevating the head of the bed (at least 30 degrees above horizontal, but preferably 45 degrees) and using specially modified endotracheal tubes that allow removal of secretions pooled above the cuff can prevent microaspiration

TABLE 39-6 Empirical Antibiotic Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia

NO RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN	RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN[a] *(CHOOSE ONE FROM EACH COLUMN)*	
Piperacillin-tazobactam (4.5 g IV q6h)	Piperacillin-tazobactam (4.5 g IV q6h)	Amikacin (15–20 mg/kg IV q24h)
Cefepime (2 g IV q8h)	Cefepime (2 g IV q8h)	Gentamicin (5–7 mg/kg IV q24h)
Levofloxacin (750 mg IV q24h)	Ceftazidime (2 g IV q8h)	Tobramycin (5–7 mg/kg IV q24h)
	Imipenem (500 mg IV q6h)	Ciprofloxacin (400 mg IV q8h)
	Meropenem (1 g IV q8h)	Levofloxacin (750 mg IV q24h)
	Consider newer agents[c]	Colistin (loading dose of 5 mg/kg IV followed by maintenance doses of 2.5 mg × [1.5 × CrCl + 30] IV q12h)
		Polymyxin B (2.5–3.0 mg/kg/d IV in 2 divided doses)
Risk Factors for MRSA[b] *(Add to above)*		
Linezolid (600 mg IV q12h) *or*		
Adjusted-dose vancomycin (trough level, 15–20 mg/dL)		

[a]Prior antibiotic therapy, prior hospitalization, local antibiogram. [b]Prior antibiotic therapy, prior hospitalization, known MRSA colonization, chronic hemodialysis, local documented MRSA pneumonia rate > 10% (or local rate unknown). [c]Newer agents can have activity against resistant *Pseudomonas aeruginosa* (ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, plazomicin), carbapenem-resistant *Enterobacteriaceae* (ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam), metallo-β-lactamase–producing *Enterobacteriaceae* (ceftazidime-avibactam, cefiderocol), *Stenotrophomonas* (cefiderocol), and *Acinetobacter* spp. (cefiderocol, sulbactam-durlobactam).
CrCl, creatinine clearance rate; MRSA, methicillin-resistant *Staphylococcus aureus*.
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ADJUNCTIVE MEASURES

- Oxygen supplementation for hypoxemia
- Glucocorticoids
  - Hydrocortisone, continuous infusion 200 mg daily for 4–7 days followed by a taper, may be beneficial in cases of severe CAP requiring invasive or noninvasive mechanical ventilation or with shock
    - Hydrocortisone, 50 mg IV q6h, is a common regimen
  - A mortality benefit has been observed in patients with severe CAP, especially if there is a high level of systemic inflammation (CRP > 15 mg/dL) [1]
  - Emerging evidence suggests glucocorticoids provide a mortality benefit in non-severe CAP in low-resource settings
  - Glucocorticoids are continued for a total of 8–14 days
- Acetaminophen, 650 mg PO q6h as needed for pain/fever
- DVT prophylaxis via low-molecular-weight heparin or UFH

INFLUENZA INFECTION

- Oseltamivir, 75 mg PO bid for 5 days
  - Treat for 10 days if severely ill or immunocompromised
  - Adjust the dose for kidney function
- If the clinical picture also suggests a bacterial pneumonia, provide appropriate antibiotics
- Physicians should be vigilant about possible superinfection with MRSA

COVID-19 PNEUMONIA

- Caused by SARS-CoV-2; resulted in a pandemic of historic proportion
- The greatest risk of infection is close contact with persons with COVID-19, such as in household or congregate settings
- Shock, often in the setting of cardiac injury/myocarditis, dysrhythmias or cardiomyopathy, and thromboembolic complications such as PE or stroke, can occur
- Lymphopenia and elevations of LDH, CRP, D-dimer, ferritin, and interleukin (IL)-6 are present
- Treatment
  - Supportive care; delay mechanical ventilation until other interventions have been exhausted
  - Dexamethasone, 6 mg IV/PO for hypoxemic patients (improves 28-day mortality) [2]
  - Tocilizumab (an IL-6 inhibitor) may be indicated for patients with rapidly escalating oxygen requirements
  - Therapeutic dose anticoagulation to prevent venous thromboembolism [3]
  - Nirmatrelvir/ritonavir [4] (for outpatients) or remdesivir [5] (for outpatients or inpatients) can reduce the risk of progression to severe disease and hospitalization for patients with mild symptoms
  - *Vaccination* against COVID-19 has reduced progression to severe disease and hospitalization

EMPIRICAL OUTPATIENT COMMUNITY-ACQUIRED PNEUMONIA MANAGEMENT

- Empirical therapy splits patients into two groups based on either the presence of significant comorbidities or risk factors for antibiotic resistance
  - Significant comorbidities
    - Chronic heart, lung, liver, or kidney disease
    - Diabetes
    - Alcohol use disorder
    - Malignancy
    - Asplenia
  - Risk factors for antibiotic resistance
    - Antibiotic treatment within the past 3 months
    - Contact with the health care system
- No comorbidities or risk factors for antibiotic resistance
  - Choose either a combination or monotherapy strategy
    - Combination therapy
      - Amoxicillin, 1 g PO tid
      - Azithromycin (500 mg PO on day 1, then 250 mg/d for 4 days)
    - Monotherapy with a macrolide (azithromycin or doxycycline)
      - Can use monotherapy if the local prevalence of pneumococcal resistance is < 25%
- Significant comorbidities or risk factors for antibiotic resistance
  - Amoxicillin-clavulanate, 875/125 mg PO bid
  - Monotherapy with a respiratory fluoroquinolone (levofloxacin, 750 mg PO daily), or

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- Combination therapy with
  - A cephalosporin (cefpodoxime, 200 mg PO bid or cefuroxime, 500 mg PO bid)
  - A macrolide (azithromycin, 500 mg PO on day 1, then 250 mg/d for 4 days, or doxycycline, 100 mg PO bid)
- Treatment for MRSA or *Pseudomonas* is typically not needed in this population
- Duration of treatment is typically 5 days

PREVENTION OF PNEUMONIA

- Pneumococcal vaccine
- Influenza vaccine annually
- Smoking cessation
- Education about stopping excessive alcohol intake

COMPLICATIONS

- Complications of severe community-acquired pneumonia (CAP)
  - Respiratory failure
  - Shock and multiorgan failure
  - Exacerbation of comorbid illnesses
- Three particularly noteworthy conditions are
  - Metastatic infection (e.g., brain abscess or endocarditis)
    - Is unusual but requires a high degree of suspicion and a detailed workup for proper treatment
  - Lung abscess
    - May occur in association with aspiration pneumonia or with infection caused by pathogens such as community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), *Pseudomonas aeruginosa*, or (rarely) *Streptococcus pneumoniae*
  - Complicated pleural effusion
    - Significant pleural effusions should undergo thoracentesis for diagnostic and therapeutic purposes
    - Definitive drainage of fluid is needed when the thoracentesis reveals
      - A pH < 7.2
      - Glucose level < 2.2 mmol/L
      - LDH concentration > 1000 U/L, or
      - Bacteria are seen or cultured
- Cardiovascular events with pneumonia, particularly in older persons and usually in association with pneumococcal pneumonia and influenza, are increasingly recognized
  - These events, which may be acute or whose occurrence may extend to at least 1 year, include
    - HF
    - Dysrhythmia
    - MI
    - Stroke
  - These are caused by a variety of mechanisms, including
    - Increased myocardial load
    - Destabilization of atherosclerotic plaques by inflammation
- Apart from death, the major complication of ventilator-associated pneumonia is prolongation of mechanical ventilation, with corresponding increases in the duration of ICU and hospital stay
- In rare cases, necrotizing pneumonia (e.g., due to *P. aeruginosa* or *S. aureus*) can cause significant pulmonary hemorrhage or empyema
- DVT/PE

PROGNOSIS

- The mortality rate among outpatients with community-acquired pneumonia (CAP) is usually < 5% but ranges from ~ 12% to 40% among hospitalized patients
- A WBC count < 6000 cells/μL may be seen in overwhelming infection and in patients with pneumococcal pneumonia
  - This finding has a > 65% mortality rate
- See Management section for mortality rates based on the pneumonia severity index and CURB-65 score
- Overall, the prognosis depends on the patient's age, comorbidities, and site of treatment (inpatient or outpatient)
  - Young patients without comorbidities do well and usually recover fully after ~ 2 weeks
  - Recent data, especially in older patients, show that the 1-year mortality following CAP exceeds the 30-day mortality

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- Ventilator-associated pneumonia (VAP) is associated with crude mortality rates as high as 50–70%, but the real issue is attributable mortality
  - Many patients with VAP have underlying diseases that would result in death even if VAP did not occur

PATHOPHYSIOLOGY

- Pathogenesis of pneumonia
  - Pneumonia results from microbial proliferation in the alveoli combined with the patient's inflammatory response
  - Earlier view: lungs were sterile → pneumonia is caused by the introduction of pathogens (mainly via microaspiration of oropharyngeal flora)
  - Updated view: lungs have resident microbiota, and pneumonia develops from disruption of microbial homeostasis, not simply sterile space invasion
- Lung microbiota and patient immune defenses
  - The lung microbiota are diverse and dynamic
  - Mechanical defenses reduce but do not fully prevent microbial access
    - Nasal hairs and turbinates trap particles
    - The branching tracheobronchial tree creates turbulence
    - Mucociliary clearance removes inhaled material
    - Gag and cough reflexes clear larger aspirates
  - Routes of microbial entry into the lower respiratory tract
    - Inhalation of airborne organisms
    - Microaspiration of oropharyngeal contents
    - Direct mucosal spread from the upper to the lower airway
- Determinants of lung microbiota balance
  - Microbial composition is influenced by
    - Entry of organisms into the lungs
    - Elimination through patient immune defenses and clearance mechanisms
    - Regional conditions: pH, oxygen levels, temperature, nutrient availability
  - Pneumonia develops when this balance is lost → dysbiosis and overgrowth of specific pathogens
- Proposed model of pneumonia development
  - Triggering event
    - Inflammation damages epithelial and/or endothelial cells
    - Injury leads to the release of inflammatory mediators (cytokines, chemokines, and catecholamines)
  - Effect of inflammatory mediators
    - Promote the growth of bacteria such as *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*
    - Create a nutrient-rich environment (due to tissue breakdown and mediator activity) for bacteria to thrive in
  - Positive feedback loop
    - Inflammation → bacterial proliferation → more inflammation
    - Bacteria become dominant and worsen local damage
  - Different triggers by type
    - Community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP): the trigger may be a viral infection compounded by microaspiration
    - Aspiration pneumonia: macroaspiration of gastric/oropharyngeal material directly causes infection
- Immune response and escalation to pneumonia
  - Innate and adaptive immunity may initially control bacterial invasion
  - If the feedback loop sustains inflammation, the full pneumonia syndrome develops
  - Mediators involved
    - Interleukin (IL)-6 and tumor necrosis factor (TNF) → fever, systemic inflammation
    - IL-8 and granulocyte colony-stimulating factor (G-CSF) → neutrophil recruitment
  - Consequences of immune activation
    - Neutrophils and macrophages release mediators → alveolar-capillary leak
    - Alveolar flooding → impaired oxygenation, hypoxemia, radiographic infiltrates (such as lobar consolidation)
  - Direct bacterial effects
    - Bacterial toxins worsen inflammation
    - Some pathogens inhibit hypoxic vasoconstriction, worsening ventilation-perfusion mismatch

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- Clinical consequences of pneumonia
  - Local effects
    - Decreased lung compliance (stiffer lungs)
    - Increased secretions → impaired gas exchange
    - Bronchospasm in some infections
  - Respiratory effects
    - Hypoxemia from impaired oxygenation and ventilation-perfusion mismatch
    - Increased respiratory drive → dyspnea and tachypnea
  - Severe cases
    - Loss of lung volume, reduced compliance, and intrapulmonary shunting (e.g., ARDS)
    - Respiratory failure occurs when compensatory mechanisms fail
- Pathology
  - Classic pneumonia evolves through a series of stages (best described for lobar pneumococcal pneumonia)
    - Initial phase
      - Edema with a proteinaceous exudate and often bacteria in the alveoli
    - Red hepatization phase
      - Erythrocytes plus neutrophils
    - Gray hepatization phase
      - Erythrocytes are lysed, neutrophils predominant with fibrin deposition, and the bacteria have disappeared
      - This phase corresponds with successful containment of the infection and improvement in gas exchange
    - Resolution phase
      - Macrophages become the dominant cell, and the debris of neutrophils, bacteria, and fibrin has been cleared, as has the inflammatory response

RISK FACTORS

- Age > 70
- Alcohol use disorder
- Smoking
- Chronic comorbidities
  - COPD
  - HF
  - Neurologic diseases (e.g., dementia, cerebrovascular disease)
  - Diabetes mellitus
  - CKD
  - Genetic defects of neutrophil function
  - HIV/AIDS
  - Malignancy
- Skin colonization with methicillin-resistant *Staphylococcus aureus* (MRSA)
- Prior recent hospitalization and institutionalization in long-term health care settings
- Intubation (for ventilator-associated pneumonia risk)
- Long-term proton pump inhibitor use
- Steroid use

ADMITTING ORDERS

- Admit to floor (CURB-65: 2) or ICU (CURB-65: ≥ 3)
- Diagnosis: pneumonia (community-acquired or hospital-acquired)
- Condition: stable/guarded
- Vital signs: routine per unit
- Activity: as tolerated
- Nursing: supplemental oxygen via nasal cannula to maintain Spo_2 > 92%
- Diet: regular or tailored to comorbidities (if aspiration → NPO until evaluated)
- Fluids: sepsis resuscitation if indicated
- Diagnostic tests
  - Sputum Gram stain and culture prior to antibiotics
  - Blood cultures × 2 before antibiotics
  - Respiratory viral panel
  - Urinary antigen for *Legionella* and *Streptococcus pneumoniae* if indicated

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  - BMP
  - CBC with differential
  - Troponin
  - BNP
  - ABG
  - CRP
  - Procalcitonin
  - CXR
- Medications
  - Depends on the severity and patient risk factors (see Management section)
  - Acetaminophen, 650 mg PO q6h as needed for pain/fever
  - DVT prophylaxis via low-molecular-weight heparin or UFH

DISCHARGE INFORMATION

- Fever and leukocytosis usually resolve within 2–4 days in otherwise healthy patients with community-acquired pneumonia, but physical findings may persist longer
- CXR abnormalities are slowest to resolve (4–12 weeks), with the speed of clearance depending on the patient's age and underlying lung disease, and the etiologic pathogen
- Patients may be discharged from the hospital once their clinical condition, including any comorbidities, is stable
  - Temperature ≤ 37.8°C
  - Heart rate < 100 beats/min
  - Respiratory rate < 24 breaths/min
  - Systolic BP > 90 mm Hg, and
  - SpO_2 ≥ 90% on room air
- Tolerating oral antibiotics and adequate oral nutrition and hydration
- The site of residence after discharge (nursing home, home with family, home alone) is an important consideration, particularly for older patients
- For a hospitalized patient, a follow-up radiograph ~ 4–6 weeks later should be arranged
- Pneumococcal vaccine and influenza vaccine before discharge if indicated
- Smoking cessation counseling

CASE ANSWERS

1. This patient presenting with findings of sepsis secondary to pneumonia had symptoms start prior to hospitalization. Therefore, this patient has a community-acquired pneumonia.
2. Table 39-4 lists minor and major criteria to evaluate the severity of pneumonia. This patient presents with only one minor criterion (BUN ≥ 20 mg/dL). Therefore, this patient has a nonsevere community-acquired pneumonia. This, along with a CURB-65 score of 2, indicates the patient does not need ICU care but should be admitted to the general medical floor.
3. When deciding what empirical antibiotics to administer to a patient with pneumonia, the severity of illness and risks of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas* should be taken into account. This patient does not have severe pneumonia and does not have risk factors for MRSA or *Pseudomonas*. Therefore, a β-lactam (IV ceftriaxone, 1–2 g daily) plus azithromycin, 500 mg PO daily, is an appropriate regimen.

LANDMARK TRIALS

[1] Dequin PF et al. Hydrocortisone in severe community-acquired pneumonia. N Engl J Med 388:1931, 2023. [PMID: 36942789]
  - *Summary:* The CAPE COD trial showed that among patients with severe community-acquired pneumonia (CAP) being treated in the ICU, those who received hydrocortisone had a lower risk of death by day 28 than those who received placebo.

[2] RECOVERY Collaborative Group et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 384:693, 2021. [PMID: 32678530]
  - *Summary:* In patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

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[3] ATTACC Investigators et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 385:790, 2021. [PMID: 34351721]
- *Summary:* In noncritically ill patients with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support compared with usual-care thromboprophylaxis.

[4] Hammond J et al. Alleviation of COVID-19 symptoms and reduction in healthcare utilization among high-risk patients treated with nirmatrelvir/ritonavir (NMV/R): A phase 3 randomized trial. Clin Infect Dis 80:323, 2025. [PMID: 39523543]
- *Summary:* In addition to reducing COVID-19–related hospitalization or death from any cause through day 28, NMV/r was also found to reduce duration of COVID-19 symptoms and utilization of health care resources compared with placebo in patients at high risk of progressing to severe disease.

[5] Beigel JH et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 383:1813, 2020. [PMID: 32445440]
- *Summary:* Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.

FURTHER READING

- Mandell LA, Niederman MS. Pneumonia, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- McGee S. Pneumonia, in *Evidence-Based Physical Diagnosis*, 6th ed. Amsterdam, Elsevier, 2026.
- Vaughn VM et al. Community-acquired pneumonia: A review. JAMA 332:1282, 2024. [PMID: 39283629]

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40 *Clostridioides Difficile* Infection

KEY POINTS

1. *Clostridioides difficile* infection (CDI) is a colonic disease most commonly acquired in association with antibiotic use and disruption of the normal colonic microbiota. It occurs commonly in hospitals and nursing homes due to ingestion of spores of toxin-producing *C. difficile*. The spores vegetate and secrete toxins, causing diarrhea and pseudomembranous colitis.
2. Clinical presentation of CDI includes diarrhea (≥ 3 unformed stools per 24 h for ≥ 2 days) with no other recognized cause, fever (in 28% of cases), abdominal pain (in 22% of cases), and leukocytosis (in 50% of cases). Adynamic ileus may result in cessation of stool passage. Sepsis may be present, and severely ill patients may have toxic megacolon.
3. The diagnosis of CDI is based on clinical criteria (watery nonbloody diarrhea) and detection of toxin A or B in the stool, detection of toxin-producing *C. difficile* by nucleic acid amplification testing (PCR) or culture, or visualization of pseudomembranes in the colon. No single test has high sensitivity, specificity, and rapid turnaround.
4. Treatment of CDI involves discontinuation of ongoing antimicrobial administration (if possible), hydration, and avoidance of antiperistaltic agents and opiates. Antibiotics such as fidaxomicin or vancomycin are recommended for at least 10 days, with fidaxomicin preferred given its association with reduced rates of recurrence. Recurrences (first or multiple) may require alternative therapies, such as a pulse-and-taper vancomycin regimen. Fecal microbiota transplantation (FMT) may be considered for recurrent CDI. Fulminant disease is treated with oral vancomycin, IV metronidazole, and rectal vancomycin as a retention enema. In severe cases, colectomy may be required for toxic megacolon.
5. Complications of CDI include toxic megacolon, sepsis, and serious complications (shock, perforation, colectomy, or death within 30 days) in recurrent disease. Mortality rates attributed to CDI have reached 6.9% in recent outbreaks. Prevention strategies include hand hygiene, environmental decontamination, and restriction of specific antibiotics (e.g., clindamycin, second- and third-generation cephalosporins, and fluoroquinolones).

EPIDEMIOLOGY & DEFINITIONS

Clostridioides difficile infection (CDI) is a unique colonic disease that is acquired most commonly in association with antimicrobial use and the consequent disruption of the normal colonic microbiota. CDI results from ingestion of *C. difficile* spores that then vegetate, multiply, and secrete toxins, causing diarrhea. In severe cases, pseudomembranous colitis occurs. In 2011, an estimated 453,000 initial cases of CDI occurred in the United States; ~ 83,000 patients had a first CDI recurrence, and 29,300 patients died. CDI is the most common health care–associated infection in the United States, with an estimated 462,100 cases in 2017. Between 2011 and 2017, the total burden of CDI in the United States decreased by 24%, which was due primarily to decreases in health care–associated CDI (from 99.6 to 73.3 per 100,000 population).

The diagnosis of CDI is based on a combination of clinical criteria: (1) diarrhea (≥ 3 unformed stools per 24 h for ≥ 2 days) with no other recognized cause plus (2) detection of toxin A or B in the stool, detection of toxin-producing *C. difficile* in the stool by nucleic acid amplification testing (NAAT; e.g., PCR) or by culture, or visualization of pseudomembranes in the colon.

C. difficile diarrhea recurs after treatment in ~ 15–30% of cases. Recurrences—defined as resolution of CDI symptoms while on appropriate therapy followed by a reappearance of symptoms within 2–8 weeks after treatment has stopped—may represent either relapses due to the same strain or reinfections with a new strain. Susceptibility to recurrence of clinical CDI is likely a result of continued disruption of the normal fecal microbiota caused by the antibiotic used to treat CDI, making treatment challenging.

The severity of CDI is also important to recognize and is classified as:

Nonsevere CDI: WBC count ≤ 15,000 cells/μL and SCr < 1.5 mg/dL (or < 50% rise from baseline creatinine level).

Severe CDI: WBC count > 15,000 cells/μL and/or SCr ≥ 1.5 mg/dL (or ≥ 50% rise from baseline creatinine level).

Fulminant colitis (previously referred to as severe, complicated CDI): presence of hypotension or shock, ileus, or megacolon.

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CLINICAL VIGNETTE

A 68-year-old woman presents to the ED with 2 days of profuse watery diarrhea, fever, abdominal pain, and nausea with vomiting. She has been unable to tolerate oral intake as of today. She states she has had ~ 8 watery, nonbloody stools daily for 2 days. The pain is in the lower abdomen and is described as crampy. Ten years ago, she had an episode of *Clostridioides difficile* infection (CDI) treated adequately with oral vancomycin for 10 days. Two months ago, she was hospitalized for pneumonia and treated with IV ceftriaxone and azithromycin before transitioning to oral levofloxacin. Her other comorbidities include hypertension and GERD, and she takes lisinopril and omeprazole.

Her temperature is 38.2°C (100.8°F), heart rate is 110 beats/min, BP is 112/82 mm Hg, and Spo_2 is 96% on room air. She is well- appearing but is grabbing her lower abdomen because of pain. There are no signs of peritonitis on abdominal exam, but she is mildly tender to palpation in the lower quadrants. The oral mucosa is dry.

Initial lab data reveals:

- WBC count: 16,000 cells/μL
- Sodium: 132 mEq/L
- Potassium: 3.2 mEq/L
- BUN: 42 mg/dL
- SCr: 1.8 mg/dL (baseline SCr is 1.0 mg/dL), and
- Lactic acid: 2.2 mmol/L

An enzyme immunoassay stool sample for *C. difficile* is positive. An abdominal x-ray does not show signs of toxic megacolon. Sepsis fluid resuscitation is initiated.

GUIDING QUESTIONS

1. How would you rate the severity of this patient's *Clostridioides difficile* infection (CDI)?
2. What risk factors does this patient have for developing her first recurrent CDI?
3. How would you manage this patient's CDI?
4. What precautions do you need when entering and leaving this patient's room in the hospital?

HISTORY

Diarrhea is the most common manifestation of *Clostridioides difficile* (watery diarrhea [≥ 3 loose stools in 24 h] is the cardinal symptom of *Clostridioides difficile* infection [CDI]). Stools are almost never grossly bloody and range from soft and unformed to watery or mucoid in consistency, with a characteristic odor. Clinical and lab findings include fever in 28% of cases, abdominal pain in 22%, and leukocytosis in 50%. When adynamic ileus (which is seen on x-ray in ~ 20% of cases) results in cessation of stool passage, the diagnosis of CDI is frequently overlooked. A clue to the presence of unsuspected CDI in these patients is unexplained leukocytosis, with ≥ 15,000 WBC/μL. Such patients are at high risk of complications of CDI, particularly toxic megacolon and sepsis. Patients may present with recurrent symptoms that they identify are similar to the initial CDI.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - At least 3 loose, watery, nonbloody, malodorous stools in 24 h associated with fever and abdominal pain in the setting of residence in a long-term health care facility, hospitalization, or recent antibiotic use
  - May have had a prior episode of CDI presenting with similar symptoms
- Diarrhea?
  - How many episodes in the last 24 h?
  - When did the diarrhea start? Has it worsened since it started?
  - Does it have a malodorous smell?
  - Did you have diarrhea at first and now are not?
    - Adynamic ileus with CDI may be an overlooked manifestation
- Abdominal pain (present in 22% of cases)?
  - Cramping abdominal pain either in the lower abdomen or diffuse
- Fever or chills?
  - Fever is present in 28% of cases of CDI
- Contact with someone who has diarrhea?
  - Transmission of infection is via contact with *C. difficile* spores

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- Nausea and vomiting?
  - Common symptoms of CDI and may make tolerance of oral intake difficult
- Recent antibiotic use?
  - Several antibiotic classes are associated with CDI (see Medications section below)
- Recent hospitalization?
  - The rate of fecal colonization increases in proportion to the length of hospital stay
- Do you live in a long-term health care setting (e.g., a nursing home)?
  - Fecal colonization is increased in patients living in nursing homes compared to community residents

PAST MEDICAL HISTORY

- Prior CDI?
  - Recurrence of CDI is common
  - How many episodes have you had? How were they treated previously?
  - History of toxic megacolon?
- Recent hospitalization?
  - The rate of fecal colonization increases in proportion to the length of hospital stay
- History of GERD?
  - Use of proton pump inhibitors may be a risk factor for CDI, especially if patients have also recently taken antibiotics
- History of CKD?
  - Can be a risk factor for recurrence of CDI

SURGICAL HISTORY

- Previous GI surgery?
  - Risk factor for CDI

SOCIAL HISTORY

- Use of alcohol and recreational drugs, smoking
- Occupation
- Living situation
  - Patients who are long-term residents of nursing homes or other long-term care facilities have higher risks of *C. difficile* colonization and CDI
- Sexual history

MEDICATIONS

- Proton pump inhibitor use is associated with CDI, especially if taking antibiotics
- Several classes of antibiotics are associated with CDI
  - Clindamycin, ampicillin, and cephalosporins were the first antibiotics associated with CDI
  - The second- and third-generation cephalosporins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime, are agents frequently responsible for this condition
  - Fluoroquinolones are the most recent drug class recognized as a risk for CDI
  - Penicillin/β-lactamase inhibitor combinations such as ticarcillin-clavulanate and piperacillin-tazobactam pose significantly less risk
  - All antibiotics, including vancomycin (the agent most commonly used to treat CDI), have been found to carry a risk of subsequent CDI
- A minority of cases, especially in the community, are reported in patients without documentation of prior antibiotic exposure

PHYSICAL EXAM

There are no specific findings on exam to make the diagnosis of *Clostridioides difficile* infection (CDI) more likely. Gross examination of the stool can be useful if available, as the presence of bloody or formed stools makes the diagnosis less likely. When assessing a patient with possible or confirmed CDI, assess the patient's vitals, abdomen, and level of systemic toxicity. Patients may be septic with toxic megacolon, which is a complication that needs urgent management. Wear gloves and a gown when entering the room of a patient with CDI. When exiting the room, wash your hands with water and soap (not alcohol-based hand gels) to eliminate spores and prevent the spread of *C. difficile* to other patients.

- Vitals
  - Assess for fever, tachycardia, and hypotension, which may need urgent management
  - Presence of shock changes the management of CDI

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- General
  - May appear well on general exam in nonsevere cases
  - Also can present with sepsis and systemic toxicity from toxic megacolon
- Abdominal
  - Assess for peritonitis (may indicate toxic megacolon with perforation)
  - Assess pain location
  - Is stool available to visualize?
    - Bloody and formed stools make the diagnosis of CDI less likely
- Volume status
  - Evaluate for signs of hypovolemia
    - Skin turgor, mucous membranes, capillary refill, JVP
- Neurologic
  - Septic patients and those with megacolon may have encephalopathy

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- *When to suspect Clostridioides difficile infection (CDI)?*
  - The diagnosis of CDI should be suspected in patients with acute diarrhea (≥ 3 loose stools in 24 h) with no obvious alternative explanation
    - Particularly in the setting of relevant risk factors, including
      - Current or recent antibiotic use
      - Current or recent hospitalization
      - Advanced age
  - Because colonization of *C. difficile* is common in the community, many hospitals have a protocol of when it is appropriate to order *C. difficile* testing
    - Follow your local hospital's protocol if suspecting *C. difficile*
- Antibiotic-associated diarrhea
  - Antibiotics commonly cause osmotic diarrhea but usually lack the abdominal pain/cramping that is associated with CDI
  - Leukocytosis is not usually associated with antibiotic-associated diarrhea
  - Cessation of symptoms with discontinuation of the antibiotic is a distinguishing feature of osmotic diarrhea
  - Differentiation of noninfectious antibiotic-associated diarrhea from CDI may be difficult, especially in patients who are asymptomatic *C. difficile* carriers
- Infectious diarrhea
  - Infectious diarrhea can be caused by a variety of pathogens, including
    - Viruses (e.g., norovirus, rotavirus, and enteric adenovirus)
    - Bacteria (e.g., *Shigella*, *Escherichia coli* [ETEC, STEC], *Campylobacter*, and *Staphylococcus aureus* [food poisoning due to pre-formed toxin ingestion])
    - Parasites (e.g., *Giardia* and *Cryptosporidium*)
  - Bloody diarrhea can be a distinguishing feature between invasive enteric bacterial diarrhea and CDI
    - CDI rarely causes grossly bloody diarrhea
  - Otherwise, clinical manifestations are similar to those of CDI
  - Diagnosis is established by clinical history (including travel history), stool culture, ova and parasite smear, and GI multiplex nucleic acid testing
- Noninfectious diarrhea
  - The presence of fever and leukocytosis favors *C. difficile* or other infectious etiology
    - Certain inflammatory conditions, such as inflammatory bowel disease (IBD), also can present with fever
  - Celiac disease
    - Celiac disease is a small bowel disease associated with dietary gluten exposure intolerance
    - GI symptoms, including chronic or recurrent diarrhea; malabsorption; weight loss; and abdominal distension or bloating, are present
    - The diagnosis is established through serology and/or duodenal biopsy
  - IBD relapse
    - Infection with *C. difficile* may complicate the course of IBD
    - *C. difficile* may be difficult to distinguish from an IBD relapse given the similar symptoms of diarrhea, abdominal pain, and low-grade fever

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        - A high index of suspicion is required when evaluating IBD patients with apparent flares, especially those who have recently received antibiotics and/or been hospitalized
        - Often, treatment for both is initiated as it is very difficult to distinguish the cause of symptoms and rule out CDI in patients with IBD who are colonized with *C. difficile*
    - Postinfectious irritable bowel syndrome (IBS)
        - Postinfectious irritable bowel syndrome occurs in ~ 10% of patients who have been successfully treated for an initial episode of *C. difficile*
        - These patients may have up to 10 watery stools per day
        - This must be distinguished from a relapse of the original CDI based on established criteria of postinfectious IBS, which are
            - Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with ≥ 2 of the following
                - Improvement with defecation
                - Onset associated with a change in frequency of stool
                - Onset associated with a change in form (appearance) of stool
    - Microscopic colitis
        - Microscopic colitis is a chronic inflammatory disease of the colon characterized by chronic watery diarrhea
        - CDI tends to present more acutely, while microscopic colitis is chronic
        - However, the clinical manifestations are very similar
        - The diagnosis of microscopic colitis is established by histopathology following colonoscopy with biopsy
    - Ischemic colitis
        - Ischemic colitis is a noninfectious cause of colonic inflammation due to inadequate blood flow
        - Symptoms typically include severe abdominal pain (usually acute but can occasionally be chronic) and bloody diarrhea
        - Leukocytosis is common, and fever can occasionally be present
        - It can also occasionally cause pseudomembranous colitis on imaging and/or endoscopy
        - In general, the presence of blood in stool can help differentiate ischemic colitis from CDI

ETIOLOGY

- *C. difficile* is an obligately anaerobic, gram-positive, spore-forming bacillus whose spores are found widely in nature, particularly in the environment of hospitals and chronic care facilities
- CDI occurs frequently in hospitals and nursing homes where the level of antimicrobial use is high and the environment is contaminated by *C. difficile* spores
- Antibiotics are commonly associated with CDI (see Medications section)
- *C. difficile* is acquired exogenously
    - Most often in the hospital or nursing home, but also in the outpatient setting
    - *C. difficile* can be found in the stool of asymptomatic people as well as symptomatic patients
- The rate of fecal colonization increases in proportion to length of hospital stay and is often ≥ 20% among adult patients hospitalized for > 2 weeks
    - In contrast, the rate is 1–3% among community residents
- Spores of *C. difficile* are found on environmental surfaces and on the hands of hospital personnel who fail to practice good hand hygiene
- Hospital epidemics of CDI have been attributed to a single *C. difficile* strain and to multiple different strains, introduced by patients on admission, that are present simultaneously

DIAGNOSTIC TESTS

LABS

- CBC with diff
    - Leukocytosis is present in ~ 50% of patients
    - Patients with a WBC count > 15,000 cells/μL have at least severe CDI
    - The presence of thrombocytopenia may indicate severe disease
        - It may point toward another etiology of diarrhea (e.g., hemolytic uremic syndrome from *Shigella*)
- BMP
    - Assess electrolytes (especially for hyponatremia and hypokalemia)
    - An elevated SCr (≥ 1.5 mg/dL or ≥ 50% rise from baseline creatinine level) indicates at least severe CDI

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TABLE 40-1 Relative Sensitivity and Specificity of Diagnostic Tests for *Clostridioides difficile* Infection (CDI)

TYPE OF TEST	RELATIVE SENSITIVITY[a]	RELATIVE SPECIFICITY[a]	COMMENT
Stool culture for *C. difficile*	++++	+++	Most sensitive test; specificity of ++++ if the *C. difficile* isolate tests positive for toxin; turnaround time too slow for practical use
Cell culture cytotoxin test on stool	+++	++++	With clinical data, is diagnostic of CDI; highly specific but not as sensitive as stool culture; slow turnaround time
Enzyme immunoassay for toxins A and B in stool	++ to +++	+++	With clinical data, is diagnostic of CDI; rapid results, but not as sensitive as stool culture or cell culture cytotoxin test
Enzyme immunoassay for *C. difficile* common antigen in stool	+++ to ++++	+++	Detects glutamate dehydrogenase found in toxigenic and nontoxigenic strains of *C. difficile* and other stool organisms; more sensitive and less specific than enzyme immunoassay for toxins; requires confirmation with a toxin test; rapid results
Nucleic acid amplification tests for *C. difficile* toxin A or B gene in stool	++++	+++	Detects toxigenic *C. difficile* in stool; widely used in United States for clinical testing; more sensitive than enzyme immunoassay toxin testing; marked increase in CDI diagnoses when implemented
Colonoscopy or sigmoidoscopy	+	++++	Highly specific if pseudomembranes are seen; insensitive compared with other tests

[a]According to both clinical and test-based criteria.
Note: ++++, > 90%; +++, 71–90%; ++, 51–70%; +, ~ 50%.
Reproduced with permission from Gerding DN, Johnson S. *Clostridioides difficile* infection, including pseudomembranous colitis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

- Lactic acid
  - To assess for sepsis and tissue hypoxia, if present
  - In patients with toxic megacolon, surgical colectomy should be performed prior to the lactic acid rising above 5 mmol/L
- *C. difficile* testing
  - Despite the array of tests available for *C. difficile* and its toxins (Table 40-1), no single test has high sensitivity, high specificity, and rapid turnaround
  - Most hospital systems have a specific test that is used
  - Most lab tests for toxins, including enzyme immunoassays (EIAs), lack sensitivity
  - Nucleic acid amplification tests (NAATs) (including PCR) are widely used diagnostically and are both rapid and sensitive
    - However, concern has been raised that PCR may detect colonization with toxigenic *C. difficile* in patients who have diarrhea for a reason other than CDI
  - Confirmation of the presence of toxin in the stool in addition to NAAT or glutamate dehydrogenase (GDH) positivity is recommended in the European CDI guidelines for diagnosis of CDI, and inclusion of a stool toxin test is recommended in the U.S. guidelines when there are no prior criteria for stool submission
  - Test algorithms that include NAAT followed by toxin EIA for NAAT+ results, and GDH plus toxin EIA arbitrated by NAAT when the two initial test results do not agree, have become widely used
    - However, when results of individual algorithm tests are discrepant (NAAT+ or GDH+/toxin EIA–), most patients are nonetheless treated for CDI
  - Empirical treatment is appropriate if stool testing is delayed
  - *Do not test asymptomatic patients for CDI*
  - So-called tests of cure following treatment are *not* recommended
    - More than 50% of patients continue to harbor the organism and its toxin after diarrhea has ceased, and test results are not predictive of recurrence of CDI
  - Because of common colonization of *C. difficile* in the community, many hospitals have a protocol of when it is appropriate to order *C. difficile* testing
    - Follow your local hospital's protocol if suspecting *C. difficile*
- Stool culture, ova and parasite smear, and GI multiplex nucleic acid testing, if indicated
  - Can help differentiate infectious diarrhea from a different etiology than *C. difficile*

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IMAGING

- Imaging is not required for the diagnosis of CDI
- A CT scan is useful for patients in whom pseudomembranous colitis and/or toxic megacolon are suspected
- An abdominal x-ray may reveal megacolon or adynamic ileus in a patient with leukocytosis no longer having diarrhea
- Sigmoidoscopy or colonoscopy to visualize pseudomembranous colitis and an abdominal CT examination are the best diagnostic tests in patients without diarrhea and fulminant disease

MANAGEMENT

WHEN TO ADMIT THE PATIENT

- Patients with any of the following should be admitted for management and observation of complications
  - Sepsis with *Clostridioides difficile* infection (CDI)
  - Severe or fulminant disease
  - Significant comorbidities
  - Unable to tolerate adequate oral nutrition and fluids
- Patients with nonsevere CDI and none of the above can be managed as outpatients

MANAGEMENT OF CDI

- Management of CDI (Table 40-2) depends on
  - What episode of infection this is (initial, first recurrence, multiple recurrence)
  - The severity of illness

TABLE 40-2 Recommendations for the Treatment of *Clostridioides difficile* Infection (CDI)

CLINICAL SETTING	TREATMENT(S)	COMMENTS
Initial episode, mild to moderate	Fidaxomicin (200 mg bid × 10 d) *or alternatively* Vancomycin (125 mg PO qid × 10 d)	Oral metronidazole is less effective than the other options and may necessitate a longer treatment course for response. Metronidazole (500 mg tid × 10–14 d) is recommended only if vancomycin or fidaxomicin is not readily accessible and for mild to moderate disease only.
Initial episode, severe	Vancomycin (125 mg PO qid × 10 d) *or alternatively* Fidaxomicin (200 mg bid × 10 d)	Indicators of severe disease may include leukocytosis (≥ 15,000 WBCs/μL) and a creatinine level ≥ 1.5 mg/dL.
Initial episode, fulminant	Vancomycin (500 mg qid PO or via nasogastric tube) plus metronidazole (500 mg IV q8h) *plus consider* Rectal instillation of vancomycin (500 mg in 100 mL of normal saline as a retention enema q6–8h)	Fulminant CDI is defined as severe CDI with the addition of hypotension, shock, ileus, or toxic megacolon. The duration of treatment may need to be > 2 weeks and is dictated by response.
First recurrence	Fidaxomicin (200 mg bid × 10 d) *or* Vancomycin (125 mg PO qid × 10 d) *or* Oral vancomycin followed by a taper-and-pulse regimen[a]	Treatment for the initial episode may be considered when choosing treatment for the first recurrence.
Multiple recurrences	Oral vancomycin treatment followed by a taper-and-pulse regimen[a] *or* Fidaxomicin (200 mg bid × 10 d or 200 mg bid × 5 d followed by every other day × 20 d) *or* Vancomycin (125 mg qid × 10 d), then stop vancomycin and start rifaximin (400 mg bid × 2 weeks) *or* Fecal microbiota replacement therapy (FMRT)	It is recommended that FMRT by fecal microbiota (Rebyota, live-jslm) given by enema or fecal microbiota spores (Vowst, live-brpk) given orally be considered only after appropriate antibiotic treatment for recurrent CDI.

[a]A typical taper-and-pulse vancomycin regimen following a 10-day treatment course includes 125 mg bid × 1 week, then daily × 1 week, then every 2–3 days for 2–8 weeks.

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BASIC PRINCIPLES OF HOSPITALIZED PATIENTS WITH CDI

- Stop any ongoing antimicrobial administration, when possible
  - Earlier studies indicated that 15–23% of patients respond to this simple measure
  - However, with the advent of the NAP1/BI/027 epidemic strain and the associated rapid clinical deterioration of some patients, prompt initiation of specific CDI treatment has become the standard
- Hydrate the patient, including sepsis fluid resuscitation, if indicated
- Place the patient on contact isolation plus precautions
  - Wear a gown and gloves into the room
  - Wash hands with soap and water when exiting the room
- Avoid
  - Antiperistaltic agents (e.g., loperamide)
  - Opiates

INITIAL EPISODE, NONSEVERE OR SEVERE

- *Fidaxomicin 200 mg PO bid × 10 days*
  - Fidaxomicin is first-line therapy
  - Fidaxomicin compared to vancomycin reduced recurrence rates of CDI, with similar clinical resolution rates [1,2]
  - Fidaxomicin was superior to metronidazole or vancomycin for the treatment of the initial episode, first recurrence, and nonsevere CDI [3]
- If fidaxomicin is not available
  - Use vancomycin 125 mg PO qid × 10 days
    - Metronidazole 500 mg PO tid × 10–14 days can be used if vancomycin is also not available
  - Oral vancomycin compared to oral metronidazole was shown to be superior in terms of cure rates (81% vs 73%; $p = .034$) across all severity levels [4]
- Treatment should not be deemed a failure until a drug has been given for at least 6 days

INITIAL EPISODE, FULMINANT

- Patients with fulminant disease often do not have diarrhea, and their illness mimics an acute surgical abdomen
- Sepsis may result from fulminant CDI
- An acute abdomen (with or without toxic megacolon) may include signs of
  - Obstruction
  - Ileus
  - Colon-wall thickening and ascites on abdominal CT
  - Peripheral-blood leukocytosis (WBC count ≥ 20,000 cells/μL)
- Manage with a combination of
  - Oral vancomycin, 500 mg qid (either PO or via nasogastric tube)
  - Metronidazole, 500 mg IV q8h
  - Rectal vancomycin, 500 mg in 100 mL of NS as a retention enema q6–8h if ileus is present
- Surgical colectomy should be considered, especially before the serum lactate level reaches 5 mmol/L
  - Mortality and morbidity associated with colectomy may be reduced by performing instead a laparoscopic ileostomy followed by colon lavage with polyethylene glycol and vancomycin infusion into the colon via the ileostomy

FIRST RECURRENCE, NONSEVERE OR SEVERE

- Fidaxomicin, 200 mg PO bid × 10 days
  - Fidaxomicin is superior to vancomycin in reducing further recurrences in patients who have had one CDI recurrence
- If fidaxomicin is not available, and the patient was treated with oral vancomycin for the initial episode
  - Use an oral vancomycin taper-and-pulse regimen
    - 125 mg qid × 10 days, then
    - 125 mg bid × 1 week, then
    - 125 mg daily × 1 week, then
    - 125 mg every 2–3 days for 2–8 weeks

MULTIPLE RECURRENCE, NONSEVERE OR SEVERE

- There is no standard treatment for multiple recurrences
- Choose one of the following regimens
  - Oral vancomycin taper-and-pulse regimen (as above)

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- Fidaxomicin, 200 mg bid × 10 days, then stop vancomycin and start rifaximin 400 mg bid × 2 weeks
- Fecal microbiota replacement therapy (FMRT)
  - FMRT has been widely used over the past decade, and the availability of stool banks and oral capsule formulations has made this approach more practical

PREVENTION & CONTROL

- Strategies for the prevention of CDI are of two types
  - Those aimed at preventing transmission of the organism to the patient
    - Transmission of *C. difficile* in clinical practice has been prevented by
      - Gloving of personnel
      - Elimination of the use of contaminated electronic thermometers
      - Use of hypochlorite (bleach) solution for environmental decontamination of patients' rooms
    - Hand hygiene is critical
      - Wash hands with water and soap when leaving a patient's room who has CDI
      - Do *not* use alcohol hand gels, as they are not sporicidal
  - Those aimed at reducing the risk of CDI if the organism is transmitted
    - CDI outbreaks have been best controlled by restricting the use of specific antibiotics
      - Clindamycin
      - Second- and third-generation cephalosporins
      - Fluoroquinolones
    - Outbreaks of CDI due to antibiotic-resistant strains have resolved promptly when specific antibiotic use is restricted
    - Future primary prevention strategies include the use of monoclonal antibodies, as well as biotherapeutics with live organisms to prevent colonization
    - Vaccines have been unsuccessful thus far

COMPLICATIONS

- Complications of *Clostridioides difficile* infection include
  - Toxic megacolon
  - Sepsis
  - Shock, perforation, colectomy, or death within 30 days in recurrent disease

PROGNOSIS

- The mortality rate attributed to *Clostridioides difficile* infection, previously found to be 0.6–3.5%, has reached 6.9% in recent outbreaks and is progressively higher with increasing age
- Recurrent disease, once thought to be relatively mild, has now been documented to pose a significant (11%) risk of serious complications (shock, megacolon, perforation, colectomy, or death within 30 days)

PATHOPHYSIOLOGY

- Pathogenesis of *Clostridioides difficile* infection (CDI)
  - Spore survival and colonization
    - Spores of toxigenic *C. difficile* are ingested and survive gastric acidity
    - These spores germinate in the small bowel and colonize the lower intestinal tract in the setting of disrupted microbiota
  - Toxin production
    - Toxin A: enterotoxin; strong neutrophil chemoattractant
    - Toxin B: cytotoxin; glucosylates Rho-family GTP-binding proteins regulating the actin cytoskeleton
      - Causes cytoskeletal disruption → loss of cell shape, adherence, and tight junctions → fluid leakage
      - Toxin B is the more critical virulence factor (disease occurs in toxin A–negative strains but not toxin B–negative strains)
    - Binary *C. difficile* toxin (CDT): related to *C. perfringens* iota toxin
      - Found in the epidemic NAP1/BI/027 strain
      - Its pathogenic role is unclear
  - Cellular and tissue effects
    - Disruption of the epithelial barrier → diarrhea and pseudomembrane formation
    - Microscopic findings: epithelial erosion/necrosis, neutrophil infiltration, necrotic leukocytes, fibrin, mucus, and cellular debris

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- Pseudomembranous colitis (PMC)
  - Gross pathology
    - Early: 1–2 mm whitish-yellow plaques on colonic mucosa
    - Progression: plaques coalesce → confluent pseudomembrane over colon
    - Usually the entire colon is involved; ~ 10% of cases show rectal sparing
  - Microscopy
    - Pseudomembranes anchored to mucosa
    - Composition: necrotic leukocytes, fibrin, mucus, debris
    - Surrounding mucosa: focal necrosis and neutrophilic infiltration
  - Risk and protective factors for CDI
    - Colonization
      - Previously thought to increase CDI risk
      - Studies show colonization without prior CDI may *decrease* risk (often due to nontoxigenic strains)
    - Three essential events for CDI development (Fig. 40-1)
      - Antimicrobial exposure → disrupts normal microbiota and establishes susceptibility
      - Exposure to toxigenic *C. difficile*
      - Additional factors needed
        - Highly virulent *C. difficile* strain
        - Use of specific high-risk antibiotics
        - Inadequate patient immune response (especially a weak IgG response to toxin A)
- Patient immune response
  - Infants
    - Usually colonized but asymptomatic
    - Thought to lack mature toxin receptors
  - Adults
    - Antibodies (IgG) to toxins A and B are likely protective against symptomatic or recurrent CDI
    - Natural exposure during early life or childhood infection helps develop immunity
  - Clinical evidence
    - Trials with IV monoclonal antibodies
      - Anti–toxin B antibody significantly reduced recurrence
      - Combination of antibodies also effective
      - Anti–toxin A antibody alone was ineffective
      - A+in A antibody alone was ineffective

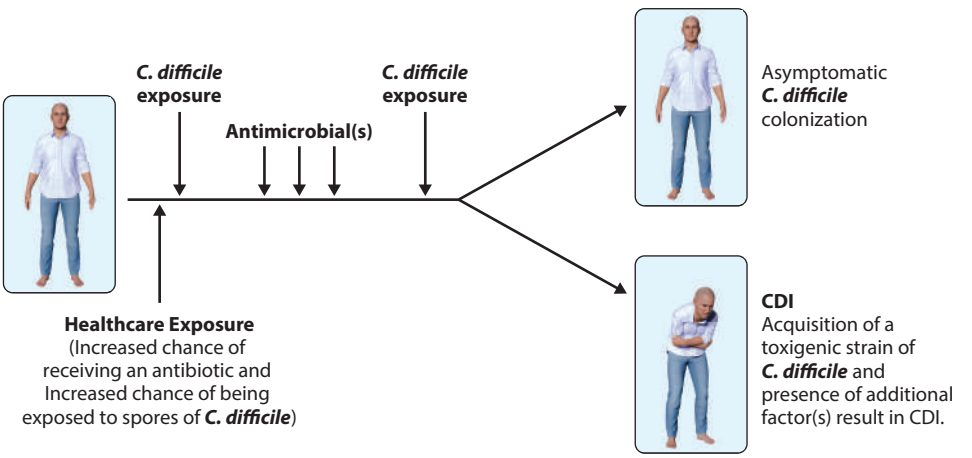

FIGURE 40-1 Pathogenesis model for *Clostridioides difficile* infection (CDI). At least three events are integral to *C. difficile* pathogenesis. Exposure to antibiotics establishes susceptibility to *C. difficile* infection. If susceptible, the patient may ingest nontoxigenic (nonpathogenic) or toxigenic strains of *C. difficile* as a second event. Acquisition of toxigenic *C. difficile* may be followed by asymptomatic colonization or CDI, depending on one or more additional factors, including the strain of *C. difficile* and an inadequate patient anamnestic antibody response to *C. difficile* toxins. (Reproduced with permission from Gerding DN, Johnson S. *Clostridioides difficile* infection, including pseudomembranous colitis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- Bezlotoxumab
  - A monoclonal antibody directed against C. difficile toxin B
  - Bezlotoxumab has been shown to reduce the risk of recurrent CDI by an absolute rate of ~ 10% when administered to patients currently receiving vancomycin, fidaxomicin, or metronidazole [5]
  - This drug was discontinued by the manufacturer in January 2025, but results suggest that other agents may be successful in the future

RISK FACTORS

- Older age
- Greater severity of underlying comorbidities
- GI surgery
- Use of electronic rectal thermometers
- Enteral tube feeding
- Antacid treatment
  - Use of proton pump inhibitors (PPIs) may be a risk factor, but this risk is probably modest, and no firm data have implicated these agents in patients who are not already receiving antibiotics
- Several classes of antibiotics are associated with *Clostridioides difficile* infection (CDI)
  - Clindamycin, ampicillin, and cephalosporins were the first antibiotics associated with CDI
  - The second- and third-generation cephalosporins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime, are agents frequently responsible for this condition
  - Fluoroquinolones are the most recent drug class recognized as a risk for CDI
- Risk factors for multiple recurrent CDIs
  - Older age
  - Women > men
  - Use of antibiotics, PPIs, or corticosteroids within 90 days of CDI diagnosis
  - CKD
  - Residence in a nursing home

ADMITTING ORDERS

- Admit to floor or ICU (if fulminant disease)
- Diagnosis: nonsevere, severe, or fulminant *Clostridioides difficile* infection (also state if this is an initial occurrence, first recurrence, or a multiple recurrence)
- Condition: stable, guarded, or critical
- Vital signs: routine or ICU routine
- Nursing: strict *I*s/*O*s, daily weight, call for heart rate > 120 beats/min, systolic BP < 90 mm Hg, or severe abdominal pain
- Diet: as tolerated and tailored to the patients' comorbidities
- Activity: as tolerated
- Fluids: sepsis fluid resuscitation if indicated
- Infection control precautions: contact isolation plus precautions (wear a gown and gloves, and wash hands with soap and water when leaving the patient's room)
- Diagnostic tests
  - CBC with differential
  - BMP
  - *C. difficile* stool testing per hospital system protocol
  - Lactic acid
  - Abdominal x-ray and/or abdominal CT if concerned for adynamic ileus or toxic megacolon
- Medications
  - Fidaxomicin, 200 mg PO bid × 10 days (if available)
    - Vancomycin, 125 mg PO daily × 10 days if fidaxomicin is not available
  - For fulminant disease
    - Combination of
      - Vancomycin, 500 mg (either PO or via NG tube)
      - Metronidazole, 500 mg IV q8h
      - Rectal vancomycin, 500 mg in 100 mL of NS as a retention enema q6–8h if ileus is present

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DISCHARGE INFORMATION

- Make sure the patient is able to eat, walk, and use the toilet appropriately prior to discharge
- Some patients may need further rehabilitation if deconditioned
  - Ensure the transitional care facility knows the patient needs to be on contact isolation plus precautions
- Ensure adequate antibiotics are prescribed on discharge
- Arrange for primary care follow-up within the next 1–2 weeks

CASE ANSWERS

1. This patient is presenting with a second episode of CDI. Because the WBC count is ≥ 15,000 cells/μL and SCr is > 1.5 mg/dL, she has severe CDI. Because she does not have hypotension or ileus, and the abdominal x-ray does not show toxic megacolon, she does not have fulminant CDI at this time.
2. Patients who develop CDI are at risk of developing recurrent CDI. Additionally, this patient recently was treated for pneumonia and received a third-generation cephalosporin and a fluoroquinolone. These two antibiotic classes are associated with an increased risk of CDI.
3. This patient's first episode of CDI was treated with oral vancomycin. Currently, fidaxomicin is considered first-line therapy for both first CDI and first recurrence of CDI. Fidaxomicin, 200 mg bid for 10 days, would be an appropriate treatment and has been shown to reduce the rate of recurrent CDI compared to oral vancomycin.
4. In order to spread *C. difficile* spores to other patients, all staff entering a patient's room need to wear gowns and gloves. When leaving the room, hands must be washed with soap and water rather than using an alcohol-based gel.

LANDMARK TRIALS

[1] Louie TJ et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 364:422, 2011. [PMID: 21288078]
  - *Summary:* The rates of clinical cure after treatment with fidaxomicin were noninferior to those after treatment with vancomycin. Fidaxomicin was associated with a significantly lower rate of recurrence of *Clostridium difficile* infection (CDI) associated with non–North American Pulsed Field type 1 strains.

[2] Rao K et al. An open-label, randomized trial comparing fidaxomicin with oral vancomycin for the treatment of *Clostridioides difficile* infection in hospitalized patients receiving concomitant antibiotics for concurrent infections. Clin Infect Dis 78:277, 2024. [PMID: 37797310]
  - *Summary:* In this study of patients with CDI receiving concurrent antibiotics (CA), a numerically higher proportion were cured with fidaxomicin versus vancomycin, but this result did not reach statistical significance. Overall recurrence was lower than anticipated in both arms compared with previous studies that did not extend duration of CDI treatment during CA.

[3] Polivkova S et al. Fidaxomicin versus metronidazole, vancomycin and their combination for initial episode, first recurrence and severe *Clostridioides difficile* infection—an observational cohort study. Int J Infect Dis 103:226, 2021. [PMID: 33188906]
  - *Summary:* Fidaxomicin was superior to metronidazole or vancomycin for the treatment of the initial episode, first recurrence, and nonsevere CDI.

[4] Conrad J et al. Comparative effectiveness of vancomycin and metronidazole on event-free survival after initial infection in patients with *Clostridioides difficile*—a German multicentre cohort study. Clin Microbiol Infect 30:1433, 2024. [PMID: 39127107]
  - *Summary:* This analysis confirms current changes in guidelines, as it supports the superiority of vancomycin compared with metronidazole across all severity levels.

[5] Wilcox MH et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. N Engl J Med 376:305, 2017. [PMID: 28121498]
  - *Summary:* Among participants receiving antibiotic treatment for primary or recurrent CDI, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo.

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FURTHER READING

- Gerding DN, Johnson S. *Clostridioides difficile* infection, including pseudomembranous colitis, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
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- Lamont JT et al. Clostridioides difficile infection in adults: Clinical manifestations and diagnosis. UpToDate. https://www.uptodate.com/contents/clostridioides-difficile-infection-in-adults-clinical-manifestations-and-diagnosis. Accessed February 6, 2026.
- van Prehn J et al. Recurrent *Clostridioides difficile* infections. JAMA 334:2128, 2025. [PMID: 41114993]

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41 Infective Endocarditis

KEY POINTS

1. Infective endocarditis (IE) is an infection of the heart valves or, less commonly, other areas of the heart, characterized by a mass (vegetations) consisting of platelets, fibrin, bacteria, and inflammatory cells.
2. Clinical presentation of IE can vary from acute to subacute, but common symptoms include fever, new or changed heart murmurs, and signs of embolization (e.g., petechiae, splinter hemorrhages). Physical exam findings may include new or changed heart murmurs and signs of peripheral embolization. Table 41-1 describes common symptoms and exam findings in IE.
3. Diagnosis of IE involves a combination of clinical, lab, and imaging findings. Blood cultures are essential for identifying the causative microorganism. Microbial etiology differs between acute (commonly *Staphylococcus aureus*) and subacute (streptococci commonly). Echocardiography, both transthoracic and transesophageal, is important for visualizing vegetations and detecting complications.
4. Treatment of IE requires prolonged, parenteral antibiotic therapy that is bactericidal and not bacteriostatic. The choice of antibiotics is based on the causative microorganism and its susceptibility. Surgery may be necessary in certain cases, particularly for complications such as valvular dysfunction, severe HF, paravalvular infections, failure of antibiotic therapy, or abscess formation.
5. Complications of IE include embolic events (e.g., stroke, MI), HF, valve destruction, and mycotic aneurysms. Mortality rates vary depending on factors such as the causative microorganism, the presence of complications, and patient comorbidities. Prognosis improves with early diagnosis and appropriate treatment.

EPIDEMIOLOGY & DEFINITIONS

In the United States (and likely other developed countries), the incidence of infective endocarditis (IE) is estimated at 15 cases per 100,000 population per year. Reported cases and their predisposing conditions are shifting from chronic rheumatic heart disease to injection drug use, degenerative valve disease, and intracardiac devices. Congenital heart disease remains a constant predisposition. IE is increasing in older persons, but mortality rates in those ≥ 55 years are declining. Some 25–35% of cases of native valve endocarditis (NVE) are health care–associated, and 16–30% of all cases are prosthetic valve endocarditis (PVE) infections. The risk of PVE infections is greatest during the initial year after valve replacement; gradually declines to a low, stable rate thereafter; and is greater for bioprosthetic valves than mechanical valves. The incidence and rate of decline of transcatheter aortic valve replacement (TAVR)-PVE are similar to those for surgically implanted bioprosthetic aortic valves. IE involving cardiovascular implantable electronic devices (CIED-IE) occurs in 0.5–1.14 cases per 1000 recipients.

IE can be classified according to the temporal evolution of disease, the site of infection, the cause of infection, or the predisposing risk factor (e.g., injection drug use, health care–associated).

Infective endocarditis (IE): infection of the endothelium of the heart (not limited to valves); the prototypic lesion (the vegetation) is a mass of platelets, fibrin, microorganisms, and scant inflammatory cells.

Infective endarteritis: infection of arteriovenous shunts, arterio-arterial shunts (patent ductus arteriosus), or coarctation of the aorta.

Acute infective endocarditis: infection of normal valves with virulent organisms (e.g., *Staphylococcus aureus*, group A or other β-hemolytic streptococci, *Streptococcus pneumoniae*) causing a strong febrile illness that rapidly damages cardiac structures and seeds extracardiac structures.

Subacute infective endocarditis: indolent infection with less virulent organisms (e.g., *Streptococcus viridians*) often on abnormal valves, causing structural damage only slowly, if at all; rarely metastasizes and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm.

Native valve endocarditis (NVE): IE of a native valve.

Prosthetic valve endocarditis PVE: IE of a nonnative valve (e.g., bioprosthetic or mechanical valves; transcatheter aortic valve [**TAVR-PVE**]; cardiovascular implantable electronic device [**CIED-IE**])

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TABLE 41-1 Clinical and Laboratory Features of Infective Endocarditis

FEATURE	FREQUENCY, %
Fever	80–90
Chills and sweats	40–75
Anorexia, weight loss, malaise	25–50
Myalgias, arthralgias	15–30
Back pain	7–15
Heart murmur	80–85
New/worsened regurgitant murmur	20–50
Arterial emboli	20–50
Splenomegaly	15–50
Clubbing	10–20
Neurologic manifestations	20–40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2–15
Petechiae	10–40
Laboratory manifestations	
Anemia	70–90
Leukocytosis	20–30
Microscopic hematuria	30–50
Elevated ESR	60–90
Elevated CRP level	> 90
Rheumatoid factor	50
Circulating immune complexes	65–100
Decreased serum complement	5–40

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CLINICAL VIGNETTE

A 65-year-old man presents to the ED with fever, chills, weakness, and myalgias over 3 weeks. He has a history of moderate aortic stenosis, HF with reduced ejection fraction, hypertension, and CAD. He denies injection drug use. His vitals reveal a temperature of 38.0°C (100.4°F), heart rate 106 beats/min, respiratory rate 22 breaths/min, BP 106/80 mm Hg, and SpO_2 92% on room air. He appears fatigued.

There is a 4/6 systolic murmur best heard at the right upper sternal border. The murmur was 2/6 on documentation 6 months ago. The JVP is elevated, and there is trace peripheral edema. There is no vertebral spinous pain on palpation. A tender nodule on the pad of the right fourth digit of the hand is present. The patient is alert and oriented without focal neurologic findings.

Lab data reveal leukocytosis, elevated ESR and CRP, and new normocytic anemia with a hemoglobin of 10 g/dL. The ED administers 30 mL/kg of LR, draws three sets of blood cultures, and admits the patient on suspicion of infective endocarditis.

GUIDING QUESTIONS

1. What organisms would you consider covering with antibiotic selection?
2. What empirical antibiotic(s) would you order?
3. What are the indications for surgical management of infective endocarditis?

HISTORY

The highly variable (and difficult to diagnose unless there is clinical suspicion) clinical infective endocarditis (IE) syndrome spans a continuum between acute and subacute presentations (Table 41-1). Fever is present in 80–90% of patients, while the second most common symptom of chills and sweats is present in 40–75% of cases. The causative organism is primarily responsible for the temporal course of IE, with β-hemolytic streptococci, *Staphylococcus aureus*, and pneumococci typically resulting in an acute course; viridans streptococci, enterococci, coagulase-negative staphylococcus, and the HACEK group cause a subacute presentation. *Bartonella*, *Tropheryma whipplei*, *Coxiella burnetii*, and *Mycobacterium chimaera* are exceptionally indolent.

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HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - Acute infective endocarditis (IE): an acute presentation with
    - High fever
    - Chills
    - Rigors
    - Myalgias
    - Encephalopathy
    - Malaise
  - Subacute IE
    - Progressive low fever
    - Chills
    - Weakness
    - Myalgias
- Fever/chills?
  - The most common symptoms of IE
  - Part of Duke minor criteria
- Weight loss/anorexia?
  - Common symptom of IE
- Abdominal pain?
  - Splenic infarcts or abscesses can manifest as left upper abdominal, pleuritic chest, or left shoulder pain
- Flank pain? Hematuria?
  - Embolic renal infarcts cause flank pain and hematuria but rarely renal dysfunction
- Myalgias?
  - Common symptom of IE
- Nail changes?
  - Splinter hemorrhages may be present
- Skin changes?
  - Janeway lesions (painless erythematous lesions on palms/soles); part of Duke minor criteria
  - Osler's nodes (painful raised lesions on fingers, toes, or feet); part of Duke minor criteria
- Cough? Pleuritic chest pain?
  - Septic pulmonary emboli (possibly from tricuspid valve IE) may result in cough and pleuritic chest pain
- Joint pain?
  - Arthralgias are common, especially in severe acute illness
  - Must be differentiated from focal metastatic infections (e.g., spondylodiscitis)
- Hematuria?
  - Can have glomerulonephritis with endocarditis
  - Part of Duke minor criteria
- Stroke symptoms (unilateral weakness, slurring of speech)?
  - Septic emboli may cause stroke symptoms or intracranial hemorrhage
  - Part of Duke minor criteria
- Vision changes? Headache?
  - Roth spots (oval, retinal hemorrhages with a clear, pale center) may occur that can cause vision changes
    - Part of Duke minor criteria
  - Headaches may be a sign of emboli, hemorrhage, or mycotic aneurysms

PAST MEDICAL HISTORY

- History of endocarditis?
  - Risk factor for recurrent endocarditis and part of Duke minor criteria
- History of valvular disease, prosthetic valve, transcatheter aortic valve replacement (TAVR), or prior heart murmur?
  - It is important to know whether a murmur has been documented previously when one is heard to know if they had one previously
  - Aortic valve disease is a Duke minor criterion
- History of rheumatic fever?
  - Rheumatic valve disease is part of Duke minor criteria

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SURGICAL HISTORY

- Recent surgeries (cardiac procedures with grafts, pacemakers, TAVR, or bioprosthetic valves)?
  - Important to know as this will change management given different likely microorganisms

SOCIAL HISTORY

- Use of alcohol or recreational (injection) drugs, smoking
- Occupation
- Living situation
- Sexual history

PHYSICAL EXAM

There are specific physical exam findings that should be looked for in suspected endocarditis (bolded below). Although these findings are rare, they are a part of the Duke criteria and should be assessed in every patient. It is important to assess the vital signs and overall toxicity of the patient, as this may help differentiate an acute versus subacute presentation.

- Vital signs
  - Fever is a Duke minor criterion
  - High fever, tachycardia, and hypotension can be seen in acute infective endocarditis (IE)
  - Low-grade fever, possibly with normal heart rate and BP, can be seen in subacute IE
  - Patients who are older, severely debilitated, or have CKD may experience a blunted fever
- HEENT
  - **Roth spots**
    - Retinal hemorrhages + pale center
    - Duke minor criteria
  - **Conjunctival petechiae** (Fig. 41-1A)
    - Discrete linear hemorrhages on the conjunctiva
    - Part of Duke minor criteria
  - Dental evaluation
    - Patients with confirmed or suspected IE should have a thorough dental examination
    - Focus on periodontal inflammation, pocketing around teeth, and caries
- Cardiac
  - **Murmur** (especially regurgitant murmur)? Worsening murmur? Friction rub?
    - Endocarditis should be suspected in a patient with fever and a murmur
      - May have valvular damage and ruptured chordae
    - Murmurs may be initially absent but are detected in 85% of cases with native valve endocarditis
  - Signs of acute HF (e.g., JVD, lower extremity edema, crackles)
    - Acute HF may indicate surgical management is required
  - Thrill, $S_{3/4}$

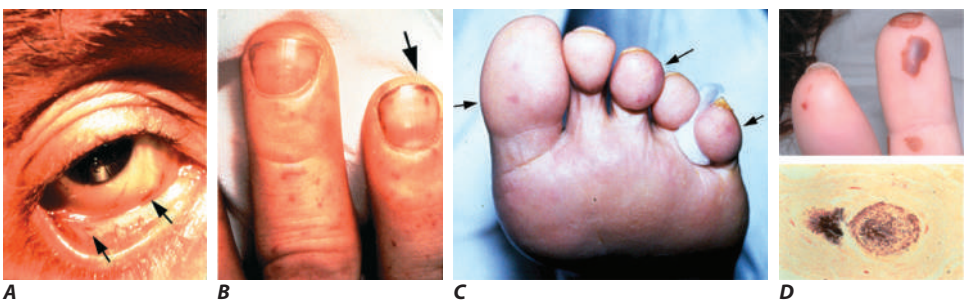

FIGURE 41-1 Embolic phenomena in infective endocarditis. A. Conjunctival petechiae: Arrows point to two discrete linear hemorrhages. **B.** Nail-bed splinter hemorrhage: Multiple petechiae are seen on both fingers. Arrow points to a splinter hemorrhage underlying the nail bed. **C.** Osler's nodes: Arrows point to subtle discolorations of the pads of the toes. These sites were raised and tender to palpation. **D.** Janeway lesions: Painless hemorrhagic lesions (upper). Biopsy of a typical lesion shows thrombosis and intravascular gram-positive cocci (lower). Culture was positive for *Staphylococcus aureus*. (Used with permission from Southwic FS. Cardiovascular infections, in *Infectious Diseases: A Clinical Short Course,* 4th ed, F Southwic (ed). New York, McGraw Hill, 2020.)

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- Conduction defects
  - Endocarditis can cause dysrhythmias, especially heart blocks
- Tenderness at a pacemaker site, if present
  - Sign of endocarditis with pacemaker involvement, which changes treatment

- Respiratory
  - Septic emboli to the lungs in right-sided IE can cause empyema or pyopneumothorax
- Abdomen
  - **Splenomegaly** and tenderness
    - Due to hematogenously seeded focal infection with possible ischemia-induced organ dysfunction
  - Embolic renal infarcts cause flank pain and hematuria but rarely renal dysfunction
- Musculoskeletal and skin
  - Hematogenously seeded focal infection or ischemia may cause musculoskeletal pain
    - May be a sign of hematogenous spread to the vertebral spine, causing an epidural abscess
  - **Nail bed splinter hemorrhages** (Fig. 41-1B)
    - Small, red to reddish-brown streaks under the fingernails or toenails
  - **Janeway lesions** (Fig. 41-1C)
    - Nontender hemorrhagic macules on palms/soles, caused by septic emboli
    - Associated with prolonged infection (infrequently seen now due to earlier diagnosis and treatment)
    - Duke minor criteria
  - **Osler's nodes** (Fig. 41-1D)
    - Tender nodules on pads of digits, caused by immune complex deposition (septic embolization) and subungual hemorrhage
    - Common in *Staphylococcus aureus* IE
    - Duke minor criteria
- Neurologic
  - Assess for signs of cerebrovascular infarction from septic embolic or encephalopathy (up to 15–25% of cases)
  - Arterial emboli, one-half of which precede the diagnosis of IE, are clinically apparent in up to 50% of patients
  - Aseptic or purulent meningitis, intracranial hemorrhage, ruptured mycotic aneurysms, and seizures may occur

DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

- Bacteremia from a noninfective endocarditis (IE) infection or sepsis without bacteremia
  - The clinical picture depends on the cause of the primary source of infection
- Valvular abnormality without endocarditis (e.g., rheumatic heart disease, mitral valve prolapse, bicuspid/calcific aortic valve)
  - Murmur without other signs/symptoms of endocarditis
- Flow murmur (e.g., anemia, pregnancy, hyperthyroidism, sepsis, high-stress state)
  - Murmur without other signs/symptoms of endocarditis, plus other signs of the disease causing the flow murmur
- Atrial myxoma
  - Possible murmur, dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea
  - May mimic right or left HF
- Noninfective endocarditis (e.g., Libman-Sacks endocarditis in antiphospholipid syndrome and SLE)
  - Murmur, possible fever, symptoms and findings of SLE
- Marantic endocarditis (nonbacterial thrombotic endocarditis)
  - Possible cerebrovascular accident and/or HF symptoms
  - Associated with hypercoagulable states and malignancies
- Hematuria, if present, due to other causes (glomerulonephritis, renal cell carcinoma)
  - Elevated BUN/SCr with no other symptoms of endocarditis
- AKI
  - Azotemia with symptoms of the underlying cause not attributable to IE
- Vasculitis
  - Can have systemic symptoms but usually without a murmur

ETIOLOGY

- Clinical clues from the patient history can help determine the pathogen causing the endocarditis
- The following include the most common organisms in each scenario, but not all possible causative organisms are listed

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- ***Staphylococcus aureus*** is the most common organism causing IE
- Injection drug use: *S. aureus*, *Pseudomonas*, *Candida*
  - Tricuspid valve involvement and pulmonary septic emboli
- Dental procedures: *Streptococcus viridians* (most common cause for left-sided subacute IE)
- Prosthetic valve endocarditis (PVE): *S. aureus* and *Staphylococcus epidermidis*
- Cardiovascular implantable electronic device (CIED) IE: *S. aureus* and coagulase-negative staphylococci
- GI malignancy/polyps: *Streptococcus gallolyticus* (previously *bovis*)
- Nosocomial UTI with IE: enterococci
- Health care–associated IE: *S. aureus,* coagulase-negative staphylococci, and enterococci

- Pathogens causing IE can also be sorted into the site of infection and whether it is device-associated (Table 41-2)
  - Site of infection: community-acquired and health care–associated IE
  - Device-associated: native valve endocarditis, PVE (and the associated timing between PVE and prosthetic valve placement), transcatheter aortic valve replacement (TAVR)-PVE, or CIED-IE
- Culture-negative IE
  - ~ 5–15% of patients with IE have negative blood cultures
  - *In about one-third to one-half of patients, cultures are negative because of prior recent antibiotic exposure*
  - The remainder are infected by fastidious organisms, such as
    - Some streptococci
    - Nutritionally variant bacteria now designated *Granulicatella*, *Gemella*, and *Abiotrophia* species

TABLE 41-2 Organisms Causing Major Clinical Forms of Infective Endocarditis (IE)

	PROPORTION OF CASES						
	NATIVE VALVE IE		PROSTHETIC VALVE IE AT INDICATED TIME OF ONSET (MONTHS) AFTER VALVE SURGERY			TAVR-PVE	CIED-IE
ORGANISM(S)	COMMUNITY-ACQUIRED (*N* = 1718)	HEALTH CARE–ASSOCIATED (*N* = 1110)	< 2 (*N* = 144)	> 2–12 (*N* = 31)	> 12 (*N* = 194)	(*N* = 295)	(*N* = 337)
Streptococci[b]	40	13	1	10	31	18	2
Pneumococci	2	—	—	—	—	—	—
Enterococci[c]	9	16	8	13	11	24	4
Staphylococcus aureus	28[a]	52[d]	22	13	18	23	36
Coagulase-negative staphylococci	5	11	33	35	11	20	41
Fastidious gram-negative coccobacilli (HACEK group)[e]	3	—	—	—	6	—	—
Gram-negative bacilli	1	1	13	3	6	1	6
Candida spp.	< 1	1	8	13	1	1	2
Polymicrobial/ miscellaneous	3	3	3	6	5	8	2
Diphtheroids	—	< 1	6	—	3		1
Culture-negative	9	3	5	7	8	5	6

[a]Includes methicillin-susceptible and -resistant isolates. [b]Includes viridans streptococci; *Streptococcus gallolyticus*; other non–group A, groupable streptococci; and *Abiotrophia* and *Granulicatella* spp. (nutritionally variant, pyridoxal-requiring streptococci). [c]Primarily *E. faecalis* or nonspeciated isolates; occasionally *E. faecium* or other less likely species. [d]Methicillin resistance is common among these *S. aureus* strains. [e]Includes *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.
Note: Data are compiled from multiple studies.
CIED, cardiac implantable electronic device; TAVR, transcatheter aortic valve replacement.
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- *Coxiella burnetii*
- *Bartonella* species

- *C. burnetii* (predilection for PVE) and *Bartonella* species occur in Europe; *Brucella* species in the Middle East
- *Tropheryma whipplei* causes an indolent, culture-negative form of IE
- *Corynebacterium* species and *Cutibacterium acnes* may involve intracardiac devices and are slow to grow in blood cultures
- Mimickers of culture-negative IE
  - Atrial myxoma
  - Marantic endocarditis
  - Libman-Sacks endocarditis in antiphospholipid syndrome and SLE

DIAGNOSTIC TESTS

LABS

- *Blood cultures* (three sets initially from different sites) every day until cultures are negative
  - Identifies a specific organism
  - Positive blood cultures with an organism that commonly causes IE (two sets of cultures) or organisms that occasionally or rarely cause IE from three or more blood cultures are a Duke major criterion
  - About 5–15% of patients with IE have negative blood cultures
- Positive lab tests for organisms that can cause IE (all are Duke major criteria)
  - PCR for *Coxiella burnetii*, *Bartonella*, or *Tropheryma whipplei*
  - Single blood culture growing *C. burnetii* or phase I IgG Ab titer ≥ 1:800
  - Indirect immunofluorescence assays for IgM Ab and IgG to *B. henselae* or *B. quintana* with IgG Ab titer ≥ 1:800
- CBC with differential
  - Leukocytosis, anemia, and neutrophilic shift are common in IE
- CMP
  - Look for elevated BUN/SCr, electrolyte abnormalities, elevated liver function tests, hyperglycemia
  - Immune complex deposition on the glomerular basement membrane causes diffuse hypocomplementemic glomerulonephritis and renal dysfunction
- ESR, CRP, rheumatoid factor, and circulating immune complex titer
  - Commonly elevated in endocarditis
- Lactic acid
  - Lactic acidosis is common, especially in acute IE with sepsis

IMAGING

- ECG
  - Evaluate for dysrhythmias (especially conduction deficits, such as heart blocks), ischemia, and LV hypertrophy
- Posterior–anterior/lateral CXR
  - Evaluating for signs of cardiac abnormalities
  - Can have lung abnormalities from septic pulmonary emboli from right-sided IE (e.g., empyema and pyopneumothorax)
  - Also helps rule out other conditions in the chest that may present with similar symptoms
- Transthoracic echocardiogram (TTE) and/or transesophageal echocardiogram (TEE)
  - Use the Modified Duke criteria (Table 41-3) to help determine the likelihood of IE
  - Table 41-4 describes risk factors in monobacterial bacteremia to identify patients who are at sufficient risk of IE to justify echocardiographic assessment
    - Patients with *Staphylococcus aureus* bacteremia should routinely undergo echocardiographic evaluation (high-quality TTE or, preferably, TEE)
      - With *S. aureus* bacteremia, a patient with any of the features listed in Table 41-4 incurs at least a 6% risk of IE, with the risk increasing when multiple features are present
    - Among patients with either monomicrobial *Enterococcus faecalis* or non–β-hemolytic streptococcal bacteremia, any three of the respective features listed in Table 41-4 are associated with a significant frequency of IE
  - Patients with low initial risk and low clinical suspicion of endocarditis but with monobacterial bacteremia justifying echocardiogram
    - TTE is the preferred initial imaging test
    - If the initial TTE is negative for endocarditis

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TABLE 41-3 The Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis (IE)

Diagnosis

Definite IE: 1. Pathologic criteria (microorganisms or active endocarditis identified in a vegetation/intracardiac abscess from cardiac tissue, prosthetic material, arterial embolus) 2. Clinical criteria (2 major or 1 major + 3 minor or 5 minor)

Possible IE: 1 major + 1 minor or 3 minor

Rejected IE: does not meet above criteria or firm alternative dx or lack of recurrence with < 4 days of antibiotics or no evidence on autopsy

Major Criteria

A. Microbiologic Criteria

1. Positive blood culture

   Microorganisms that commonly cause IE in 2 or more separate blood culture sets (Typical—i.e., *S. aureus*, *S. lugdunensis*, *E. faecalis*, all streptococcal species except *S. pneumoniae* and *S. pyogenes*, *Granulicatella* spp., *Abiotrophia* spp., *Gemella* spp., HACEK group organisms A*nd* in the setting of intracardiac prosthetic material, CoNS, *C. striatum*, *C. jeikeium*, *S. marcescens*, *P. aeruginosa*, *C. acnes*, nontuberculosis mycobacteria, *Candida* spp.)

   or

   Microorganisms that occasionally or rarely cause IE isolated from 3 or more separate blood culture sets (Nontypical)

2. Positive laboratory tests

   Positive PCR for *Coxiella burnetii*, *Bartonella* spp., or *Tropheryma whipplei* from blood

   or

   Single blood culture growing *C. burnetii* or phase I IgG Ab titer ≥ 1:800

   or

   Indirect immunofluorescence assays (IFA) for IgM Ab and IgG Ab to *B. henselae* or *B. quintana* with IgG Ab titer ≥ 1:800

B. Imaging Criteria

1. Echocardiography or cardiac CT showing vegetation, valvular/leaflet perforation/aneurysm, abscess, pseudoaneurysm or intracardiac fistula

   or

   New valvular regurgitation (new/worsening murmur is *not* sufficient; requires echocardiographic evidence)

   or

   New prosthetic valve dehiscence/insufficiency

2. FDG-PET/CT with abnormal metabolic activity involving a native or prosthetic valve, ascending aortic graft, intracardiac device leads, or other prosthetic material

C. Surgical Criteria

Evidence of IE documented by direct inspection during heart surgery

Minor Criteria

A. Predisposition: previous history of IE, injection drug use, prosthetic valve, previous valve repair, congenital heart disease (e.g., bicuspid AV), CIED, more than mild regurgitation or stenosis, hypertrophic cardiomyopathy

B. Fever: T > 38.0°C (100.4°F)

C. Vascular phenomenon: arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions, cerebral/splenic abscesses, purulent purpura

D. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, positive rheumatoid factor

E. Microbiologic evidence: positive blood cultures (not meeting above criteria)

or

Positive culture, PCR, or other nucleic acid–based test for an organism consistent with IE from a nonendovascular site or single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiologic supporting evidence

F. Imaging criteria: abnormal metabolic activity on FDG-PET/CT within 3 months of implantation of a prosthetic valve, ascending aortic graft, intracardiac device lead

G. Physical exam criteria: New valvular regurgitation on auscultation

Ab, antibody; AV, aortic valve; CIED, cardiac implantable electronic device; CoNS, coagulase-negative staphylococci; FDG, ^{18}F-fluorodeoxyglucose; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; PET, positron emission tomography.

Reproduced with permission from VG Fowler Jr et al: The 2023 Duke-International Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: Updating the modified Duke criteria. Clin Infect Dis. 77:518, 2023.

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TABLE 41-4 Features Guiding the Need for Echocardiographic Assessment in Patients with Selected Monomicrobial Bacteremia

Streptococcus aureus[a]
Intracardiac device
Preexisting valve disease (including prior endocarditis or valve prosthesis)
Injection drug use
Cerebral/peripheral emboli
Meningitis
Persistent bacteremia (≥ 72 h)
Vertebral osteomyelitis
Community acquisition
Nonnosocomial health care–associated (including hemodialysis)
Enterococcus faecalis[b]
Symptoms ≥ 7 days
Emboli
≥ 2 positive cultures
Unknown origin (no focus)
Heart murmur
Preexisting valve disease (including prior endocarditis or valve prosthesis)
Non–β-Hemolytic Streptococci[c]
Symptoms ≥ 7 days
> 2 positive cultures
One species: *S. gallolyticus*, *S. sanguinis*, *S. mutans* (not *S. anginosus*)
Preexisting valve disease (including prior endocarditis or valve prosthesis)
Heart murmur
Community acquisition

[a]S Tubiana et al: J Infect 72:544, 2016 and A Showler et al: JACC Cardiovasc Imaging 8:924, 2015. [b]A Berge et al: Infection 47:45, 2019. [c]T Sunnerhagen et al: Clin Infect Dis 66:693, 2018.
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        - Look for other sources of symptoms and treat if diagnosis is discovered
        - Perform a TEE if the clinical suspicion for endocarditis increases during the clinical course
    - Patients with high initial risk or the presence of intracardiac complications (e.g., new regurgitant murmur, new ECG conduction changes, HF), moderate to high clinical suspicion, or difficult imaging candidates
        - TEE is the preferred initial imaging test
        - If the initial TEE is negative for endocarditis
            - Look for other sources of symptoms and treat when the diagnosis is discovered
            - Repeat TEE if high suspicion for IE persists
- MRI/MR angiography brain
    - MRI should be obtained in patients with neurologic signs or symptoms, including unusual headache, to assess for
        - Septic emboli
        - Hemorrhage
        - Mycotic aneurysms
    - Evidence of clinically asymptomatic emboli is found on MRI in 30–65% of patients with left-sided IE
    - Aseptic or purulent meningitis, intracranial hemorrhage, ruptured mycotic aneurysms, and seizures may occur
    - Microabscesses in the brain and meninges occur commonly in *S. aureus* IE
- MRI spine
    - Patients with recalcitrant back pain or focal spine tenderness should undergo spine MRI targeted to the appropriate level based on symptoms to assess for associated
        - Osteomyelitis
        - Epidural abscess

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MANAGEMENT

PRINCIPLES OF INPATIENT MANAGEMENT OF INFECTIVE ENDOCARDITIS (IE)

- Daily blood cultures until sterile; recheck cultures if there is recrudescent fever
  - How many days blood cultures remain positive depends on the virulence of the organism and the antibiotic susceptibility to the ongoing treatment
    - For example, viridans streptococci take ~ 2 days, while MRSA may take 5 days or longer
  - Recrudescence of fever may indicate
    - Paravalvular abscess
    - Extracardiac abscess (spleen, kidney)
    - Embolic events
    - Drug reactions and complications of hospitalization
- Telemetry for dysrhythmia monitoring
- Daily blood tests to detect renal, hepatic, and hematologic toxicity
- Monitoring of aminoglycoside and vancomycin serum concentrations with dose adjustments as needed
- Frequent history and exams to assess interval development of complications of IE
- Tailor specific antibiotics once cultures yield specific microorganisms and their susceptibilities
- Infectious disease consultation is recommended for cases of IE
- If present, all active sources of oral infection should be eradicated in addition to management as below

EMPIRICAL ANTIBIOTIC TREATMENT

- Consider the following when choosing antibiotics before culture results are known (or when cultures are truly negative)
  - Clinical clues to etiology; for example
    - Acute versus subacute presentation
    - Native valve endocarditis (NVE)
    - Early or late prosthetic valve endocarditis (PVE)
    - The patient's predispositions
  - Epidemiologic clues—for example
    - Region of residence
    - Animal exposure
- Refer to Table 41-2 to understand which microorganisms should be covered with empirical therapy

ACUTE IE

- Cover methicillin-resistant *Staphylococcus aureus* (MRSA) in all patients
- In patients with injection drug use or health care–associated NVE, gram-negative bacilli coverage should be considered
- Empirical combination therapy example
  - Vancomycin, 15 mg/kg IV q12h
  - Gentamicin, 3 mg/kg daily IV/IM, or cefepime, 2 g IV q8h

NATIVE VALVE ENDOCARDITIS (NVE) WITH A SUBACUTE PRESENTATION

- Cover MRSA and streptococcus for all patients
- Combination antibiotic therapy of
  - Vancomycin, 15 mg/kg IV q12h
  - Ceftriaxone, 2 g IV daily

PROSTHETIC VALVE ENDOCARDITIS (PVE)

- If the valve has been in place for < 1 year
  - Vancomycin, 15 mg/kg IV q12h +
  - Gentamicin, 3 mg/kg daily IV/IM +
  - Cefepime, 2 g IV q8h
- If the valve has been in place for > 1 year
  - Vancomycin, 15 mg/kg IV q12h +
  - Ampicillin-sulbactam, 2 g IV q4h or ceftriaxone, 2 g IV daily +
  - Doxycycline, 100 mg q12h (for enhanced *Bartonella* coverage)
  - Treatment is the same as true culture-negative NVE

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TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR)-PROSTHETIC VALVE ENDOCARDITIS

- Selection of empirical therapy pending blood culture results similarly parallels that for classic PVE but with a recognition that enterococcal infection occurs with increased frequency

CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICE (CIED)-IE

- *Removal of the device* is the primary treatment
  - Antibiotics are an adjunctive therapy
- Coincident NVE, PVE, or remote-site infection (e.g., osteomyelitis) may complicate bacteremic CIED
- Empirical therapy should cover
  - MRSA and coagulase-negative staphylococci
    - Vancomycin, 15 mg/kg IV q12h
  - Gram-negative bacilli
    - Either with ceftriaxone, 2 g IV daily, or gentamicin, 3 mg/kg IV/IM daily

TRUE CULTURE-NEGATIVE IE

- Marantic endocarditis and the antiphospholipid antibody syndrome must be considered
- In the absence of prior antibiotic therapy, it is unlikely that infection due to *S. aureus*, coagulase-negative staphylococci, enterococci, or *Enterobacterales* will present with negative blood cultures
  - Therefore, recommended empirical therapy targets fastidious streptococci, *Abiotrophia*, *Gemella*, *Granulicatella*, the HACEK group, and *Bartonella* species
  - Vancomycin, 15 mg/kg IV q12h +
  - Ampicillin-sulbactam, 2 g IV q4h or ceftriaxone, 2 g IV daily + doxycycline, 100 mg q12h
- If cultures are negative due to prior antibiotic administration
  - Consider pathogens likely inhibited by those antibiotics and
  - Choose empirical therapy based on that data

ORGANISM-SPECIFIC THERAPIES AND DURATION OF ANTIBIOTICS

- Tailor antibiotics once cultures yield specific microorganisms with susceptibilities
- Table 41-5 describes antibiotic treatment choices and duration for infective endocarditis (IE) caused by common organisms
  - The 2-week penicillin/gentamicin and ceftriaxone/gentamicin regimens should not be used to treat NVE complicated by cardiac or extracardiac abscess or PVE
  - Caution should be exercised in considering aminoglycoside-containing regimens in patients at increased risk for aminoglycoside toxicity (renal disease)
  - The combination of vancomycin or gentamicin with ceftriaxone is not bactericidal for *Enterococcus faecalis* and is not recommended for treatment of enterococcal IE
  - Treatment of IE caused by *E. faecium*, which is generally more antibiotic resistant than *E. faecalis* and may be vancomycin- resistant, is not well established
  - Infectious disease consultation has been associated with improved outcomes for *S. aureus* bacteremia and IE [1]
  - The addition of gentamicin to a β-lactam antibiotic or vancomycin to enhance therapy for left-sided NVE has not improved survival rates and is associated with nephrotoxicity
  - Vancomycin, dosed to achieve trough concentrations of 15 μg/mL (or an area under the time-concentration curve/broth microdilution MIC ratio [AUC:MIC] > 400 achieved with the assistance of a pharmacist), is recommended
    - Higher concentrations may lead to nephrotoxicity

PARTIAL ORAL ANTIBIOTIC TREATMENT OF IE

- A noninferiority, multicenter, randomized study found that mortality among patients with left-sided IE caused by streptococci, enterococci, and staphylococci who received partial oral treatment was comparable to that of patients who were treated intravenously for the full course of therapy (6.5% and 7.5%, respectively) [2]
  - IE was caused by streptococci (49%), enterococci (24%), and methicillin-susceptible *S. aureus* (22%)
  - *No patients had MRSA*
  - The median duration of IV treatment before the switch to oral agents was 16 days (interquartile range, 13–23 days)
    - Thus, some patients may have been effectively cured by IV therapy with or without surgery prior to transition to oral therapy
  - Consultation with infectious disease is highly recommended if considering oral therapy

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TABLE 41-5 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a]

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
Streptococci		**For PVE 6-week regimens are preferred.**
Penicillin-susceptible streptococci, *S. gallolyticus* (MIC ≤ 0.12 µg/mL)	• Penicillin G (2–3 mU IV q4h for 4 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Ceftriaxone (2 g daily for 4 weeks)	Can use ceftriaxone in patients with nonimmediate penicillin allergy.
	• Vancomycin[b] (15 mg/kg IV q12h for 4 weeks)	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of β-lactam desensitization.
	• Penicillin G (2–3 mU IV q4h) *or* ceftriaxone (2 g IV daily) for 2 weeks *plus* Gentamicin[c] (3 mg/kg daily IV or IM, as a single dose[d] for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic-valve or complicated endocarditis. Penicillin G at a dose of 4 mU IV q4h or ceftriaxone 2 g daily for 6 weeks both with or without gentamicin during the initial 2 weeks preferred for PVE caused by streptococci with penicillin MICs ≤ 0.12 µg/mL.
Relatively penicillin-resistant streptococci, *S. gallolyticus* (MIC > 0.12 µg/mL and < 0.5 µg/mL[e])	• Penicillin G (4 mU IV q4h) *or* ceftriaxone (2 g IV daily) for 4 weeks *plus* Gentamicin[c] (3 mg/kg daily IV or IM, as a single dose[d] for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin G at a dose of 4 mU IV q4h or ceftriaxone 2 g once daily for 6 weeks both with gentamicin during the initial 2 weeks preferred for PVE caused by streptococci with penicillin MICs > 0.12 µg/mL.
	• Vancomycin[b] as noted above for 4 weeks	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of β-lactam desensitization. Ceftriaxone alone or with gentamicin can be used in patients with nonimmediate β-lactam allergy.
Moderately penicillin-resistant streptococci (MIC, ≥ 0.5 µg/mL and < 8 µg/mL); *Granulicatella*, *Abiotrophia*, or *Gemella* spp.	• Penicillin G (4–5 mU IV q4h) *or* ceftriaxone (2 g IV daily) for 6 weeks *plus* Gentamicin[c] (3 mg/kg daily IV or IM in 2–3 equally divided doses for 6 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Vancomycin[b] as noted above for 6 weeks	Regimen is preferred by some.
Enterococci[e]		**For PVE, 6-week regimens are preferred.**
	• Ampicillin (2 g IV q4h) *plus* ceftriaxone (2 g IV q12h), both for 6 weeks	Use for *E. faecalis* isolates with or without high-level resistance to gentamicin or for patients at risk for aminoglycoside nephrotoxicity.
	• Penicillin G (4–5 mU IV q4h) for 4–6 weeks *plus* gentamicin[c] (3 mg/kg/d IV or 1 mg/kg IV q8h) for 2–6 weeks	Can treat NVE for 4 weeks if symptoms last < 3 months. Treat NVE for 6 weeks if > 3 months of symptoms. Can abbreviate gentamicin course in some patients.

(*Continued*)

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TABLE 41-5 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a] (*Continued*)

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
	• Ampicillin (2 g IV q4h) for 4–6 weeks *plus* gentamicin[c] (3 mg/kg daily IV or 1 mg/kg IV q8h) for 2–6 weeks	Can use IV amoxicillin in lieu of ampicillin (same dose). Can abbreviate gentamicin course in some patients.
	• Vancomycin[b] (15 mg/kg IV q12h) for 6 weeks *plus* gentamicin[c] (3 mg/kg/d IV or 1 mg/kg IV q8h) for 2–6 weeks	Use vancomycin plus gentamicin only for penicillin-allergic patients (preferable to desensitize to penicillin if immediate [urticarial] allergy; consult allergy) and for isolates resistant to penicillin/ampicillin.
Staphylococci (*S. aureus* and coagulase-negative)		
MSSA infecting native valves (no foreign devices) including complicated right-sided and left-sided endocarditis.	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 4–6 weeks)	Addition of gentamicin is not recommended. For uncomplicated right-sided endocarditis, a 2-week course may be effective.
	• Cefazolin (2 g IV q8h for 4–6 weeks)	Can use cefazolin regimen for patients with nonimmediate penicillin allergy; see text regarding cefazolin vs antistaphylococcal penicillin as primary therapy. Addition of gentamicin not recommended.
	• Vancomycin[b] (15 mg/kg IV q12h for 4–6 weeks)	Only use vancomycin for patients with immediate (urticarial) or severe penicillin allergy until allergy consultation can be obtained for β-lactam desensitization evaluation; addition of gentamicin not recommended.
MRSA infecting native valves (no foreign devices)	• Vancomycin[b] (15 mg/kg IV q8–12h) or daptomycin (8–10 mg/kg/d) for 4–6 weeks	No role for routine use of rifampin. For daptomycin treatment, see text.
MSSA infecting prosthetic valves	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 6–8 weeks) *plus* Gentamicin[c] (1 mg/kg IM or IV q8h for 2 weeks) *plus* • Rifampin[f] (300 mg PO tid for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin; if patient is highly allergic to penicillin, use regimen for MRSA and obtain allergy consultation; if β-lactam allergy is of the minor nonimmediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin.
MRSA infecting prosthetic valves	• Vancomycin[b] (15 mg/kg IV q12h for 6–8 weeks) *plus* Gentamicin[c] (1 mg/kg IM or IV q8h for 2 weeks) *plus* • Rifampin[f] (300 mg PO tid for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin. Daptomycin (8–10 mg/kg/d) is an alternative to vancomycin.
HACEK organisms		**For PVE, 6-week regimens are preferred.**
	• Ceftriaxone (2 g once daily IV for 4 weeks)	
	• Ampicillin/sulbactam (3 g IV q6h for 4 weeks)	Use ampicillin alone (2 g IV q4h) only if β-lactamase production can be excluded. If the isolate is susceptible, ciprofloxacin (500 mg PO q12h or 400 mg IV q12h) can be used.

(*Continued*)

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TABLE 41-5 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a] (*Continued*)

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
Coxiella burnetii		
	• Doxycycline (100 mg PO q12h) *plus* hydroxychloroquine (200 mg PO q8h), both for at least 18 (native valve) or 24 (prosthetic valve) months	Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased fourfold and IgM antiphase II negative) and thereafter for relapse.
***Bartonella* spp.**		
	• Doxycycline (100 mg PO q12h) for 6 weeks *plus* Gentamicin (1 mg/kg IV q8h for 2 weeks)	If doxycycline is not tolerated, use azithromycin (500 mg PO daily). Some experts recommend that doxycycline be continued for 3–6 months unless all infection is resected surgically.

[a]Regimens adapted from the guidelines of the American Heart Association and the European Society of Cardiology (ESC). Doses of gentamicin, vancomycin, and daptomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and daptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet). [b]Vancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections. [c]Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~ 3.5 μg/mL and ≤ 1 μg/mL, respectively. [d]Netilmicin (4 mg/kg daily, as a single dose) can be used in lieu of gentamicin for streptococcal infection only. [e]Antimicrobial susceptibility must be evaluated. [f]Rifampin increases warfarin and dicumarol requirements for anticoagulation.
HACEK, *H*aemophilus species, *A*ggregatibacter species, *C*ardiobacterium hominis, *E*ikenella corrodens, and *K*ingella kingae; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.
Reproduced with permission from Cosgrove SE, Melia MT. Infective endocarditis, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

LONG-ACTING LIPOGLYCOPEPTIDE AGENTS

- Dalbavancin
  - Lipoglycopeptide with a long half-life allowing for infrequent dosing
  - FDA-approved for treatment of skin and soft tissue infections
- Only limited data are available supporting its use in the treatment of IE, particularly due to *S. aureus* [3]
- Most trial patients received several weeks of active IV therapy prior to dalbavancin upon discharge
- May be an option for patients who are not candidates for continued hospitalization or for transition to outpatient parenteral therapy
  - For example, patients who use injection drugs
- Infectious disease consultation is recommended if considering dalbavancin

ANTITHROMBOTIC THERAPY

- Neither anticoagulant nor antiplatelet therapy reduces the risk of emboli in patients with NVE
- If the patient is on anticoagulation for another purpose, therapy can be continued in the absence of contraindications, which include
  - No clinical or imaging of a recent large embolic stroke
  - Intracerebral hemorrhage
  - Mycotic aneurysm

TRANSITION TO OUTPATIENT PARENTERAL ANTIBIOTIC THERAPY

- Afebrile, fully compliant, and clinically stable patients may complete IV antibiotics as outpatients
  - Can occur either in a skilled nursing facility or at home
  - If occurring at home, patients and their caregivers require training on antibiotic administration
- Long-term IV access (e.g., peripherally inserted central catheter [PICC] line placement) is necessary for discharge
- Frequent monitoring of lab data to monitor for antibiotic toxicities

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TABLE 41-6 Indications for Cardiac Surgical Treatment in Patients with Endocarditis
Surgery Required for Optimal Outcome
NVE or PVE
Moderate or severe HF or shock due to valve dysfunction
Paravalvular extension of infection with abscess, fistula, or heart block
Persistent bacteremia without an extracardiac cause despite 7–10 days of optimal antimicrobial therapy
Lack of effective antimicrobial therapy (e.g., fungal [see text regarding *Candida* spp.], *Brucella*, multidrug-resistant gram-negative bacillary endocarditis)
PVE
Partially dehisced unstable prosthetic valve
Surgery to Be Strongly Considered for Improved Outcome[a]
PVE
S. aureus infection with intracardiac complications
Relapse after optimal antimicrobial therapy
NVE
Large (> 10-mm) hypermobile vegetation, particularly with prior systemic embolus and significant valve dysfunction
Very large (> 30-mm) vegetation
Persistent unexplained fever (≥ 10 days) in blood culture–negative endocarditis
Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli

[a]Carefully consider surgery. Multiple findings are often combined to justify surgery.
NVE, native valve endocarditis; PVE, prosthetic valve endocarditis
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SURGICAL MANAGEMENT OF IE

- Indications for surgery (Table 41-6) and timing of surgery (Table 41-7)
  - The strength of specific indications varies
    - Thus, the risks and benefits as well as the timing of surgery must be individualized and are best decided with a multidisciplinary team
  - Surgery for NVE based on current indications appears to convey a significant survival benefit (27–55%), which is greatest among those with the most pressing indications
  - Early surgery compared with conventional treatment for infective endocarditis and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism [4]
  - Duration of antibiotics after surgical intervention should equal the total duration of recommended therapy

PROPHYLAXIS FOR IE

- Prevention of IE has been a goal of clinical practice
- However, the evidence from antibiotic prophylaxis for IE is insufficient to recommend it as a widespread standard of care
- The AHA and ESC recommend limiting prophylactic antibiotics to *only patients at highest risk of severe morbidity or death from IE prior to dental procedures,* and include
  - Prosthetic heart valves or materials
  - LV assist devices or implantable heart
  - Prior endocarditis
  - Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
  - Completely repaired congenital heart defects during the 6 months after repair
  - Repaired congenital heart disease with residual deficits adjacent to prosthetic material
  - Surgical or transcatheter pulmonary artery valve or conduit placement
  - Valvulopathy developing after cardiac transplantation
- Notice mitral valve prolapse is *not* an indication for antibiotic prophylaxis anymore
  - Neither rheumatic heart disease nor bicuspid aortic valve is an indication either
- Management
  - Table 41-8 lists antibiotic regimens for prophylaxis prior to dental procedures for endocarditis in adults with high-risk cardiac lesions

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TABLE 41-7 Timing of Cardiac Surgical Intervention in Patients with Endocarditis

	INDICATION FOR SURGICAL INTERVENTION	
TIMING	STRONG SUPPORTING EVIDENCE	CONFLICTING EVIDENCE, BUT MAJORITY OF OPINIONS FAVOR SURGERY
Emergent (same day)	Valve dysfunction with pulmonary edema or cardiogenic shock Acute aortic regurgitation plus preclosure of mitral valve Sinus of Valsalva abscess ruptured into right heart Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation Unstable (dehisced) prosthesis Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV) Septal perforation Paravalvular extension of infection with or without new electrocardiographic conduction system changes Lack of effective antibiotic therapy	Vegetation diameter > 10 mm plus severe but not urgent aortic or mitral valve dysfunction[a] Major embolus plus persisting large vegetation (> 10 mm) Mobile vegetation > 30 mm
Elective (earlier usually preferred)	Progressive paravalvular prosthetic regurgitation Valve dysfunction plus persisting infection after ≥ 7–10 days of antimicrobial therapy Fungal (mold) endocarditis	Staphylococcal prosthetic valve endocarditis with intracardiac complications Early prosthetic valve endocarditis (≤ 2 months after valve surgery) *Candida* spp. endocarditis Antibiotic-resistant organisms

[a]Supported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment. If surgery is elected, it must be done early.
Reproduced with permission from L Olaison, G Pettersson: Current best practices and guidelines: Indications for surgical intervention in infective endocarditis. Infect Dis Clin North Am 16:453, 2002.

TABLE 41-8 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults with High-Risk Cardiac Lesions[a,b]

A. Standard oral regimen	Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication	Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy	Cephalexin[c]: 2 g PO 1 h before procedure Clarithromycin or azithromycin: 500 mg PO 1 h before procedure Doxycycline: 100 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication	Cefazolin[c] or ceftriaxone[c]: 1 g IV or IM 30 min before procedure

[a]Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV. Prophylaxis is not advised for other lesions. [b]Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.
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COMPLICATIONS

- HF
  - Results from valve dysfunction or, occasionally, intracardiac fistulae, which develop in 30–40% of patients
- Conduction defects (e.g., third-degree heart block, second-degree type II Mobitz heart block)
- Perivalvular abscess
- Splenic abscess
  - Develops in 3–5% of patients
  - Management comprises either image-guided percutaneous drainage or splenectomy
- Coronary artery emboli
  - Occur in 2% of patients
  - May result in MI
- Cerebral aneurysm
  - Should be monitored by angiography if found
  - Should be treated surgically, if possible, if leakage or enlargement occurs
- Extracerebral aneurysms
  - Present as local pain, a mass, local ischemia, or bleeding
  - Treated surgically
- Mycotic aneurysm
  - Occurs in 2–15% of IE patients
- Pericarditis
- Systemic emboli (e.g., pulmonary, kidney, spleen, brain)
  - The frequency of stroke is 8 per 1000 patient-days during the week prior to diagnosis and decreases to 4.8 and 1.7 per 1000 patient-days during the first and second weeks of effective antimicrobial therapy, respectively
  - Emboli occurring late during or after effective therapy do not in themselves constitute evidence of failed antimicrobial treatment
- Glomerulonephritis
- Meningitis

PROGNOSIS

- In developed countries, overall survival rates are 80–85%
  - However, rates vary considerably among subpopulations of IE patients
- Comorbidities and IE-related end-organ complications often cause death or poor outcomes instead of failure of antibiotic therapy
- Adverse outcomes are associated with
  - Older age
  - Severe comorbid conditions and diabetes mellitus
  - Delayed diagnosis
  - Involvement of prosthetic valves or the aortic valve
  - An invasive (*Staphylococcus aureus*) or antibiotic-resistant (*Pseudomonas aeruginosa*, yeast) pathogen
  - Intracardiac and major neurologic complications
  - Health care–associated infection
- Recently, there has been an acceleration in mortality in people aged 25–44 years
  - This is likely associated with an increase in opioid use disorder and injection drug use in this age group
- About 85–90% of patients with native valve endocarditis (NVE) caused by viridans streptococci, HACEK organisms, or enterococci (susceptible to synergistic therapy) survive
- For *S. aureus* NVE in patients who do not inject drugs, survival rates are 55–70%; survival rates are 85–90% among people who inject drugs (PWID)
  - 1-year mortality rises to 20–30% among PWID if substance use disorder is not successfully addressed
- Prosthetic valve endocarditis (PVE) beginning within 2 months after valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in late-onset cases
- In older patient populations with transcatheter aortic valve replacement (TAVR)-PVE, the in-hospital mortality is 35–50% and increases to 60–75% at 1 year

PATHOPHYSIOLOGY

- Endothelial resistance and injury
  - Normal endothelium → naturally resistant to bacterial colonization
  - Endothelial injury (causes include turbulent/high-velocity blood flow or structural lesions)

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        - Allows direct infection by particularly virulent bacteria (*e.g., Staphylococcus aureus*)
        - Promotes platelet–fibrin thrombus formation, known as nonbacterial thrombotic endocarditis (NBTE)
    - Transient bacteremia (e.g., from dental procedures, mucosal trauma, skin infections) enables bacteria to attach to NBTE lesions
- Cardiac and systemic conditions predisposing to NBTE
    - Structural heart lesions
        - Mitral regurgitation (especially with jet lesions)
        - Aortic stenosis
        - Aortic regurgitation
        - Ventricular septal defects (especially jet lesions on the low-pressure side)
        - Complex congenital heart disease (cyanotic and repaired lesions)
    - Hypercoagulable states
        - Malignancy → "marantic endocarditis" (sterile vegetations, often along valve closure lines)
        - Chronic diseases → hypercoagulability
        - Autoimmune diseases
            - SLE (Libman-Sacks endocarditis)
        - Antiphospholipid antibody syndrome (bland vegetations)
- Entry of microorganisms into the bloodstream
    - Sources
        - Colonized mucosal surfaces (oral cavity, respiratory tract, GI tract, genitourinary tract)
        - Sites of active infection (skin abscesses, urinary tract, pneumonia)
    - Organisms in circulation must resist innate immune defenses (complement, serum bactericidal activity, platelet microbicidal peptides)
- Adherence of bacteria to endothelium or thrombus
    - *S. aureus*
        - On intact endothelium → local inflammation induces von Willebrand factor (vWF) expression → binds platelets and *S. aureus*
        - On injured endothelium → fibrin + circulating vWF bind exposed subendothelial tissue → *S. aureus* directly adheres
    - Other bacteria preferentially adhere to NBTE lesions rather than intact surfaces
- Microbial surface adhesion molecules (MSCRAMMs)
    - Enable bacterial binding to extracellular matrix proteins (fibrin, fibrinogen, collagen, fibronectin)
    - Examples
        - Gram-positive bacteria → fibronectin-binding proteins (FnBPs)
        - *S. aureus*
            - Clumping factor → binds fibrinogen and fibrin
            - FnBPs → required for invasion of intact endothelium (may infect normal valves)
        - *Enterococcus faecalis*
            - Fibrinogen-binding proteins (Fss2)
            - Collagen-binding surface protein (Ace)
            - Ebp pili → mediate platelet binding and aggregation
        - Viridans streptococci/oral streptococci
            - Glucans (from sucrose metabolism)
            - FimA adhesin (oral mucosal binding)
- Vegetation formation
    - After adherence
        - Bacteria resist serum and platelet-derived microbicidal activity
        - Multiply into dense microcolonies
        - Trigger platelet aggregation and fibrin deposition via
            - Tissue factor release from endothelial cells
            - In *S. aureus*, tissue factor induction from monocytes
    - Infected vegetations consist of
        - Platelets + fibrin + layers of microorganisms
        - Organisms at surface = actively growing, shed into blood → persistent bacteremia
        - Organisms deep inside = metabolically dormant, shielded from immune attack and antimicrobials
- Clinical manifestations of infective endocarditis (IE)
    - Systemic/constitutional symptoms

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        - Fever, malaise, anorexia, weight loss → largely cytokine-mediated (interleukin 1, tumor necrosis factor α)
    - Cardiac damage
        - Valve destruction → regurgitation, HF
        - Abscess formation and conduction abnormalities
    - Embolic phenomena
        - Vegetation fragments → infarcts or secondary infections (brain, spleen, kidneys, lungs in right-sided IE)
    - Hematogenous spread
        - Bacteremia seeds distant sites (osteomyelitis, septic arthritis, abscesses)
    - Immune-mediated injury
        - Circulating immune complex deposition → glomerulonephritis, vasculitis, Osler's nodes, Roth's spots
        - Antibody responses to bacterial antigens contribute to tissue injury

RISK FACTORS

- While congenital heart diseases remain a constant predisposition, predisposing conditions in developed countries have shifted from chronic rheumatic heart disease (still common in developing countries) to
    - Injection drug use
    - Degenerative valve disease
    - Intracardiac devices
- Presence of an indwelling venous catheter
- Valvular disease
- Poor dentition
- Hemodialysis
- Diabetes mellitus
- Pacemakers
- Implantable cardioverter-defibrillators
- Risk factor for prosthetic valve endocarditis after transcatheter aortic valve replacement
    - Male sex
    - Diabetes
    - AKI and CKD
    - Moderate postimplantation aortic valve regurgitation

ADMITTING ORDERS

- Admit to floor or ICU
- Diagnosis: infective endocarditis
- Condition: serious
- Vital signs: vitals q4h until afebrile and stabilized for 24 h, then per routine
- Activity: as tolerated
- Nursing: daily weights, strict inputs/outputs, telemetry monitoring, frequent neurochecks
- Diet: regular or tailored to comorbidities
- Fluids: sepsis resuscitation if indicated
- Diagnostic tests
    - Blood cultures × 3 before antibiotics, then daily until cultures become sterile
    - CBC with differential
    - CMP
    - UA
    - Posterior-anterior/lateral CXR
    - ECG
    - Transthoracic or transesophageal echocardiogram based on clinical suspicion
    - Daily CBC until WBC count is normal
    - Daily CMP for monitoring of antibiotic toxicity effects
    - Monitoring of vancomycin and aminoglycoside levels
- Medications
    - Tylenol, 325–650 mg PO q4–6h as needed
    - Empirical antibiotic therapy (see Management section)
- Infectious disease consultation and, if indicated, cardiac surgery consult

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DISCHARGE INFORMATION

- For home IV antibiotic infusions
  - Ensure long-term vascular access is in place
  - Ensure patient/caregivers have been educated about line care and antibiotic infusion management
- Referral to addiction treatment and counseling for patients who inject drugs
- Education about endocarditis recurrence or metastatic complications, such as
  - Fevers and chills
  - Dyspnea and edema suggestive of new HF
  - Palpitations or dizziness suggestive of cardiac dysrhythmias, or
  - Neurologic events suggestive of systemic emboli
- Education about the need for antibiotic prophylaxis prior to dental procedures, if indicated
- Scheduled follow-up with primary care, cardiology, infectious disease, and cardiothoracic surgery (when indicated)
- Arrangement for lab monitoring of
  - Serum antimicrobial levels
  - CBCs
  - Creatinine
  - Liver enzymes

CASE ANSWERS

1. This patient is presenting with a subacute course of symptoms that are concerning for infective endocarditis (IE). He does not have a prosthetic heart valve but has aortic stenosis as a predisposing risk factor for native valve endocarditis (NVE). For NVE that is community-acquired, streptococci and *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) are the two most common organisms.
2. Adequate MRSA and streptococci coverage is indicated for this patient. A combination of vancomycin, 15 mg/kg IV q12h, and ceftriaxone, 2 g IV daily, provides appropriate antibiotic coverage.
3. The strength of evidence for surgical intervention of IE varies by the specific indication. Surgery for NVE confers a survival benefit, especially among those with the most pressing indications. Pressing indications that are required for optimal outcomes include:
   a. Moderate or severe HF or shock due to valve dysfunction
   b. Paravalvular extension of infection with abscess, fistula, or heart block
   c. Persistent bacteremia without an extracardiac cause despite 7–10 days of optimal antimicrobial therapy
   d. Lack of effective antimicrobial therapy
   e. Prosthetic valve endocarditis
   f. Partially dehisced unstable prosthetic valve

LANDMARK TRIALS

[1] Bai AD et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: Results from a large multicenter cohort study. Clin Infect Dis 60:1451, 2015. [PMID: 25701854]

- *Summary:* Infectious disease consultation is associated with better adherence to quality measures, reduced in-hospital mortality, and earlier discharge in patients with *Staphylococcus aureus* bacteremia.

[2] Iversen K et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 380:415, 2019. [PMID: 30152252]

- *Summary:* The POET trial showed that in patients with endocarditis of the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued IV antibiotic treatment.

[3] Suárez M et al. Comparison of dalbavancin with standard of care in the management of infective endocarditis: Efficacy, safety, and cost analysis. Int J Infect Dis 138:41, 2024. [PMID: 37931892]

- *Summary:* Dalbavancin could be a safe and effective option in the sequential treatment of patients with infective endocarditis (IE). Also, a cost reduction was detected due to a significant shortness of hospital stay.

[4] Kang DH et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 366:2466, 2012. [PMID: 22738096]

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- *Summary:* The EASE trial showed that early surgery compared with conventional treatment for IE and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.

FURTHER READING

- Cosgrove SE, Melia MT. Infective endocarditis, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- McDonald EG et al. Guidelines for Diagnosis and Management of Infective Endocarditis in Adults: A WikiGuidelines Group Consensus Statement. JAMA Netw Open 6:e2326366, 2023. [PMID: 37523190]

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43 Cellulitis

KEY POINTS

1. Cellulitis is an acute inflammatory condition of the skin caused by infection. A variety of bacteria cause it.
2. Symptoms of cellulitis often include pain, swelling, redness, and warmth at the affected area. Other signs may include fever, bullae formation, and lymphadenopathy.
3. The diagnosis of cellulitis can be challenging (given other conditions may mimic the appearance of cellulitis) and often requires a high level of suspicion. Lab tests such as Gram stain and culture can help identify the causative organism when the cellulitis is purulent. Imaging tests such as CT or MRI may be useful in determining the extent of the infection, such as in necrotizing fasciitis.
4. Treatment options depend on the specific infection and may include antibiotics, surgical drainage, and debridement of necrotic tissue. Antimicrobial agents are used to target specific pathogens based on the history and exam. Purulent cellulitis should cover MRSA with antibiotics.
5. Complications of cellulitis can be serious, with the potential for systemic toxicity, shock, multiorgan failure, and even death. The prognosis for cellulitis is generally positive, as most cases respond well to treatment. Certain serious infections (e.g., necrotizing fasciitis) have a poor prognosis.

EPIDEMIOLOGY & DEFINITIONS

This chapter will focus on cellulitis of the limbs in the spectrum of skin, soft tissue, and muscle infections. The differential diagnosis section will briefly discuss infections of the skin, soft tissue, and muscle other than cellulitis.

Cellulitis is observed most frequently among middle-aged and older adults. The incidence of cellulitis is ~ 200 cases per 100,000 patient-years and has a predilection for the warmer months in nontropical regions. The most common microorganisms causing cellulitis include β-hemolytic streptococci (groups A, B, C, G, and F) with group A *Streptococcus* or *Streptococcus pyogenes* most commonly identified in some series. *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), is a notable but less common cause. Gram-negative bacilli are identified in a minority of cases.

Cellulitis: an acute inflammatory condition of the skin that is characterized by localized pain, erythema, swelling, and heat.

Purulent infections: cellulitis caused by *S. aureus* (methicillin-susceptible *S. aureus* [MSSA] or MRSA) that spreads from a central localized infection, such as an abscess, folliculitis, or an infected foreign body.

Nonpurulent cellulitis: cellulitis that is a more rapidly diffuse and spreading process, is frequently associated with lymphangitis and fever and is more common with *S. pyogenes*.

CLINICAL VIGNETTE

A 54-year-old woman presents to the ED with right lower extremity pain and fever that have been progressively worsening over the last 3 days. She denies any trauma to the leg. Her medical history includes HF with bilateral venous stasis, insulin-dependent type 2 diabetes, and hypertension. She has been compliant with all of her medications, including her diuretic. She has not had exposure to hot tubs or salt/freshwater.

On physical exam, the temperature is 38.4°C (101.2°F), heart rate is 106 beats/min, respiratory rate is 18 breaths/min, BP is 124/82 mm Hg, and Spo_2 is 96% on room air. She appears tired but is neurologically intact. The right leg has erythema, warmth, 2+ edema, and pain to palpation from the proximal ankle to the mid-shin circumferentially. There is an open ulcer on the right posterior calf with light-colored seeping drainage but no evidence of an abscess. Sensation of the right leg is intact. The left leg has redness that appears chronic, with trace edema and no ulcers and is not tender to palpation.

Initial lab data reveal:

- WBC count: 14,500 cells/μL
- Hemoglobin: 9.8 g/dL
- Platelets: 180,000/μL
- SCr: 2.1 mg/dL (baseline 1.3 mg/dL)

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- BUN: 43 mg/dL
- Lactic acid: 2.5 mmol/L

The ED calls you to admit the patient for sepsis secondary to cellulitis and asks what antibiotic they should start.

GUIDING QUESTIONS

1. Is this a purulent or nonpurulent cellulitis? What are the most common microorganisms associated with this type of cellulitis?
2. What risk factors does this patient have for developing cellulitis?
3. What empirical antibiotic(s) would you suggest the ED start(s)? Should the ED provide any other early adjunctive management?
4. What parameters would allow you to deescalate the patient from IV to oral antibiotics during this hospitalization?

HISTORY

The classic symptoms of inflammation from cellulitis are explained by rubor (redness), tumor (swelling), calor (warmth), and dolor (pain). If you observe symptoms of cellulitis, it is important to ask questions about how this infection was acquired. Indigenous flora colonizing the skin and appendages (e.g., *Staphylococcus aureus*, *Streptococcus pyogenes*) may penetrate tissues through open cuts, sores, cracks in the skin, abrasions, burns, insect bites, surgical incisions, and IV catheters. Exogenous bacteria cause cellulitis through unique niches in nature; therefore, a thorough history (including epidemiologic data) offers important clues to etiology. Cultures can provide some guidance toward the etiology, but cultures are positive in only 20% of cases, making the history important. Signs of systemic toxicity (fever, rapid heart rate, and encephalopathy) should be assessed. Orbital cellulitis can lead to devastating consequences of proptosis, blindness, septic cavernous sinus thrombosis, and meningitis.

HISTORY OF PRESENT ILLNESS

- COLIDDERRS (*C*haracter, *O*nset, *L*ocation, *I*ntensity, *D*escription, *D*uration, *E*xacerbating factors, *R*elieving factors, *R*adiation, associated *S*igns/symptoms—or use your preferred mnemonic)
  - A patient with chronic edema, ulcer, puncture, or laceration who has an area on the skin that is hot and tender and has clear demarcations or lymphangitic streaking
- Painful?
  - Cellulitis and other skin and soft tissue infections are painful
- Is the lesion spreading?
  - Where did it start?
  - How fast has it spread?
- Fever/chills?
  - Signs of systemic infection and possible sepsis
- Bites?
  - What kind of animal (may change antibiotic choice)
    - Cat bites → *Pasteurella multocida*
    - Dog bites → *P. multocida, Streptococcus intermedius*, and *Capnocytophaga canimorsus*
    - Human and dog bites → above organisms plus anaerobic organisms of *Fusobacterium*, *Bacteroides*, aerobic and anaerobic streptococci, and *Eikenella corrodens*
- Puncture wound?
  - What made the puncture?
  - How deep was the puncture?
    - *Pseudomonas* is introduced into the deep tissues following penetrating injuries, such as when someone steps on a nail
- Drainage from the lesion?
  - Describe the draining material
  - When did it start, and has it changed?
- Nausea and vomiting?
  - Common symptom of cellulitis and systemic illness
- Hot tub use?
  - Can lead to hot tub folliculitis, especially in patients with diabetes mellitus (caused by *Pseudomonas*)
- Salt, freshwater, and/or fish/oyster exposure?
  - Can acquire infections by specific organisms
    - *Erysipelothrix* (fish, swine)
    - *Mycobacterium marinum* (fish, fish tanks, swimming pools, boat hulls)

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        - *Vibrio vulnificus* (brackish water, uncooked shellfish, especially in patients with cirrhosis)
        - *Aeromonas hydrophilia* (an aggressive cellulitis and occasionally necrotizing fasciitis in tissues surrounding lacerations sustained in freshwater, such as lakes, rivers, and streams)
- Gardening?
    - *Sporothrix* can be a concern if exposed to dirt, such as through rose thorn puncture
- Numbness?
    - Can have numbness in certain infections, such as necrotizing fasciitis
    - Patients with diabetes mellitus may have neuropathy, causing less pain to the cellulitis site
- If concern for orbital cellulitis
    - Pain of the eye?
    - Proptosis?
    - Limited eye movements?
    - Decreased vision?
    - Recent upper respiratory tract infection?

PAST MEDICAL HISTORY

- History of cellulitis?
    - Cellulitis recurrence is common, especially with lymphedema (either post-surgical or congenital)
- History of methicillin-resistant *Staphylococcus aureus* (MRSA)?
    - More susceptible to recurrent MRSA infection
- History of peripheral vascular disease?
    - Can look like cellulitis but is also a risk factor for infections, as immune cells are not able to penetrate tissues as effectively
- History of venous stasis?
    - Can look like cellulitis if venous stasis ulcers develop, but is also a risk factor for infections
    - Venous stasis is a bilateral manifestation in the lower extremities, and cellulitis is very rarely (if ever) a bilateral lower extremity process
- History of HF?
    - Can lead to chronic lower extremity edema and venous stasis ulcers that may mimic the appearance of cellulitis
- History of diabetes mellitus?
    - More susceptible to *Pseudomonas* infections, osteomyelitis
    - May have neuropathy in which the patient may not be able to feel a developing wound or cellulitis
- History of an immunocompromised state (HIV/AIDS, malignancy, autoimmune conditions, steroid use, organ transplantation)?
    - Gram-negative bacilli, including *P. aeruginosa*, are common amongst hospitalized and immunocompromised patients

SURGICAL HISTORY

- Cellulitis of recent surgical sites is a risk factor for *S. aureus* (MSSA or MRSA) cellulitis

SOCIAL HISTORY

- Alcohol, smoking, recreational drugs (injection drug use)
- Occupation
- Living situation
- Sexual history
- Recent travel history and exposure to epidemiologic risk factors

PHYSICAL EXAM

Vital signs, mental status, and toxicity of the patient are important in the initial exam. Also, if there is a wound, examining it for purulent secretions, abscess, and visibility of bone is important to distinguish between purulent and nonpurulent cellulitis or osteomyelitis. Lymphangitic streaking, rapid spread, and systemic toxicity are more common for *Streptococcus pyogenes* infection but can occur in any cellulitis.

- Vital signs
    - Evaluate for fever, tachycardia, hypotension
        - Signs of sepsis and systemic toxicity

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- Skin and musculoskeletal
  - Purulent drainage or exudate?
    - More likely a sign of *S. aureus* infection (either methicillin-susceptible or methicillin-resistant *S. aureus* [MSSA or MRSA]) for which empirical MRSA coverage should be used initially
  - Abscess? Carbuncle?
    - Sign of infection that may need drainage
  - Ulcers?
    - Ulcers may be present in cellulitis, but they can also be present in venous stasis
  - Spreading?
    - It is common to mark the "lines of demarcation" to assess whether the infection is spreading quickly (**Fig. 43-1**)
  - Lymphangitic involvement?
    - Lymphangitic spreading is more common in *S. pyogenes* infection
  - Puncture marks?
    - Can change the type of antibiotic chosen, especially if what type of animal bit them is known
  - Heat?
    - Sign of infection; if absent, consider noninfectious etiologies
  - Tenderness to palpation?
    - Cellulitis is tender to palpation, whereas venous stasis is not
  - Is the redness bilateral?
    - Cellulitis is rarely a bilateral process
    - Assess for venous stasis (including stasis ulcers) or peripheral arterial disease as an alternative cause
  - Evaluate pulses
    - Need to make sure pulses are present, as absence may make antibiotics ineffective and may need surgical evaluation
- HEENT
  - For concern of orbital cellulitis
    - Painful eye movements?
    - Cranial nerve abnormalities of eye movement?
    - Swelling and proptosis?
- Neurologic
  - Mental status exam
    - Altered mental status may be a sign of systemic infection



FIGURE 43-1 Nonpurulent cellulitis. (Used with permission from Lindy Fox, MD.) (Used with permission from Rojek NW, Worswick S. Cellulitis, in *Current Medical Diagnosis & Treatment 2026,* MA Papadakis et al (eds). New York, McGraw Hill, 2026.)

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DIFFERENTIAL DIAGNOSIS & ETIOLOGY

DIFFERENTIAL DIAGNOSIS

When considering the differential diagnosis of cellulitis, it is important to understand the structural components of the skin and soft tissues and which layers are affected by infection types (Fig. 43-2). Infections can be present in the most superficial layers (e.g., erysipelas) to the deeper structures (e.g., myositis).

- Common noninfectious conditions to consider in the differential diagnosis of cellulitis
  - Venous stasis (and venous stasis ulcers)
    - Bilateral leg swelling with redness and potentially the development of venous stasis ulcers, which can be painful
    - Does not have warmth, and may worsen in states of increased venous pressure (e.g., HF exacerbation)
  - Edema from HF
    - Pitting edema of the lower extremities without warmth or erythema (unless associated with venous stasis)
    - Typically nonpainful on palpation
  - Lymphedema
    - Initially is soft, but over time becomes hardened and nonpitting; associated with discoloration, verrucous (wart-like) hyperplasia, hyperkeratosis, papillomatosis, dermal thickening and grainy appearance, and ulcers
    - Can be unilateral or bilateral depending on the lymphatic obstruction location
    - Is rarely warm to the touch but can predispose patients to developing cellulitis
  - DVT
    - Unilateral limb swelling and edema that is tender to the touch and can be warm
    - Primarily does not present with systemic symptoms
  - Contact dermatitis
    - Erythema and edema with pruritus, vesicles, bullae, weeping, or crusting
    - Associated with an irritant contact and can be acute or chronic
  - Erythema nodosum
    - An acute inflammatory condition (panniculitis) causing tender, warm, red or purplish bumps or nodules to form under the skin, most commonly on the shins
    - Associated with streptococcal infections, tuberculosis, fungal infections, sarcoidosis, and inflammatory bowel disease
  - Hematoma
    - Presents with pain, swelling, redness, and possibly an open wound
    - Associated usually with trauma

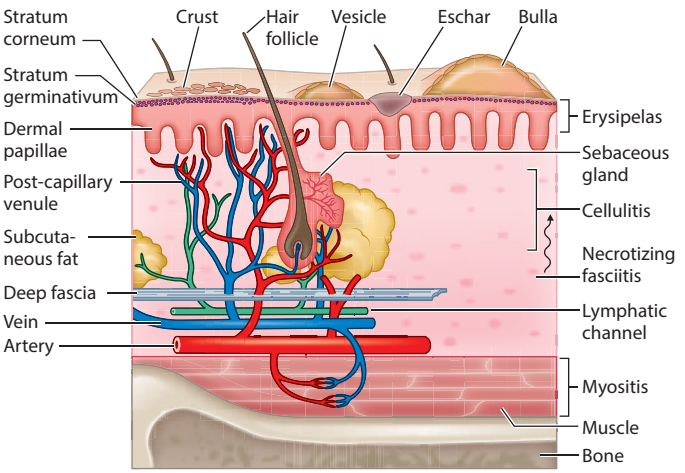

FIGURE 43-2 Structural components of the skin and soft tissues, superficial infections, and infections of the deeper structures. The rich capillary network beneath the dermal papillae plays a key role in the localization of infection and in the development of the acute inflammatory reaction. (Reproduced with permission from Stevens DL, Bryant AE. Infections of the skin, muscles, and soft tissues, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- Calciphylaxis
  - Painful livedo reticularis and subcutaneous nodules that advance to patches of ischemic necrosis
  - Observed in patients with CKD, severe hyperparathyroidism, and warfarin administration

ETIOLOGY

- *The initial question for cellulitis is* Staphylococcus aureus *(including methicillin-resistant* S. aureus *[MRSA]) or not* S. aureus
  - Purulent infections are more likely *S. aureus* (including MRSA)
  - Nonpurulent infections are more likely from *Streptococcal* species or from microorganisms other than *S. aureus*
- *Streptococcus pyogenes*
- *Pasteurella* (cat/dog bite)
- *Eikenella* (dog and human bites)
- *Fusobacterium* (human and dog bites)
- *Bacteroides* (human and dog bites)
- *Aeromonas hydrophilia* (lacerations sustained in freshwater, such as lakes, rivers, and streams)
- *Pseudomonas* (hot tub use, diabetes, penetrating wound, subtropical climate with water exposure)
- *Erysipelothrix* (fish, swine)
- *Mycobacterium marinum* (fish, fish tanks, swimming pools, boat hulls)
- *Vibrio vulnificus* (salt or fresh water or raw shellfish exposure in a cirrhotic patient)
- *Mycobacterium fortuitum* (footbaths/pedicures, recent shaving)

Findings on physical exam can give clues to the pathogenic cause (including viral infections) of skin and soft tissues of cellulitis and other types of skin, soft tissue, and muscle infections (Table 43-1).

TABLE 43-1 Skin and Soft Tissue Infections

LESION, CLINICAL SYNDROME	INFECTIOUS AGENT(S)
Vesicles	
Smallpox	Variola virus
Chickenpox	Varicella-zoster virus
Shingles (herpes zoster)	Varicella-zoster virus
Cold sores, herpetic whitlow, herpes gladiatorum	Herpes simplex virus
Hand-foot-and-mouth disease	Coxsackievirus A16
Orf	Parapoxvirus
Molluscum contagiosum	Molluscum contagiosum poxvirus
Rickettsialpox	*Rickettsia akari*
Blistering distal dactylitis	*Staphylococcus aureus* or *Streptococcus pyogenes*
Bullae	
Staphylococcal scalded-skin syndrome	*S. aureus*
Necrotizing fasciitis	*S. pyogenes*, *Clostridium* spp., mixed aerobes and anaerobes
Gas gangrene	*Clostridium* spp.
Halophilic *Vibrio*	*Vibrio vulnificus*
Crusted lesions	
Bullous impetigo/ecthyma	*S. aureus*
Impetigo contagiosa	*S. pyogenes*
Ringworm	Superficial dermatophyte fungi
Sporotrichosis	*Sporothrix schenckii*
Histoplasmosis	*Histoplasma capsulatum*
Coccidioidomycosis	*Coccidioides immitis* or *posadasii*
Blastomycosis	*Blastomyces dermatitidis*
Cutaneous leishmaniasis	*Leishmania* spp.
Cutaneous tuberculosis	*Mycobacterium tuberculosis*
Nocardiosis	*Nocardia* spp.
Folliculitis	
Furunculosis	*S. aureus*
Hot-tub folliculitis	*Pseudomonas aeruginosa*

(*Continued*)

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TABLE 43-1 Skin and Soft Tissue Infections (*Continued*)

LESION, CLINICAL SYNDROME	INFECTIOUS AGENT(S)
Swimmer's itch	*Schistosoma* spp.
Acne vulgaris	*Propionibacterium acnes*
Papular and nodular lesions	
Fish-tank or swimming-pool granuloma	*Mycobacterium marinum*
Creeping eruption (cutaneous larva migrans)	*Ancylostoma braziliense*
Dracunculiasis	*Dracunculus medinensis*
Cercarial dermatitis	*Schistosoma mansoni*
Verruca vulgaris	Human papillomaviruses 1, 2, 4
Condylomata acuminata (anogenital warts)	Human papillomaviruses 6, 11, 16, 18
Onchocerciasis nodule	*Onchocerca volvulus*
Cutaneous myiasis	*Dermatobia hominis*
Verruca peruana	*Bartonella bacilliformis*
Cat-scratch disease	*Bartonella henselae*
Lepromatous leprosy	*Mycobacterium leprae*
Secondary syphilis (papulosquamous and nodular lesions, condylomata lata)	*Treponema pallidum*
Tertiary syphilis (nodular gummatous lesions)	*T. pallidum*
Ulcers with or without eschars	
Anthrax	*Bacillus anthracis*
Ulceroglandular tularemia	*Francisella tularensis*
Bubonic plague	*Yersinia pestis*
Buruli ulcer	*Mycobacterium ulcerans*
Leprosy	*M. leprae*
Cutaneous tuberculosis	*M. tuberculosis*
Chancroid	*Haemophilus ducreyi*
Primary syphilis	*T. pallidum*
Erysipelas	*S. pyogenes*
Cellulitis	*Staphylococcus* spp., *Streptococcus* spp., various other bacteria
Necrotizing fasciitis	
Streptococcal gangrene	*S. pyogenes*
Fournier gangrene	Mixed aerobic and anaerobic bacteria
Staphylococcal necrotizing fasciitis	Methicillin-resistant *S. aureus*
Myositis and myonecrosis	
Pyomyositis	*S. aureus*
Streptococcal necrotizing myositis	*S. pyogenes*
Gas gangrene	*Clostridium* spp.
Nonclostridial (crepitant) myositis	Mixed aerobic and anaerobic bacteria
Synergistic nonclostridial anaerobic myonecrosis	Mixed aerobic and anaerobic bacteria

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DIAGNOSTIC TESTS

LABS

- Blood cultures × 2 if sepsis or systemic toxicity is present
- CBC with diff
  - Leukocytosis, anemia, and neutrophilic shift support an infectious cause
- BMP
  - Assess for electrolyte and kidney function abnormalities
- Lactic acid
  - May indicate tissue hypoxia and severe illness
- ESR and CRP
  - Aid in ruling out noninfectious causes of presentation

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- Gram stain and culture
  - When there is drainage, an open wound, or an obvious portal of entry, Gram stain and culture can provide a definitive diagnosis
  - Otherwise, without drainage, an open wound, or obvious portal of entry, needle aspiration of the leading edge or biopsy of the cellulitis itself leads to positive cultures in only 20% of cases

IMAGING

- Not all patients need imaging for cellulitis
- Consider an x-ray to assess for osteomyelitis, if indicated, and further delineation with MRI
- CT can be useful in assessing for gas gangrene, necrotizing fasciitis, abscess, and osteomyelitis
- CT of the orbits may be necessary in the evaluation of orbital cellulitis

MANAGEMENT

ADMITTING CRITERIA

- Admit the patient if any of the following are present
  - Signs of sepsis and systemic toxicity or concern about rapidly spreading infection
  - The patient is unable to keep the affected leg elevated (if leg infection)
  - The patient is unable to tolerate oral antibiotics (e.g., from nausea and vomiting)
  - The patient has attempted oral antibiotics but the infection is worsening (failure of oral antibiotics)
  - Unreliable living environment or concern with adherence to oral antibiotics

ANTIBIOTIC THERAPY

- Table 43-2 describes common diagnoses, conditions, and their primary and alternative empirical treatment regimens
- In general, duration of therapy for cellulitis is 5–7 days
  - May need to extend duration if the infection is severe and/or clinical improvement is not rapid
- All antibiotics have specific adverse effects
  - Clindamycin and fluoroquinolones pose a risk for *Clostridioides difficile* infection (see Chap. 40)
- Transition to oral therapy can occur with
  - The resolution of systemic symptoms
  - A WBC count that has fallen toward normal levels, and
  - Improvement in skin appearance

PURULENT CELLULITIS

- Methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) coverage are empirically needed at first
  - Tailor therapy if cultures provide specific organism data
- Empirical IV antibiotic options for extensive disease and/or signs of systemic toxicity
  - Vancomycin, or
  - Linezolid, 600 mg q12h
- Oral antibiotics that provide MRSA coverage
  - Clindamycin, 300 mg qid
  - Trimethoprim-sulfamethoxazole, 1–2 double-strength tablets bid
  - Doxycycline, 100 mg bid
  - Linezolid, 600 mg bid
- If associated with an abscess, incision and drainage may be necessary for source control

NONPURULENT CELLULITIS

- More likely, the infection is from *Streptococcus* or MSSA
  - Less likely a MRSA infection
- Empirical IV antibiotic options for extensive disease and/or signs of systemic toxicity
  - Nafcillin, 1–2 g q4h
  - Oxacillin, 1–2 g q4h
  - Ceftriaxone, 1–2 g daily
  - Cefazolin, 1–2 g q8h
- Oral antibiotic options that cover *Streptococcus* or MSSA
  - Cefpodoxime, 400 mg bid
  - Cephalexin, 500 mg qid

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TABLE 43-2 Treatment of Common Infections of the Skin

DIAGNOSIS/CONDITION	PRIMARY TREATMENT	ALTERNATIVE TREATMENT
Animal bite (prophylaxis or early infection)[a]	Amoxicillin–clavulanate (875/125 mg PO bid)	Doxycycline (100 mg PO bid)
Animal bite[a] (established infection)	Ampicillin–sulbactam (1.5–3 g IV q6h)	Clindamycin (600–900 mg IV q8h) *plus* Ciprofloxacin (400 mg IV q12h) *or* cefoxitin (2 g IV q6h)
Bacillary angiomatosis	Erythromycin (500 mg PO daily)	Doxycycline (100 mg PO bid)
Herpes simplex (primary genital)	Acyclovir (400 mg PO tid for 10 days)	Famciclovir (250 mg PO tid for 5–10 days) *or* valacyclovir (1000 mg PO bid for 10 days)
Herpes zoster (immunocompetent host > 50 years of age)	Acyclovir (800 mg PO five times daily for 7–10 days)	Famciclovir (500 mg PO tid for 7–10 days) *or* valacyclovir (1000 mg PO tid for 7 days)
Cellulitis (staphylococcal or streptococcal[b,c])	Nafcillin or oxacillin (2 g IV q4–6h)	Cefazolin (1–2 g q8h) *or* ampicillin/sulbactam (1.5–3 g IV q6h) *or* erythromycin (0.5–1 g IV q6h) *or* clindamycin (600–900 mg IV q8h)
Methicillin-resistant *Staphylococcus aureus* skin infection[d]	Vancomycin (1 g IV q12h)	Linezolid (600 mg IV q12h)
Necrotizing fasciitis (group A streptococcal[b])	Clindamycin (600–900 mg IV q6–8h) *plus* penicillin G (4 million units IV q4h)	Clindamycin (600–900 mg IV q6–8h) *plus* a cephalosporin (first- or second-generation)
Necrotizing fasciitis (mixed aerobes and anaerobes)	Ampicillin (2 g IV q4h) *plus* clindamycin (600–900 mg IV q6–8h) *plus* ciprofloxacin (400 mg IV q6–8h)	Vancomycin (1 g IV q6h) *plus* metronidazole (500 mg IV q6h) *plus* ciprofloxacin (400 mg IV q6–8h)
Gas gangrene	Clindamycin (600–900 mg IV q6–8h) *plus* penicillin G (4 million units IV q4–6h)	Clindamycin (600–900 mg IV q6–8h) *plus* cefoxitin (2 g IV q6h)

[a]*Pasteurella multocida,* a species commonly associated with both dog and cat bites, is resistant to cephalexin, dicloxacillin, clindamycin, and erythromycin. *Eikenella corrodens*, a bacterium commonly associated with human bites, is resistant to clindamycin, penicillinase-resistant penicillins, and metronidazole but is sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones. [b]The frequency of erythromycin resistance in group A *Streptococcus* is currently ~ 5% in the United States but has reached 70–100% in some other countries. Most, but not all, erythromycin-resistant group A streptococci are susceptible to clindamycin; clindamycin-resistant group A streptococci are susceptible to linezolid and to tedizolid. Approximately 90% of *Staphylococcus aureus* strains are sensitive to clindamycin, but resistance—both intrinsic and inducible—is increasing. [c]Severe hospital-acquired *S. aureus* infections or community-acquired *S. aureus* infections that are not responding to the β-lactam antibiotics recommended in this table may be caused by methicillin-resistant strains, requiring vancomycin, daptomycin, or linezolid or tedizolid. [d]Some strains of methicillin-resistant *S. aureus* (MRSA) remain sensitive to tetracycline and trimethoprim-sulfamethoxazole. Daptomycin (4 mg/kg IV q24h) or tigecycline (100-mg loading dose followed by 50 mg IV q12h) is an alternative treatment for MRSA.
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- Dicloxacillin, 500 mg qid
- Clindamycin, 300 mg qid

CELLULITIS FROM ANIMAL OR HUMAN BITES

- Ampicillin-sulbactam, 1.5–3g IV q6h, for extensive disease and/or signs of systemic toxicity
- Amoxicillin–clavulanic acid, 875/125 mg PO bid
- All human bites require amoxicillin–clavulanic acid

ORBITAL CELLULITIS

- Initially cover MRSA and *Streptococcus* with combination therapy of
  - IV vancomycin plus either
    - Ceftriaxone, 2 g IV daily and metronidazole, 500 mg tid, or
    - Ampicillin-sulbactam, 3 g IV q6h
- Ophthalmology consultation is indicated for potential surgical intervention

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SPECIFIC MICROORGANISM TREATMENTS

- *Aeromonas hydrophila*
  - Aminoglycosides
  - Fluoroquinolones
  - Chloramphenicol
  - Trimethoprim-sulfamethoxazole, or
  - Third-generation cephalosporins
- *Pseudomonas aeruginosa*
  - Surgical incision and drainage when necessary, along with
    - An aminoglycoside
    - A third- or fourth-generation cephalosporin (e.g., ceftazidime, cefoperazone, or cefepime)
    - Piperacillin-tazobactam, or
    - A fluoroquinolone
  - Empirical antibiotic coverage of *Pseudomonas* in cellulitis is rarely necessary unless culture-proven *Pseudomonas* or significant risk factors (e.g., penetrating foot wound in a patient with diabetes, subtropical climate with exposure of water to the infection)
- *Erysipelothrix rhusiopathiae*
  - β-Lactams (including penicillin), erythromycin, clindamycin, tetracycline, or cephalosporins
- *Mycobacterium marinum*
  - Ethambutol and either clarithromycin or azithromycin
- *Vibrio vulnificus*
  - Tetracycline therapy
- *Sporothrix*
  - Itraconazole, 200 mg PO daily
  - Treatment should be continued for 2–4 weeks after all lesions have resolved

ANCILLARY TREATMENTS

- Sepsis fluid resuscitation if indicated
- Leg elevation
- Wound dressing/cleaning
- Aggressive risk factor management of
  - Arterial insufficiency
  - Diabetes mellitus
  - Venous stasis
  - Obesity
- Treatment of chronic fungal infections, if present
- Compression stocking to the affected leg
  - In patients with chronic edema of the leg and cellulitis, compression therapy resulted in a lower incidence of recurrence of cellulitis than conservative treatment [1]
- In patients with several recurrent episodes of cellulitis, some patients may benefit from eradication of colonization (e.g., for *S. aureus* skin abscess, 1–4 weeks of doxycycline, rifampin, topical mupirocin to the nares, and chlorhexidine oral rinse and bleach baths during the last week of antibiotic therapy have been successful to prevent recurrent abscesses) [2]
  - When eradication is not feasible (e.g., chronic wounds and drug interactions with rifampin), then chronic antibiotic administration for several months may decrease the frequency of episodes

COMPLICATIONS

- Abscess formation
- Bacteremia, sepsis, endocarditis, and septic shock
- Chronic edema and lymphedema
- Loss of limb or life in severe infections (e.g., necrotizing fasciitis)
- Orbital cellulitis can lead to devastating consequences of
  - Proptosis
  - Blindness
  - Septic cavernous sinus thrombosis
  - Meningitis
- Recurrent cellulitis
- Suppurative thrombophlebitis

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PROGNOSIS

- The prognosis for cellulitis is generally positive, as most cases respond well to treatment
- Very mild cases may resolve on their own within a few days, but most require appropriate antibiotic treatment
- Symptoms typically improve within 3–5 days, with infections usually clearing up in ~ 10 days if antibiotics are taken as prescribed

PATHOPHYSIOLOGY

- A breach in the skin barrier allows bacterial colonization and invasion
  - Trauma (cuts, abrasions, lacerations, burns, surgical wounds)
  - Skin conditions (eczema, athlete's foot, ulcers)
  - Insect bites, animal bites, or injection sites
  - Provides an entry point for microorganisms, most commonly *Streptococcus pyogenes* and *S. aureus*
- Bacterial colonization and invasion
  - Bacteria adhere to extracellular matrix proteins (fibronectin, laminin, collagen)
  - Enzymes are produced (hyaluronidase, streptokinase, lipases, proteases) and degrade connective tissue barriers
  - Toxins and virulence factors facilitate deeper spread into the dermis and subcutaneous fat
- Immune system activation
  - The innate immune response is triggered by pathogen-associated molecular patterns (PAMPs)
  - Activation of the complement system → opsonization and chemotaxis
  - Recruitment of neutrophils and macrophages to the site of infection
  - Release of proinflammatory cytokines (interleukin [IL]-1, tumor necrosis factor α, IL-6) and chemokines
- Inflammatory changes in the tissues
  - Vasodilation → erythema and warmth
  - Increased vascular permeability → plasma leakage → swelling and edema
  - Neutrophil infiltration → tissue damage, pain, and tenderness
  - The lymphatic system may become involved → lymphangitis (red streaking) and lymphadenitis (tender nodes)
- Clinical manifestations
  - Local: erythema, heat, edema, tenderness, and ill-defined borders
  - Systemic: fever, malaise, and leukocytosis when the infection spreads or the immune response is strong
- Complications if uncontrolled infection
  - Localized: abscess formation and suppurative thrombophlebitis
  - Systemic: bacteremia, sepsis, endocarditis
  - Severe tissue involvement: necrotizing fasciitis
  - Chronic changes: recurrent cellulitis can cause lymphatic damage and chronic lymphedema

RISK FACTORS

- Chronic dermatophyte infections
- Chronic limb edema
- History of cellulitis
- Immunocompromised states
- Injection drug use
- Lymphedema
- Obesity and diabetes
- Peripheral arterial disease
- Skin breaks
- Venous insufficiency

ADMITTING ORDERS

- Admit to the medicine floor or ICU
- Diagnosis: cellulitis
- Condition: guarded
- Vital signs: q4h until stable
- Activity: ad lib
- Nursing: call for temperature > 38.5°C, heart rate > 110 beats/min, systolic BP < 100 mm Hg, or changing neurologic status

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- Diet: adjusted to comorbidities
- Fluids: sepsis fluid resuscitation if indicated
- Diagnostic tests
  - Blood cultures × 2 before antibiotics if sepsis or systemic infection are present
  - CBC with differential
  - BMP
  - ESR and CRP
  - Lactic acid
  - Culture of wound
  - X-ray, CT, or MRI of the affected site may be necessary to rule out an abscess, osteomyelitis, or necrotizing fasciitis
- Medications
  - Empirical antibiotics are chosen based on the impression of the most likely pathogen causing infection (see Management section)

DISCHARGE INFORMATION

- Transition to oral antibiotics with
  - Resolution of systemic symptoms
  - A WBC count that has fallen toward normal levels, and
  - Improvement in skin appearance
- Education and appropriate management of predisposing factors, such as
  - Diabetes mellitus
  - Arterial insufficiency
  - Venous stasis, and
  - Fungal infections
- Compression stocking supplies and education for cellulitis associated with chronic leg edema
- Follow up with primary care in 10–14 days to
  - Confirm resolution of infection
  - Assess for complications of antibiotic therapy
  - Educate about preventative measures, including wound care

CASE ANSWERS

1. This cellulitis does not have a central localized infection, such as an abscess, folliculitis, or an infected foreign body, making it a nonpurulent cellulitis. *Streptococcal* infections (including β-hemolytic streptococci [groups A, B, C, G, and F] with group A *Streptococcus* or *S. pyogenes*) are the most common microorganisms associated with a nonpurulent cellulitis.
2. Risk factors in this patient for developing cellulitis include chronic edema of the leg (from both HF and bilateral venous stasis) and diabetes mellitus. With her history of cardiac disease, diabetes mellitus, and hypertension, she may have underlying peripheral arterial disease as well.
3. IV nafcillin, oxacillin, ceftriaxone, or cefazolin would be an appropriate empirical antibiotic therapy for a nonpurulent cellulitis presenting with sepsis and systemic toxicity. Because this patient is presenting with sepsis, the ED should also provide 30 mL/kg of either IV NS or LR.
4. Transition to oral antibiotics can occur with resolution of systemic symptoms, a WBC count that has fallen toward normal levels, and improvement in skin appearance.

LANDMARK TRIALS

[1] Webb E et al. Compression therapy to prevent recurrent cellulitis of the leg. N Engl J Med 383:630, 2020. [PMID: 32786188]
  - *Summary:* In this small, single-center, nonblind trial involving patients with chronic edema of the leg and cellulitis, compression therapy resulted in a lower incidence of recurrence of cellulitis than conservative treatment.

[2] Fritz SA et al. Effectiveness of measures to eradicate *Staphylococcus aureus* carriage in patients with community-associated skin and soft-tissue infections: A randomized trial. Infect Control Hosp Epidemiol 32:872, 2011. [PMID: 21828967]

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- *Summary:* An inexpensive regimen of dilute bleach baths, intranasal mupirocin, and hygiene education effectively eradicated *Staphylococcus aureus* over 4 months. High rates of recurrent skin and soft tissue infection suggest factors other than endogenous colonization as important determinants of infection.

FURTHER READING

- Baddour LM. Cellulitis and skin abscess: Epidemiology, microbiology, clinical manifestations, and diagnosis. UpToDate. https://www.uptodate.com/contents/cellulitis-and-skin-abscess-epidemiology-microbiology-clinical-manifestations-and-diagnosis. Accessed February 6, 2026.
- Raff AB, Kroshinsky D. Cellulitis: A review. JAMA 316:325, 2016. [PMID: 27434444]
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49 Inpatient Diabetes Management

CLINICAL VIGNETTE

A 55-year-old man is admitted to the hospital for pneumonia. He has type 2 diabetes mellitus with a recent hemoglobin A_{1c} of 10.5%. He takes metformin, glimepiride, insulin glargine 20 U every evening, and insulin aspart 7 U tid with meals at home. He has been adherent with his medications. His SCr is 1.0 mg/dL, and his current blood glucose is 320 mg/dL. His labs do not show signs of diabetic ketoacidosis. He weighs 80 kg. A consistent carbohydrate-controlled diet is started.

GUIDING QUESTIONS

1. Would you resume this patient's metformin and glimepiride while admitted to the hospital?
2. What is the goal glucose level range while the patient is hospitalized?
3. What initial insulin doses (basal and bolus) would you order for this patient's insulin regimen while hospitalized?
4. After 24 h in the hospital, the patient received a total of 12 U of correctional insulin for hyperglycemia. How would you adjust his insulin regimen?
5. On day 2 of hospitalization, the pulmonary consult team informs you that they want to perform a bronchoscopy on day 3. They ask you to make the patient NPO at midnight. How would you adjust the patient's insulin regimen while NPO?

BACKGROUND INFORMATION

- Optimal glycemic goals for hospitalized patients are incompletely defined
  - The NICE-SUGAR trial found an increased mortality rate and a greater number of episodes of severe hypoglycemia with very strict glycemic control (target blood glucose of 81–108 mg/dL) compared to individuals with a more moderate glycemic goal (target blood glucose of 180 mg/dL)
    - These patients were critically ill in the ICU, and many were mechanically ventilated
  - The American Diabetes Association suggests the following glycemic goals for hospitalized patients
    - In critically or noncritically ill patients, glucose of 140–180 mg/dL
    - In select patients, glucose of 110–140 mg/dL with avoidance of hypoglycemia
    - The target range in the perioperative period should be 80–180 mg/dL
- General anesthesia, surgery, infection, or concurrent illness raises the levels of counterregulatory hormones (cortisol, growth hormone, catecholamines, and glucagon) and cytokines that may lead to transient insulin resistance and hyperglycemia in hospitalized patients
  - These factors increase insulin requirements by increasing glucose production and impairing glucose utilization and thus may worsen glycemic control
- Concurrent illness or surgical procedures may lead to variable insulin absorption and also prevent the patient with diabetes mellitus from eating normally and, thus, may promote hypoglycemia
- *Hypoglycemia is frequent in hospitalized patients, and many of these episodes are avoidable*
  - Hospital systems should have a diabetes management protocol to avoid inpatient hypoglycemia
  - Measures to reduce or prevent hypoglycemia include frequent glucose monitoring
  - It is also important to prevent hypoglycemia by anticipating drops in insulin requirement by factors such as
    - Decreasing renal function
    - Decreasing glucocorticoid doses
    - Interruption of nutrition (parenteral, enteral, or PO)
- Individuals using a continuous glucose monitor and/or an insulin pump prior to admission should continue to use these devices
  - The provider, nursing staff, and the patient must all agree that this can be safely done within the context of the patient's current reason for hospitalization
    - Patients with encephalopathy are unsafe to manage their insulin pump
- Use basal, bolus (preprandial), and correctional insulin for noncritically ill patients who are eating
  - Basal insulin: glargine or detemir

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- Bolus insulin: aspart or lispro
- Correctional insulin: should match the bolus insulin formulation (and can be adjusted from "low-dose," "medium-dose," and "high-dose" depending on the patient's level of insulin resistance)
  - The sole use of correctional insulin *is not recommended* because it is a reactive, nonphysiologic approach that leads to large glucose fluctuations

COMMON QUESTIONS

HOW OFTEN SHOULD I MONITOR POINT-OF-CARE (POC) GLUCOSE IN THE HOSPITAL?

- POC glucose should occur in the morning, before meals (preprandial), and before bed
  - Occasionally, overnight POC measurements are warranted if undetected hypoglycemia is a concern
- Critically ill patients requiring an insulin infusion (regular insulin) should receive POC glucose every 30 min to 2 h

SHOULD I CONTINUE THE PATIENT'S ORAL DIABETES MEDICATION(S) UPON ADMISSION?

- Oral glucose-lowering agents should be discontinued upon admission
- They are not useful in regulating the blood glucose in clinical situations where the insulin requirements and glucose intake are changing rapidly
  - Moreover, these oral agents may be dangerous
    - Hypoglycemia may occur with sulfonylureas
    - Euglycemic diabetic ketoacidosis may occur with SGLT-2Is
    - Lactic acidosis may occur with metformin (relatively rare complication)
- Once clinically stable, oral glucose-lowering agents may be resumed in anticipation of discharge

HOW MUCH INSULIN SHOULD I ORDER?

- If the patient has type 2 diabetes mellitus and takes insulin at home
  - Either start with their home regimen or reduce it by 25–50%, depending on the initial glucose levels and adherence of insulin at home
  - Provide the same total units of basal insulin as bolus insulin, and add correctional insulin
    - For example, if the basal dose is 12 U of glargine, order 4 U of aspart (bolus insulin) tid with meals with correctional insulin
- Patients with type 1 diabetes should resume insulin (especially long-acting insulin) near or slightly reduced from their home dose
- If the patient does *not* take insulin at home and has type 2 diabetes mellitus
  - Calculate the total daily insulin (TDI)
    - If SCr < 1.5 mg/dL, age < 70, and blood glucose > 200 mg/dL
      - Use 0.3 U/kg for the TDI
    - If SCr > 1.5 mg/dL, age > 70, or blood glucose < 200 mg/dL
      - Use 0.2 U/kg for the TDI
  - Half of the TDI is administered as basal insulin every evening or morning
  - The other half of the TDI is administered as bolus insulin split between meals three times a day
  - Add correctional insulin
  - For example, if a patient aged 65 years, weighs 100 kg, the glucose is 300 mg/dL, and the SCr is 1.0 mg/dL
    - TDI is 30 U
    - Basal insulin (glargine or detemir) is 15 U
    - Bolus insulin (lispro or aspart) is 5 U tid with meals
    - Add correctional insulin

HOW DO I ADJUST THE INSULIN DOSES IF THE POC GLUCOSES ARE ELEVATED?

- Each 24 h, calculate the total amount of correctional insulin given the day before, then add that amount to the current TDI to get your new TDI
  - Divide the total correctional equally between basal and bolus insulin regimens
  - For example, if a patient had a TDI of 30 U and was administered 10 U of correctional insulin over the past 24 h
    - Add 5 U to the old bolus regimen
    - Add 5 U to the old basal regimen (add either 2 or 3 U to each mealtime dose)
    - Continue correctional insulin

WHAT DO I DO IF THE PATIENT IS NPO FOR A PROCEDURE?

- Stop the mealtime bolus insulin
- Continue the basal insulin (may need to reduce the dose depending on how long they are NPO)

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CASE ANSWERS

1. It is generally not advised to continue oral diabetes medications while a patient is hospitalized. Oral diabetes medications are not useful in regulating the blood glucose level in clinical situations where glucose intake and insulin requirements may change rapidly depending on the illness. Additionally, these agents may be dangerous if the patient is fasting (causing hypoglycemia or euglycemic diabetic ketoacidosis) or at risk for declining kidney function (e.g., radiographic contrast media).
2. For patients with both noncritical and critical illness, the goal glucose range is 140–180 mg/dL. Lower targets do not improve outcomes and have a higher risk of hypoglycemia.
3. Because the patient has been adherent to their insulin regimen at home and the glucose level is elevated, starting at their home dose (20 U of glargine and 7 U of aspart tid with meals) with the addition of correctional insulin is reasonable at first to avoid hypoglycemia. Adjustments to the regimen should be made on a daily basis to reach the target glucose range of 140–180 mg/dL.
4. The amount of correctional insulin from the past 24 h (12 U) can be equally split into the basal and bolus insulin regimen. Therefore, 6 U of glargine can be added to the basal glargine regimen (now a total of 26 U) while 6 U of aspart can be split into the three mealtime doses (now a total of 9 U tid with meals).
5. When a patient is NPO in the hospital, discontinue the bolus (mealtime) insulin while continuing the basal insulin. Sometimes, the basal insulin may need to be reduced when the patient is NPO for prolonged periods of time.

FURTHER READING

- Powers AC et al. Diabetes mellitus: Management and therapies, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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50 Abnormal Liver Function Tests

CLINICAL VIGNETTE

A 76-year-old man presents to the ED after seeing his primary care physician for yellowing of the skin. His only complaint is itching of the skin for the past 2 weeks. He denies having abdominal pain but has had an unintentional 9-kg weight loss over the last 3 months. He has a 100-pack-year smoking history. Labs were drawn yesterday and revealed an alkaline phosphatase of 840 IU/L, total bilirubin of 18.9 mg/dL, and normal AST/ALT. The γ-glutamyl transpeptidase (GGT) is elevated. An abdominal ultrasound reveals biliary dilatation and a pancreatic head mass.

GUIDING QUESTIONS

1. Does this patient have intra- or extrahepatic cholestasis?
2. Would you expect this patient's hyperbilirubinemia to be from predominantly unconjugated or conjugated bilirubin?
3. What potential imaging studies/procedures are indicated in this patient's workup?

GENERAL PRINCIPLES

- Serum biochemical tests, often referred to as "liver function tests," can be used to
  - Detect the presence of liver disease
  - Distinguish between different types of liver disorders
  - Gauge the extent of liver damage
  - Follow the response to treatment
- However, these tests have shortcomings, including a lack of sensitivity and specificity
  - They can be normal in patients with serious liver disease
  - They can be abnormal in patients with diseases that do not affect the liver
- Liver tests rarely suggest a specific diagnosis
  - Rather, they suggest a general category of liver disease (e.g., hepatocellular or cholestatic) which then further directs the evaluation
- Therefore, to increase the sensitivity and specificity, it is best to use these tests together
- When more than one test is abnormal, or the finding(s) are abnormal on serial determinations, the probability of liver disease is high

CHARACTERISTICS OF HEPATIC MARKERS

MARKERS OF CHRONIC LIVER (HEPATOCELLULAR) FUNCTION

- Albumin
  - Synthesized exclusively by hepatocytes and has a long half-life (18–20 days)
    - Albumin is a poor indicator of acute or mild hepatic dysfunction
  - Albumin should *not* be measured to screen patients in whom there is no suspicion of liver disease
    - A study showed albumin testing in patients with no indications revealed 12% of patients had abnormal test results, where only 0.4% were clinically relevant
- Serum globulins
  - Serum globulins are a group of proteins made up of γ-globulins (immunoglobulins) produced by B lymphocytes and α- and β-globulins produced primarily in hepatocytes
  - Globulins are increased in chronic liver disease (e.g., chronic hepatitis and cirrhosis)
- PT and INR
  - PT and INR can be useful in assessing both acute and chronic liver injury
  - All but one of the blood clotting factors are made exclusively in hepatocytes
    - Factor VIII is produced by vascular endothelial cells
  - Their serum half-lives are much shorter than albumin, ranging from 6 h for factor VII to 5 d for fibrinogen
  - Because of their rapid turnover
    - Measurement of the clotting factors is the single best acute measure of hepatic synthetic function
    - They are helpful in diagnosing and assessing the prognosis of acute parenchymal liver disease
  - The PT collectively measures factors II, V, VII, and X
  - Biosynthesis of factors II, VII, IX, and X depends on vitamin K and is measured by the INR

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MARKERS OF ACUTE LIVER (HEPATOCELLULAR) FUNCTION

- The aminotransferases (transaminases) are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases such as hepatitis
- They include AST and ALT
  - Normal serum values range from 10 IU/L to 40 IU/L
- These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane
- Liver cell necrosis is *not* required for the release of aminotransferases
  - There is a poor correlation between the degree of liver cell damage and the level of the aminotransferases
  - Thus, the absolute elevation of the AST/ALT is of *no prognostic significance* in acute hepatocellular disorders
- AST
  - Found in liver, cardiac muscle, skeletal muscle, kidneys, brain, lungs, leukocytes, and erythrocytes in decreasing order of concentration
- ALT
  - Found primarily in the liver, and is therefore a more specific indicator of liver injury

MARKERS OF LIVER & BILIARY FUNCTION

- Bilirubin: normal value ranges between 1 mg/dL and 1.5 mg/dL
  - A breakdown product of the porphyrin ring of heme-containing proteins into two forms
    - Conjugated (direct)
    - Unconjugated (indirect)
  - In most liver diseases, both the conjugated and unconjugated bilirubin tend to be elevated
  - In some but not all liver diseases with hyperbilirubinemia, the degree of elevation of the serum bilirubin indicates increased damage
  - Conjugated bilirubin is water-soluble and can be excreted by the kidney
    - Conjugated hyperbilirubinemia almost always implies liver or biliary tract disease
    - Conjugated bilirubin is important in
      - Viral hepatitis
      - Drug-induced liver disease
      - Model for End-stage Liver Disease (MELD) score calculation
    - The conjugated bilirubin does not correlate with the severity of damage in alcohol-associated hepatitis
    - The presence of bilirubin in the urine (bilirubinuria) implies the presence of liver disease or obstructive jaundice
  - Unconjugated bilirubin is insoluble in water and is bound to albumin in the blood
    - Isolated unconjugated hyperbilirubinemia is rarely due to liver disease (see Table 50-4)
      - Evaluate for hemolytic disorders and genetic conditions (e.g., Crigler-Najjar and Gilbert syndromes)
- Alkaline phosphatase
  - The normal serum alkaline phosphatase consists of many distinct isoenzymes found in the liver, bone, placenta, and, less commonly, small intestine
  - Elevation of liver-derived alkaline phosphatase is not totally specific for cholestasis
    - Less than threefold elevations can be seen in almost any type of liver disease
    - Elevations greater than four times normal occur primarily in
      - Cholestatic liver disorders
      - Infiltrative liver diseases (e.g., cancer and amyloidosis)
      - Bone conditions characterized by rapid turnover (e.g., Paget's disease)
  - The level of serum alkaline phosphatase elevation is *not* helpful in distinguishing between intrahepatic and extrahepatic cholestasis
- γ-Glutamyl transpeptidase (GGT)
  - Produced primarily in the liver
  - Elevated levels of GGT can help confirm an elevated alkaline phosphatase is originating from a liver disorder

INTERPRETATION, DIAGNOSTIC EVALUATION, & ETIOLOGIES OF ABNORMAL MARKERS

- Further evaluation of abnormal liver tests is determined by the category of liver disease (Fig. 50-1)
- Categories of liver disease include
  - Hepatocellular (acute and chronic)
  - Cholestatic

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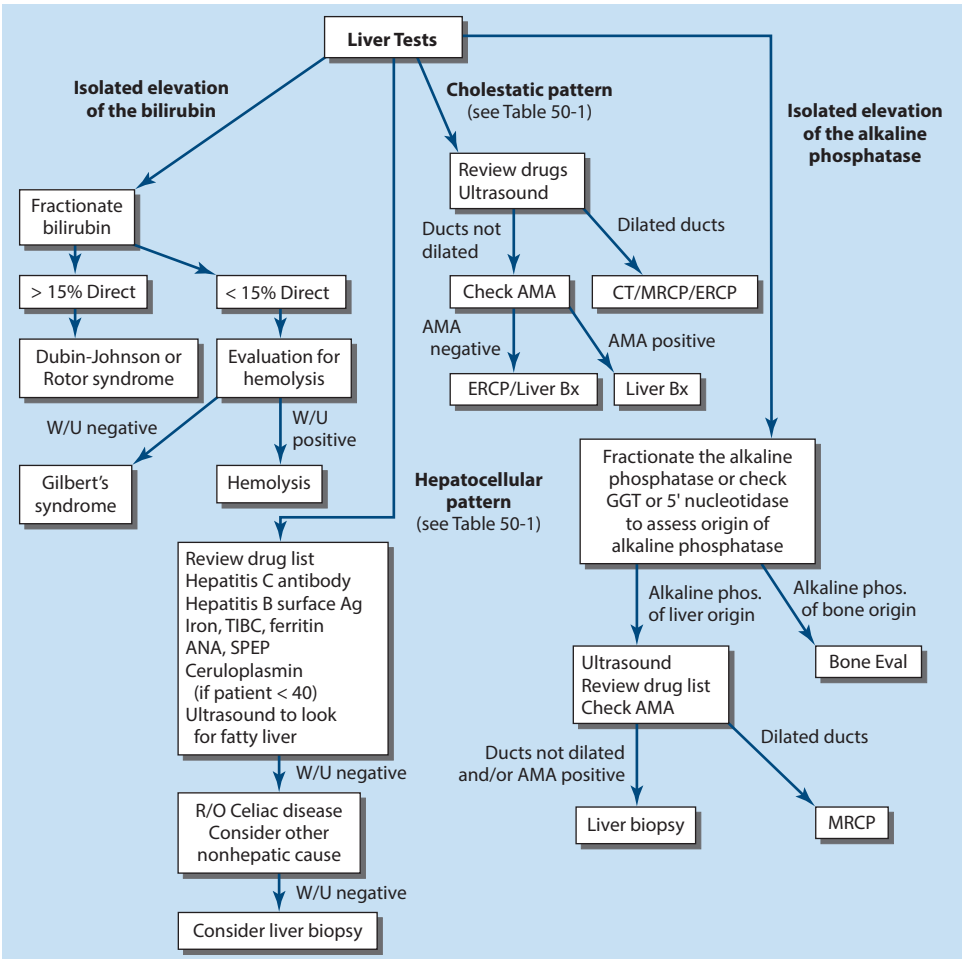

FIGURE 50-1 Algorithm for the Evaluation of Abnormal Liver Tests. Ag, antigen; AMA, antimitochondrial antibody; Bx, biopsy; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyl transpeptidase; MRCP, magnetic resonance cholangiopancreatography; R/O, rule out; SPEP, serum protein electrophoresis; TIBC, total iron-binding capacity; W/U, workup. (Reproduced with permission from Bethea ED, Pratt DS. Evaluation of liver function, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

  - Isolated elevated alkaline phosphatase
  - Isolated hyperbilirubinemia
- Jaundice can occur from either isolated hyperbilirubinemia or a combination of hyperbilirubinemia, cholestatic, and hepatocellular disease
- Liver test patterns can help identify specific hepatobiliary disorders (Table 50-1)

JAUNDICE

- Jaundice is a yellowish discoloration of body tissues resulting from the deposition of bilirubin
- Jaundice is a sign of
  - Liver disease
  - Hemolytic disorder of bilirubin (less common)
- Subungual and scleral icterus are the first locations where jaundice appears
  - A bilirubin level of 3 mg/dL is when scleral icterus first appears
- Another sensitive indicator of increased serum bilirubin is darkening of the urine (urobilinogen)
  - Due to renal excretion of conjugated bilirubin

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TABLE 50-1 Liver Test Patterns in Hepatobiliary Disorders

TYPE OF DISORDER	BILIRUBIN	AMINOTRANSFERASES	ALKALINE PHOSPHATASE	ALBUMIN	PT
Hemolysis/Gilbert syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral, ischemic, and drug- or toxin-induced hepatitis)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often > 500 IU, ALT > AST	Normal to < 3 × normal elevation	Normal	Usually normal. If > 5 s above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually < 300 IU	Normal to < 3 × normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcohol-associated hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT > 2 suggests alcohol-associated hepatitis or cirrhosis	Normal to < 3 × normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis (obstructive jaundice)	Both fractions may be elevated Bilirubinuria	Normal to moderate elevation Rarely > 500 IU	Elevated, often > 4 × normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
Infiltrative diseases (tumor, granulomata)	Usually normal	Normal to slight elevation	Elevated, often > 4 × normal elevation Fractionate, or confirm liver origin with 5′-nucleotidase or γ-glutamyl transpeptidase	Normal	Normal

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- Bilirubin levels increase when there is an imbalance between bilirubin production and clearance
- Jaundice can occur in conjunction with any category of liver disease
- Figure 50-2 offers a framework in the evaluation of jaundice
- The initial step in evaluation of jaundice is to perform appropriate blood tests to determine whether the patient has an isolated elevation of serum bilirubin
  - If so, is the isolated bilirubin elevation due to an increased unconjugated or conjugated fraction?
- If hyperbilirubinemia is accompanied by other liver test abnormalities
  - Is the disorder hepatocellular or cholestatic (see below)?

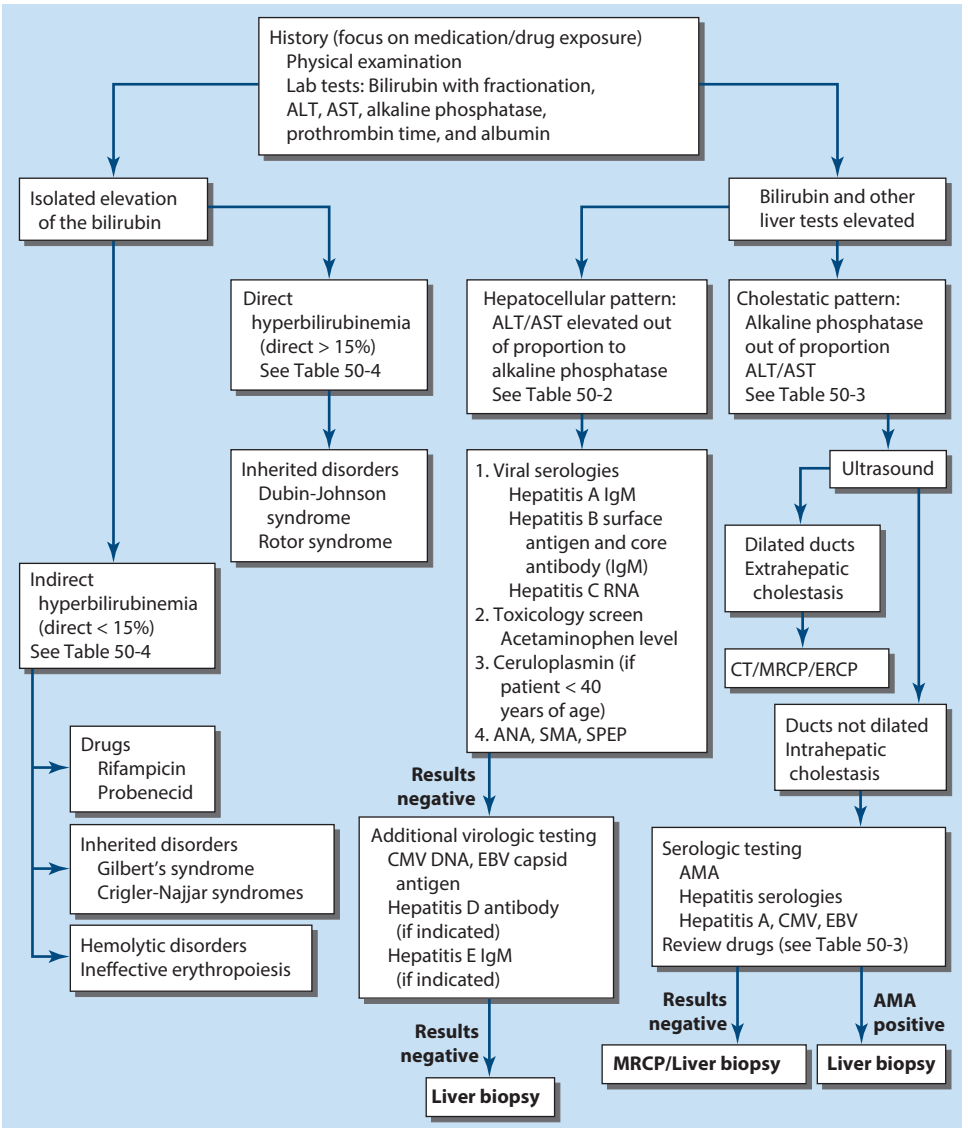

FIGURE 50-2 Evaluation of the patient with jaundice. AMA, antimitochondrial antibody; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; LKM, liver-kidney microsomal antibody; MRCP, magnetic resonance cholangiopancreatography; SMA, smooth-muscle antibody; SPEP, serum protein electrophoresis. (Reproduced with permission from John S, Pratt DS. Jaundice, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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- If cholestatic, is the cause intra- or extrahepatic?
- If hepatocellular, the history and exam help guide further workup

ACUTE HEPATOCELLULAR DISEASE

- Primarily elevated AST and ALT levels
  - When combined with hyperbilirubinemia, the AST and ALT are disproportionately higher than the alkaline phosphatase levels
- Ratios of the AST:ALT can be helpful diagnostically
  - Ratio < 1
    - Chronic viral hepatitis
    - Metabolic dysfunction-associated steatotic liver disease
  - Ratio > 2:1
    - Suggestive of alcohol-related liver injury (highly suggestive if ratio is > 3:1)
    - The AST in alcohol-related liver injury is rarely > 300 IU/L, and the ALT is often normal
- AST and ALT values > 1000 IU/L
  - Occurs almost exclusively in disorders associated with extensive hepatocellular injury, including
    - Ischemic liver injury (e.g., prolonged hypotension or acute heart failure)
    - Acute viral hepatitis (A, B)
    - Autoimmune hepatitis
    - Toxin- or drug-induced liver injury (e.g., acetaminophen poisoning, aflatoxin)
    - Budd-Chiari syndrome
- Isolated AST elevations can come from muscle breakdown (e.g., in rhabdomyolysis)

CHRONIC HEPATOCELLULAR DISEASE

- Albumin levels < 3 g/dL (hypoalbuminemia) should raise the possibility of chronic liver disease
  - Hypoalbuminemia is more common in chronic liver disorders such as cirrhosis
    - Hypoalbuminemia reflects severe liver damage and decreased albumin synthesis
  - However, hypoalbuminemia is *not* specific for liver disease and may occur in protein malnutrition of any cause, as well as
    - Protein-losing enteropathies
    - Nephrotic syndrome
    - Chronic infections that are associated with prolonged increases in levels of cytokines that inhibit albumin synthesis
  - There are three general mechanisms of hypoalbuminemia
    - Loss of albumin in the urine (nephrosis and nephrotic syndrome)
    - Inability to synthesize albumin (cirrhosis and liver failure)
    - Inability to absorb albumin (gastroparesis and protein malnutrition)
- Serum globulin levels are increased in chronic hepatocellular disease
  - Increases in the concentration of specific isotypes of γ-globulins are often helpful in the recognition of certain chronic liver diseases
  - Diffuse polyclonal increases in IgG levels are common in autoimmune hepatitis
    - Increases > 100% should alert the clinician to this possibility
  - Increases in IgM levels are common in primary biliary cholangitis
  - Increases in the IgA levels occur in alcohol-related liver disease
- Elevated PT and INR
  - PT may be elevated in
    - Hepatitis
    - Cirrhosis
    - Disorders that lead to vitamin K deficiency (e.g., obstructive jaundice, fat malabsorption of any kind)
  - Marked prolongation of PT > 5 s above control and not corrected by parenteral vitamin K administration is a poor prognostic sign in acute viral hepatitis and other acute and chronic liver diseases
  - The INR, along with the total serum bilirubin, creatinine, albumin, and sodium
    - Are components of the Model for End-stage Liver Disease (MELD) 3.0 score
    - Are used as a measure of hepatic decompensation and to allocate organs for liver transplantation
- Low total protein levels are observed in chronic hepatocellular disease

HEPATOCELLULAR CONDITIONS THAT MAY PRODUCE JAUNDICE

- Figure 50-2 describes the approach to hepatocellular disease causing jaundice
- Table 50-2 lists hepatocellular conditions that may produce jaundice

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TABLE 50-2 Hepatocellular Conditions That May Produce Jaundice
Viral hepatitis
Hepatitis A, B, C, D, and E
Epstein-Barr virus
Cytomegalovirus
Herpes simplex virus
Alcoholic hepatitis
Chronic liver disease and cirrhosis
Drug toxicity
Predictable, dose-dependent (e.g., acetaminophen)
Unpredictable, idiosyncratic (e.g., isoniazid)
Environmental toxins
Vinyl chloride
Jamaica bush tea—pyrrolizidine alkaloids
Kava kava
Wild mushrooms—*Amanita phalloides*, *A. verna*
Wilson's disease
Autoimmune hepatitis

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- The history and exam will provide clues as to what diagnostic testing is necessary
  - In some cases, further testing is not required (e.g., obvious alcohol-associated hepatitis)
- Consider testing for
  - Viral hepatitis (A, B, C, D, and E)
  - Epstein-Barr virus, cytomegalovirus, and herpes simplex virus
  - Various causes of cirrhosis (see **Chap. 24**)
  - Medication toxicity, such as acetaminophen
  - Wilson's disease (ceruloplasmin and serum copper)
  - Autoimmune hepatitis (antimitochondrial antibody)

CHOLESTASIS

- Primarily an elevated alkaline phosphatase and direct bilirubin
  - When combined with hyperbilirubinemia, the alkaline phosphatase is disproportionally higher than the AST and ALT
- Alkaline phosphatase comes from both the biliary tree and bone
  - An elevated alkaline phosphatase can be confirmed to be from the biliary tree by ordering a GGT
  - GGT primarily is produced by the liver
- **Table 50-3** lists the differential diagnosis of cholestasis producing jaundice
  - Cholestasis is separated into intra- and extrahepatic
  - Distinguishing intrahepatic from extrahepatic cholestasis may be difficult from history and exam alone
  - The next appropriate test is an ultrasound
    - Detects dilation of the intra- and extrahepatic biliary tree with a high degree of sensitivity and specificity
    - The presence of biliary dilatation indicates extrahepatic cholestasis
      - Ultrasound rarely identifies the site or cause of extrahepatic cholestasis
      - The scarring in primary sclerosing cholangitis prevents the intrahepatic ducts from dilating
      - CT, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or endoscopic ultrasound are next steps in extrahepatic cholestasis after ultrasound
    - Absence of biliary dilation suggests intrahepatic cholestasis
      - Serologic testing in combination with liver biopsy is the next step in evaluation (see Fig. 50-2)

ISOLATED ELEVATED ALKALINE PHOSPHATASE

- When present in an otherwise healthy person, identification of the source of elevated isoenzymes is helpful (Fig. 50-1)
- Either fractionate the alkaline phosphatase by electrophoresis (more precise method) or measure the GGT

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TABLE 50-3 Cholestatic Conditions That May Produce Jaundice

I. Intrahepatic
- a. Viral hepatitis
  - i. Fibrosing cholestatic hepatitis—hepatitis B and C
  - ii. Hepatitis A, Epstein-Barr virus infection, cytomegalovirus infection
- b. Alcohol-associated hepatitis
- c. Drug toxicity
  - i. Pure cholestasis—anabolic and contraceptive steroids
  - ii. Cholestatic hepatitis—chlorpromazine, erythromycin estolate
  - iii. Chronic cholestasis—chlorpromazine and prochlorperazine
- d. Primary biliary cholangitis
- e. Sclerosing cholangitis, primary and secondary
- f. Vanishing bile duct syndrome
  - i. Chronic rejection of liver transplants
  - ii. Sarcoidosis
  - iii. Drugs
- g. Congestive hepatopathy and ischemic hepatitis
- h. Inherited conditions
  - i. Progressive familial intrahepatic cholestasis
  - ii. Benign recurrent intrahepatic cholestasis
- i. Cholestasis of pregnancy
- j. Total parenteral nutrition
- k. Nonhepatobiliary sepsis
- l. Benign postoperative cholestasis
- m. Paraneoplastic syndrome
- n. Veno-occlusive disease
- o. Graft-versus-host disease
- p. Infiltrative disease
  - i. Tuberculosis
  - ii. Lymphoma
  - iii. Amyloidosis
  - iv. Primary hepatocellular cancer
  - v. Metastatic cancer in the liver
- q. Infections
  - i. Malaria
  - ii. Leptospirosis

II. Extrahepatic
- a. Malignant
  - i. Cholangiocarcinoma
  - ii. Pancreatic cancer
  - iii. Gallbladder cancer
  - iv. Ampullary cancer
  - v. Malignant involvement of the porta hepatis lymph nodes
- b. Benign
  - i. Choledocholithiasis
  - ii. Postoperative biliary strictures
  - iii. Primary sclerosing cholangitis
  - iv. Chronic pancreatitis
  - v. AIDS cholangiopathy
  - vi. Mirizzi's syndrome
  - vii. Parasitic disease (ascariasis)

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- GGT primarily comes from the biliary tree
- If elevated, it confirms the elevated alkaline phosphatase is from a liver source

- Isolated elevated alkaline phosphatase confirmed of liver origin suggests early cholestasis or, less often, hepatic infiltration by tumor or granulomata
- Other conditions that cause isolated elevations of the alkaline phosphatase include
  - Primary biliary cholangitis
  - Primary or secondary sclerosing cholangitis
  - Hodgkin's disease
  - Diabetes mellitus
  - Hyperthyroidism
  - HF
  - Amyloidosis

ISOLATED UNCONJUGATED HYPERBILIRUBINEMIA

- Table 50-4 lists the causes of isolated hyperbilirubinemia
- A critical determination in isolated unconjugated hyperbilirubinemia is whether the patient is suffering from a hemolytic process or from impaired hepatic uptake/conjugation of bilirubin
  - Measure serum LDH and haptoglobin, and review a peripheral smear to rule out hemolytic anemia
  - See Chap. 32 for further information on hemolytic anemias
- In the absence of hemolysis
  - Consider a problem with hepatic uptake or conjugation of bilirubin
  - Certain drugs (e.g., rifampin, probenecid, cephalosporins) may diminish hepatic uptake of bilirubin
  - Inherited conditions of impaired bilirubin conjugation
    - Crigler-Najjar type I
      - Rare condition causing severe jaundice, neurologic impairment, and frequently death in infancy and childhood
    - Crigler-Najjar type II
      - More common than type I
      - Live into adulthood with bilirubin levels 6–25 mg/dL
      - May be susceptible to kernicterus under times of stress (illness or surgery)
    - Gilbert's syndrome
      - Common condition causing mild unconjugated hyperbilirubinemia (bilirubin < 6 mg/dL) that may fluctuate with stress, illness, alcohol use, or fasting

TABLE 50-4 Causes of Isolated Hyperbilirubinemia

I. Indirect hyperbilirubinemia
   a. Hemolytic disorders
   b. Ineffective erythropoiesis
   c. Increased bilirubin production
      i. Massive blood transfusion
      ii. Resorption of hematoma
   d. Drugs
      i. Rifampin
      ii. Probenecid
      iii. Atazanavir
      iv. Antibiotics—cephalosporins and penicillins
   e. Inherited conditions
      i. Crigler-Najjar types I and II
      ii. Gilbert's syndrome
II. Direct hyperbilirubinemia (inherited conditions)
   a. Dubin-Johnson syndrome
   b. Rotor syndrome

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ISOLATED CONJUGATED HYPERBILIRUBINEMIA

- Found in two rare benign inherited conditions
  - Dubin-Johnson syndrome
    - Altered excretion of bilirubin into the bile ducts
  - Rotor syndrome
    - Deficiency of the major hepatic drug reuptake transporters

CASE ANSWERS

1. This patient has a predominantly cholestatic liver injury picture with an elevated alkaline phosphatase, hyperbilirubinemia, and normal AST/ALT levels. The history and exam rarely help evaluate for intra- or extrahepatic causes of cholestasis; therefore, the ultrasound was performed. Patients with biliary dilatation on ultrasound primarily have extrahepatic cholestasis.
2. Extrahepatic cholestasis primarily causes conjugated hyperbilirubinemia from obstruction of the bile ducts. This leads to a backup of conjugated bilirubin to buildup in the bloodstream.
3. This patient has painless jaundice with an extrahepatic cholestatic picture and an ultrasound showing a pancreatic head mass. With his extensive smoking history, pancreatic cancer is the primary concern. A CT, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasound should be performed next to further characterize the mass, with a need for biopsy soon after.

FURTHER READING

- Bethea ED, Pratt DS. Evaluation of liver function, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- John S, Pratt DS. Jaundice, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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51 Pain Control

CLINICAL VIGNETTE

A 55-year-old man presents to the ED with epigastric abdominal pain and nausea. He states that he went to a party the previous night and drank a large quantity of alcohol. The serum lipase is 3005 U/L. An abdominal ultrasound reveals acute interstitial pancreatitis with no evidence of gallstones. The patient is administered a 10 mL/kg bolus of LR and hydromorphone 1 mg IV with little relief of the pain. Two hours later, hydromorphone 1.5 mg IV also provides little relief of the patient's pain.

GUIDING QUESTIONS

1. What acute pain strategies for opiate therapy are options for this patient?
2. What side effects would you monitor with opiate therapy?

INTRODUCTION

- Pain is an unpleasant sensation localized to a part of the body
- Any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling
- These properties illustrate the duality of pain
    - Pain is both a *sensation* and an *emotion*
- When pain is acute, it is characteristically associated with behavioral arousal and a stress response consisting of increases in BP, heart rate, pupil diameter, and plasma cortisol levels
- Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a clinician's attention
- The function of the pain sensory system is to protect the body and maintain homeostasis
- Because different diseases produce characteristic patterns of tissue damage, the quality, time course, and location of a patient's pain lend important diagnostic clues to its underlying etiology

APPROACH TO ACUTE PAIN

- Pain is often under-treated in the hospital
- Complete absence of pain is often an unrealistic goal, and this expectation should be discussed early with patients
- Frequent reassessment of patients is necessary during analgesic treatment
- In patients naïve to opiates, start with nonopiate pain strategies (acetaminophen, NSAIDs [pills and/or gels], heat and ice packs) unless a condition requires opiates (e.g., trauma patients, burns, pancreatitis, sickle cell crisis)
- Scheduling analgesics is often better at controlling pain than providing them prn
- Before prescribing analgesics, always consider comorbidities, allergies, drug interactions, and potential side effects
- Select alternative agents to meperidine and codeine to limit side effects and drug interactions
- Patients with chronic pain who are hospitalized may have acute on chronic pain due to inflammation from a medical condition or may have an acute injury worsening the chronic pain
- Questions to ask when assessing a patient with acute pain
    - Can nonopiate medications be administered initially, or does the condition require opiates?
    - Is the patient talking or resting comfortably?
        - Can estimate the pain level, but this may be misleading in patients with chronic pain, and should not be assumed to be a sign of deception in such patients
    - Does pain relief occur after administration of the analgesic regimen?
        - If it does, does it provide adequate control?
        - Is the pain adequately controlled between scheduled doses? Or does it become uncontrolled before the next medication is available?
        - If pain relief does not occur, consider escalating doses or increasing the frequency of analgesics
    - If the patient is receiving opiates, is the pain reduced after receiving the opiate?
        - If not, may need to increase the dose and/or frequency

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        - If the dose/frequency are increased but pain relief does not occur, the patient's pain may not be opiate responsive
            - Consider neuropathic or emotional pain, which may respond to anticonvulsants (e.g., gabapentin) or antidepressants (e.g., amitriptyline)
        - In certain cases, a patient-controlled analgesia (PCA) strategy may be necessary
    - Is the patient sleepy or lethargic? Is their respiratory rate decreasing?
        - These are signs the opiate doses may be too high
    - Does the patient ask for pain medications only when you are in the room? Is the patient "splitting" the staff, playing one against the other? Is the patient unwilling to accept any adjunctive nonopioid treatment?
        - These may be signs that the patient is opiate-seeking
        - However, objective pain assessments are still important

TREATMENT OF ACUTE PAIN

- The ideal treatment for any pain is to remove the cause
    - Thus, while treatment can be initiated immediately, efforts to establish the underlying etiology should always proceed as treatment begins
- Some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, pancreatitis, or sickle cell crisis)
- When using opiates for acute pain, calculate the total daily morphine equivalent used to adjust daily dosages, and wean opiates as the underlying etiology of the pain improves
- Commonly used drugs for pain relief
    - Nonopioids (Table 51-1)
    - Opioids (Table 51-2)
    - Antidepressants (Table 51-3)
    - Anticonvulsants and antiarrhythmics (Table 51-4)
- Aspirin, acetaminophen, and NSAIDs have a similar mechanism of action (COX inhibition) with anti-inflammatory actions
    - Particularly effective for mild to moderate headaches and for pain of musculoskeletal origin
    - Prolonged use can lead to gastric irritation (aspirin and NSAIDs)
    - Long-term NSAID use can lead to
        - Nephrotoxicity for patients at risk (hypovolemia and long-term diuretic use)
        - Hypertension
    - IV ketorolac (15 mg) is particularly effective in nephrolithiasis
    - Topical diclofenac gel is an alternative to oral NSAIDs with fewer systemic side effects
- Opiates are the most potent pain-relieving drugs currently available
    - Provide the broadest range of efficacy and the most reliable and effective treatment for rapid pain relief
    - Nausea, vomiting, pruritus, sedation, and constipation are the most frequent side effects
    - Respiratory depression is uncommon at standard analgesic doses but can be life-threatening
    - Come in a variety of formulations (e.g., IV, PO, liquid solution, transdermal patches) and can be used in a PCA
    - Basic principles of PCA use
        - Uses a microprocessor-controlled infusion device that can deliver preprogrammed additional doses whenever the patient pushes a button and, if needed, a baseline continuous dose of an opiate
        - The patient can titrate the dose for optimal pain control

TABLE 51-1 Nonopioid Analgesics for Pain Relief

GENERIC NAME	DOSAGE	COMMENTS
Acetylsalicylic acid	650 mg PO q4h	Enteric-coated preparations available
Acetaminophen	650–1000 mg q6–8h	Side effects uncommon
Ibuprofen	400 mg PO q4–6h	Available without prescription
Naproxen	250–500 mg PO q12h	Common NSAID that poses the least cardiovascular risk, but it has a somewhat higher incidence of GI bleeding
Indomethacin	25–50 mg PO q8h	GI side effects common
Ketorolac	15–60 mg IM/IV q4–6h	Available for parenteral use
Celecoxib	100–200 mg PO q12–24h	Useful for arthritis

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TABLE 51-2 Opioid Analgesics for Pain Relief

GENERIC NAME	ROUTE OF ADMINISTRATION AND DOSAGE	COMMENTS
Codeine	IV: 30–60 mg q4h PO: 30–60 mg q4h	Nausea common
Oxycodone	PO: 5–10 mg q4–6h	Available with acetaminophen or aspirin
Oxycodone extended-release	PO: 10–40 mg q12h	Oral extended-release tablet; high potential for misuse
Morphine	IV: 5 mg q4h PO: 30 mg q4h	—
Morphine sustained release	PO: 15–60 mg bid to tid	Oral slow-release preparation
Hydromorphone	IV: 0.5–2 mg q4h PO: 2–4 mg q4h	Shorter acting than morphine sustained release
Levorphanol	IV: 2 mg q6–8h PO: 4 mg q6–8h	Longer acting than morphine sulfate; absorbed well PO
Methadone	IV: 5–10 mg q6–8h PO: 5–20 mg q6–8h	Due to long half-life, respiratory depression and sedation may persist after analgesic effect subsides; therapy should not be initiated with > 40 mg/d, and dose escalation should be made no more frequently than every 3 days
Meperidine	IV: 50–100 mg q3–4h PO: 300 mg q4h	Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended
Butorphanol	PO: 1–2 mg q4h	Intranasal spray formulation available
Fentanyl	Transdermal: 25–100 µg/h 72 h patch	—
Buprenorphine	Transdermal: 5–20 µg/h applied for 7 days	—
Buprenorphine	IV/IM: 0.3 mg q6–8h	—
Tramadol	PO: 50–100 mg q4–6h	Mixed opioid/adrenergic action

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TABLE 51-3 Antidepressants[a] Used for Pain Relief and Possible Side Effects

GENERIC NAME	DOSE, mg/d	ANTICHOLINERGIC POTENCY	ORTHOSTATIC HYPOTENSION	CARDIAC DYSRHYTHMIA	SEDATIVE POTENCY
Doxepin	Average: 200 Range: 75–400	Moderate	Moderate	Less	High
Amitriptyline	Average: 150 Range: 25–300	Highest	Moderate	Yes	High
Nortriptyline	Average: 100 Range: 40–150	Moderate	Low	Yes	Moderate
Venlafaxine	Average: 150 Range: 75–400	None	None	No	Low
Duloxetine	Average: 40 Range: 30–60	None	None	No	Low

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.
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TABLE 51-4 Anticonvulsants and Antiarrhythmics[a] Used for Pain Relief

GENERIC NAME	PO DOSAGE	COMMENTS
Carbamazepine	200–300 mg q6h	Rare aplastic anemia, GI irritation, hepatotoxicity
Oxcarbazepine	300 mg bid	Similar to carbamazepine
Gabapentin[b]	600–1200 mg q8h	Dizziness, GI irritation; useful in trigeminal neuralgia
Pregabalin	150–600 mg bid	Similar to gabapentin; dry mouth, edema

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain. [b]Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.
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        - Features of a PCA when ordering
            - What opiate will you be using (most commonly morphine, hydromorphone, or fentanyl)?
            - Bolus dose (e.g., morphine 1 mg, hydromorphone 0.2 mg, or 10 μg fentanyl)
            - Lockout period
                - How often the PCA will allow the patient to receive a bolus dose when they push the button (typically starts at 10-min lockout periods)
                - Includes a maximum amount in 1 h
                - Lockout periods help prevent opiate overdosing
            - Adjust the lockout bolus dose daily (either increasing the dose or decreasing as the patient's underlying pain condition improves)
            - A continuous infusion of the opiate can also be administered (at a set dose rate/hour)
                - However, this does increase the risk of respiratory depression and has not been shown to increase the overall efficacy of the technique
    - Other routes of opiate administration are possible, including
        - Spinal administration
        - Intranasally (butorphanol)
        - Rectally and transdermally (fentanyl and buprenorphine)
        - Through the oral mucosa (fentanyl)
- Equipotent analgesic doses of opioids
    - If using long-acting oral opiates with prn short-acting opiates, understanding equipotent analgesic doses allows appropriate cross-titration
    - Calculate the total opiate dose used in the previous 24 h
    - Convert the total dose to an oral morphine equivalent (see Table 51-5)
    - Convert the oral morphine equivalent to the opiate being used
    - Administer 25–50% of the calculated daily dose to account for incomplete cross-tolerance between opioids
        - Methadone dosing should be reduced by 75–90%
    - Schedule the dosing frequency based on the analgesic half-life (e.g., for morphine every 4 h)
    - Divide the calculated 24 h dosage by the number of doses to be given daily
    - Add prn doses of the new opioid (short-acting form) at 5–15% of the total daily dose for breakthrough pain

APPROACH TO CHRONIC PAIN

- Managing patients with chronic pain is intellectually and emotionally challenging
- Sensitization of the nervous system can occur without an obvious precipitating cause, e.g., fibromyalgia or chronic headache

TABLE 51-5 Equipotent Analgesic Doses of Opioids in Converting to Morphine equivalents

DRUG	SQ/IV DOSE, mg	PO DOSE, mg	DURATION, h	HALF-LIFE, h
Morphine	10	30	4	2–4
Hydrocodone	–	30	4	3–4
Oxycodone	–	20	4	3–5
Hydromorphone	1.5	7.5	4	2–3
Fentanyl	0.1	–	1–2	2–4
Methadone	–	1.7–6.7	4–48	15–60

Note: This table does not provide a complete list of opiate conversions.

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- The pain-generating mechanism is often difficult or impossible to determine with certainty
  - Lack of certainty of the pain mechanism and pain relief can be frustrating for both the clinician and patient
- The traditional medical approach of seeking an obscure organic pathology is often unhelpful
  - On the other hand, psychological evaluation and behaviorally based treatment paradigms are frequently helpful, particularly in the setting of a multidisciplinary pain-management center
- There are several factors that can cause, perpetuate, or exacerbate chronic pain
  - The patient may simply have a disease that is characteristically painful for which there is presently no cure; for example
    - Arthritis
    - Cancer
    - Chronic daily headaches
    - Fibromyalgia
    - Diabetic neuropathy
  - There may be secondary perpetuating factors that are initiated by disease and persist after that disease has resolved (e.g., damaged sensory nerves, sympathetic efferent activity, painful reflex muscle contraction [spasm])
  - A variety of psychological conditions can exacerbate or even cause pain
  - Depression is the most common emotional disturbance in patients with chronic pain
    - Patients should be asked about their mood, appetite, sleep patterns, and daily activity
- A guiding principle in evaluating patients with chronic pain is to assess both emotional and somatic causal and perpetuating factors before initiating therapy

CARE OF THE HOSPITALIZED PATIENT WITH ACUTE ON CHRONIC PAIN

- Identify underlying cause of patient's acute flare of chronic pain (e.g., an underlying medical condition, injury, or emotional distress)
- Set expectations that the acute pain will be managed while long-term treatment strategies will be continued but not necessarily escalated (unless the chronic pain was previously uncontrolled)
- Optimize nonopiate therapies in the patient's chronic pain regimen (e.g., TCAs, anticonvulsants, and antiarrhythmics)
- Explore the idea of referral for outpatient interventions to address the chronic pain more thoroughly if not already performed (e.g., referral to a multidisciplinary chronic pain center, cognitive-behavioral therapy, physical therapy, nerve blocks, glucocorticoid injections, spinal cord stimulators) where appropriate
- If the patient is established with a chronic pain multidisciplinary team, ensure timely follow-up
- Avoid escalating outpatient opiate therapy on discharge for the chronic pain unless the patient's chronic pain team has communicated a desire for an increase

CASE ANSWERS

1. Patients with pancreatitis usually require opioid therapy for pain management. Tylenol may also be used, but NSAIDs are usually avoided due to risk of AKI in patients with pancreatitis due to hypovolemia. Scheduled IV opiates (such as hydromorphone) with prn doses available is one strategy. This patient has had two doses that have not provided adequate pain relief. Therefore, another option is to initiate a patient-controlled analgesia (PCA) pump. This allows the patient to self-deliver additional doses when their pain is uncontrolled with the push of a button. A PCA strategy requires the clinician to set a bolus dose (e.g., hydromorphone 0.2 mg) and a set lockout period (e.g., 10 min). Additionally, a continuous infusion of the opiate at a set dose rate/hour can be administered if necessary. As a patient's pancreatitis and pain improves, weaning of the IV opiates to PO formulation and eventual discontinuation of opiates is standard.
2. Common side effects of opiates include nausea, vomiting, pruritus, sedation, and constipation. Respiratory depression is uncommon at standard analgesic doses but can be life-threatening when it occurs. When patients require a continuous infusion as part of their PCA pump, the risk of respiratory depression increases.

FURTHER READING

- Rathmell JP, Fields HL. Pain: Pathophysiology and management, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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52 Reading Chest X-Rays

CLINICAL VIGNETTE

A 66-year-old woman with mesothelioma, hypertension, CAD, and venous stasis presents to the ED for worsening of shortness of breath over the last 2 weeks. She describes worsening of her baseline cough without an increase in sputum production. She denies fever or chills. Over the last week, she has intermittently noticed mild chest pain on the left side with inspiration. She has mild tachypnea on exam, and her Spo_2 is 92% on room air. Figure 52-1 shows the patient's posterior–anterior CXR in the ED.

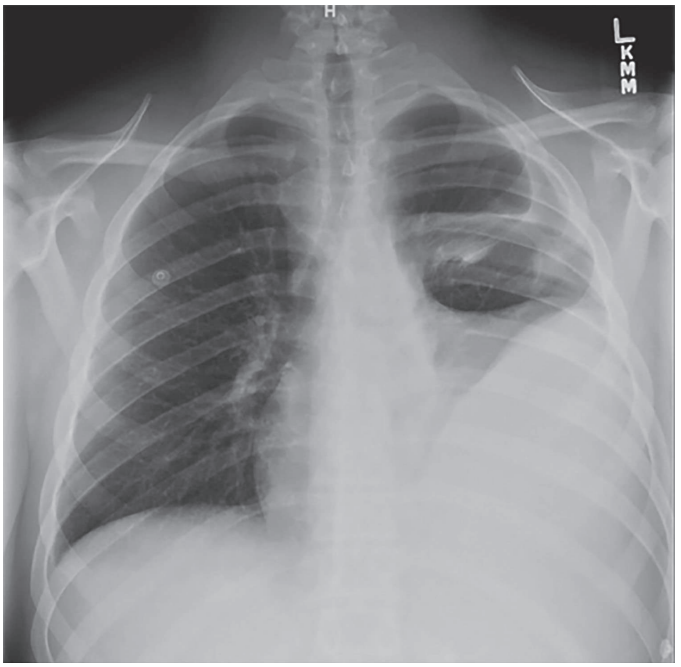

FIGURE 52-1 Posterior–anterior CXR in the ED. (Used with permission from Ash SY, Washko GR. Atlas of chest imaging, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

GUIDING QUESTIONS

1. What is the significant finding on this patient's CXR?
2. What is the most likely underlying etiology of the finding on CXR?
3. How would you confirm the etiology of the finding on CXR?

APPROACH TO CHEST X-RAYS

- Figure 52-2 depicts a normal posterior–anterior/lateral CXR
- Be systematic when reading CXRs in order not to miss subtle findings
- Technique
  - Identify the correct patient information and date of exam
  - Is the exposure correct?
    - Correct exposure allows the intervertebral disc spaces to be faintly visible through the cardiac silhouette

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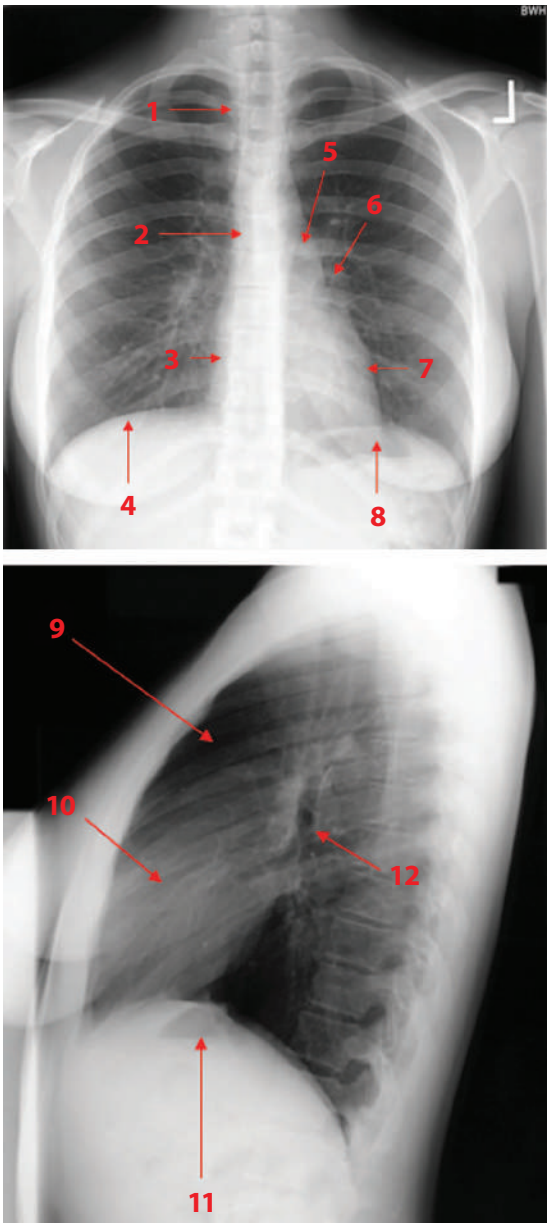

FIGURE 52-2 Normal CXR—review of anatomy. 1. Trachea. 2. Carina. 3. Right atrium. 4. Right hemidiaphragm. 5. Aortic knob. 6. Left hilum. 7. Left ventricle. 8. Left hemidiaphragm (with stomach bubble). 9. Retrosternal clear space. 10. Right ventricle. 11. Left hemidiaphragm (with stomach bubble). 12. Left upper lobe bronchus. (Reproduced with permission from Jameson JL et al. Diagnostic imaging in internal medicine, in *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). New York, McGraw-Hill Education, 2020.)

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        - Underexposure causes the CXR to appear "grainy" and to display poor penetration of the mediastinal structures leading to an inaccurate representation of anatomy
        - Overexposure can cause the CXR to appear "saturated" or in extreme cases "burnt out" whereby anatomy is completely obliterated (i.e., pathology may not be visible)
    - Is the patient properly positioned?
        - The spinous process and trachea should be midline
        - The clavicular heads should be equidistant from the spinous processes
    - Is it posterior–anterior (PA) or anterior–posterior (AP)?
        - PA and lateral views are preferred (allows multiple views)
            - Can be performed only if the patient can stand for the exam
        - AP images are usually obtained urgently when a patient cannot stand (e.g., sick in a hospital bed)
    - Was the image taken at full inspiration?
        - Small lung volumes can produce vascular crowding and apparent mediastinal widening and atelectasis
- Lines and tubes
    - Check the position of the endotracheal tube if present
        - The tube should terminate 2 cm above the carina with 3–5 cm above optimal
    - Central venous catheters should follow expected venous courses and generally end at the superior vena cava near the level of the carina along the right aspect of the mediastinum
    - Ensure that you can partially visualize nasogastric and enteric feeding tubes and that they do not coil in the esophagus or extend into the lung
- Airway
    - Trachea should be midline and not deviated
        - The trachea deviates away from the lung pathology in tension pneumothorax (**Fig. 52-3**)
        - The trachea deviates toward the lung pathology in volume loss (e.g., atelectasis) or lobar collapse

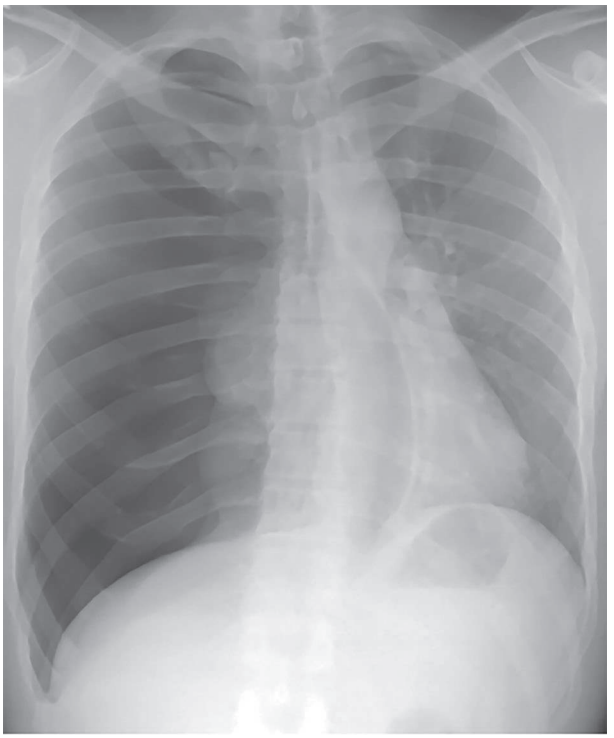

FIGURE 52-3 Tension pneumothorax. Expiratory radiograph of right tension pneumothorax increases the apparent shift of midline structures including the azygoesophageal line, seen here behind the heart, to the left of the spine. The three lobes of the right lung are seen separating from each other centrally with complete absence of lung markings peripherally. Increased space between ribs and depression of the right hemidiaphragm also indicate expansion of the space occupied by the pneumothorax. (Reproduced with permission from Barile MF, Jacobson FL. Basic chest radiography (CXR), in *Principles and Practice of Hospital Medicine,* 2nd ed, SC McKean et al (eds). New York, McGraw-Hill Education, 2017.)

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- Bones
  - Evaluate the sternum, ribs, clavicles, spine, and shoulders for
    - Fractures
    - Osteolytic or osteoblastic lesions
    - Arthritic changes
- Diaphragm
  - Sides of the diaphragm should be equal and slightly rounded
    - The right side may be higher than the left (normal anatomy)
  - Abnormal elevation of one side may suggest
    - Diaphragm paralysis
    - Loss of lung volume on that side
    - Diaphragmatic eventration
    - Diaphragmatic tear (in trauma)
  - Assess the costophrenic angles for blunting in pleural effusion evaluation
  - A flat hemidiaphragm indicates hyperexpansion, often seen in COPD
  - Evaluate for free air under the diaphragm on an upright radiograph (sign of bowel perforation)
- Soft tissues
  - Examine soft tissues for symmetry, subcutaneous air, edema, and breast tissue anatomy
- Heart and mediastinum
  - Evaluate heart size
    - Greater than half of the chest width suggests cardiomegaly or pericardial effusion
  - The aortic knob should be distinct
  - Mediastinal widening may indicate
    - Thoracic aortic dissection or aneurysm
    - Left atrial dilation
    - A mass
    - Mediastinal fat deposition in obese patients
  - Tension pneumothorax may produce mediastinal deviation (Fig. 52-3)
- Hilar structures
  - The left hilum is usually 2–3 cm higher than the right
  - Enlarged hila suggest lymphadenopathy or pulmonary artery enlargement
- Lung markings
  - Assess for normal lung markings all the way out to the chest wall to rule out pneumothorax (Fig. 52-3)
    - If lung markings do not appear at the periphery, look for a thin white visceral pleural line *(do not miss this)* to identify a pneumothorax
  - Normal lung markings taper as they travel out to the periphery and are smaller in the upper lungs
    - Lung markings in the upper lung fields that are as large or larger than those in the lower lung ("cephalization") suggest pulmonary edema
  - HF causes Kerley B lines (small linear densities perpendicular to the pleural surface, often best seen in the lung bases; see **Fig. 52-4**)
  - Hyperlucent lungs with increased retrosternal clear space on the lateral image are seen in emphysema
  - Examine the lungs for areas of consolidation (**Fig. 52-5**) and nodules
  - Obscuration of all or part of the heart border (silhouette sign) implies that a lesion is contiguous with or abuts the heart border and likely lies within the right middle lobe or lingua
  - A small pleural effusion is suggested by blunting of the costophrenic angle, best seen on the lateral image
  - ARDS on CXR reveals bilateral alveolar infiltrates (**Fig. 52-6**)

CASE ANSWERS

1. There is a large left-sided pleural effusion on the posterior–anterior CXR.
2. The pleural effusion is most likely secondary to the mesothelioma.
3. Given the pleural effusion is large and unilateral, a thoracentesis should be performed to evaluate its characteristics (i.e., transudate versus exudate). In addition, the pleural fluid should be sent for cytology review to assess for mesothelioma cells.

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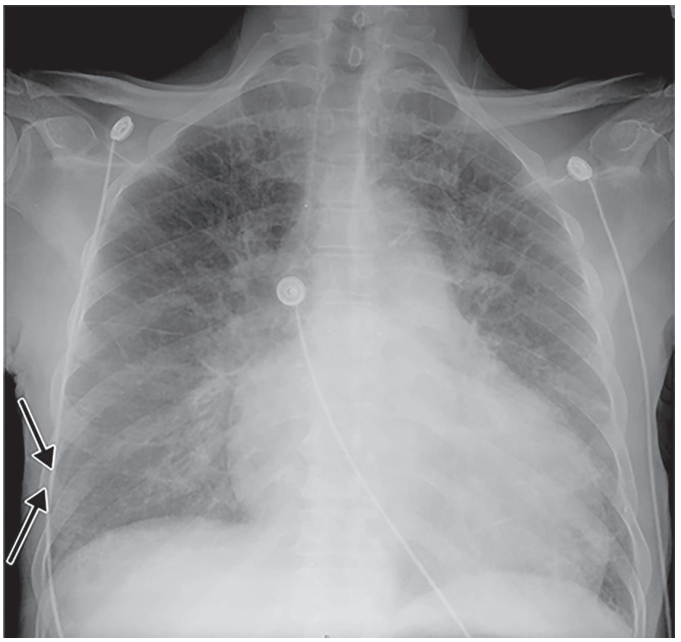

FIGURE 52-4 Interstitial pulmonary edema. Frontal CXR demonstrates diffuse bilateral reticular opacity as well as Kerley B lines (two are annotated with black arrows). These represent distended pulmonary lymphatic channels within the interlobular septae due to fluid overload. The cardiac silhouette is grossly enlarged in this patient with HF. (Reproduced with permission from Gupta N et al. Cardiothoracic imaging, in *Introduction to Diagnostic Radiology,* KM Elsayes, SAA Oldham (eds). New York, McGraw-Hill Education, 2014.)

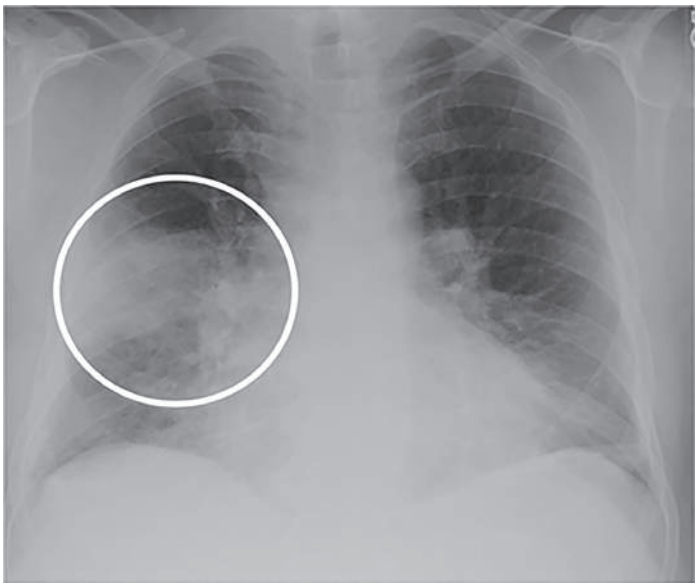

FIGURE 52-5 Right upper lobe pneumonia. Posterior–anterior view of the chest demonstrates a large airspace opacity in the right mid lung zone. (Reproduced with permission from Gupta N et al. Cardiothoracic imaging, in *Introduction to Diagnostic Radiology,* KM Elsayes, SAA Oldham (eds). New York, McGraw-Hill Education, 2014.)

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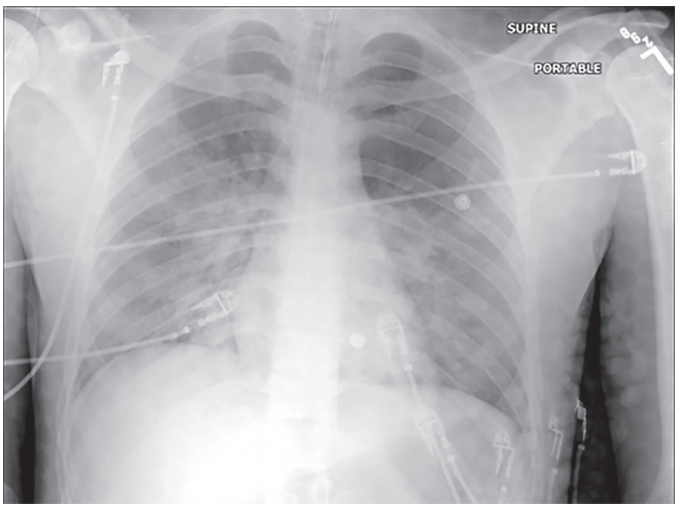

FIGURE 52-6 Drowning causing ARDS. Anterior–posterior CXR demonstrating bilateral alveolar infiltrates consistent with severe ARDS in the setting of freshwater drowning. (Used with permission from Ash SY, Washko GR. Atlas of chest imaging, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

FURTHER READING

- Ash SY, Washko GR. Atlas of chest imaging, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.
- Barile MF, Jacobson FL. Basic chest radiography (CXR), in *Principles and Practice of Hospital Medicine*, 2nd ed, SC McKean et al (eds). New York, McGraw-Hill Education, 2017.
- Gupta N et al. Cardiothoracic imaging, in *Introduction to Diagnostic Radiology*, KM Elsayes, SAA Oldham (eds). New York, McGraw-Hill Education, 2014.
- Washko GR et al. Diagnostic procedures in respiratory disease, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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53 Reading ECGs

CLINICAL VIGNETTE

A 70-year-old man with CAD, rheumatoid arthritis, COPD, and hyperlipidemia was admitted 1 day ago to the medical floor for the evaluation of chest pain. Thus far, serial troponins were within normal limits. His last ECG, which was performed during an episode of recurrent chest pain and palpitations, is shown in Fig. 53-1.

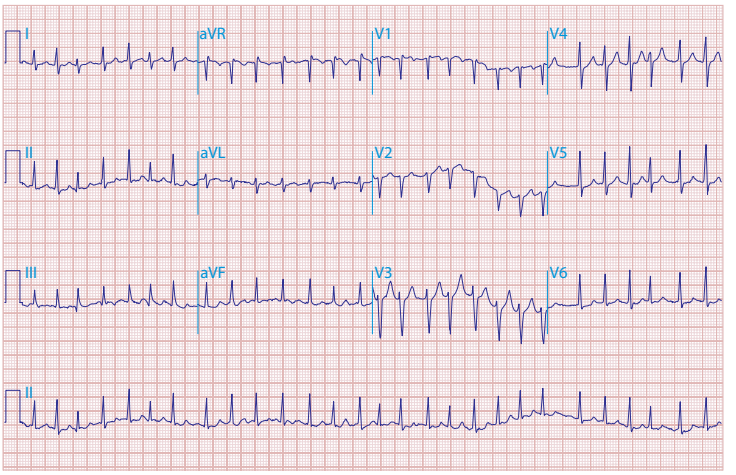

FIGURE 53-1 (Reproduced with permission from Goldberger AL. Atlas of cardiac arrhythmias, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

GUIDING QUESTIONS

1. Describe the rhythm and rate of the ECG in Fig. 53-1.
2. Does this patient have any evidence of myocardial ischemia on the ECG?
3. What is the underlying rhythm disorder on the ECG?

APPROACH TO READING ECGs

- Read and interpret *every* ECG you order for a patient
- Always try to compare a previous ECG with the new one
- Read every ECG systematically in the following order to avoid missing important findings
  - Rate
  - Rhythm
    - Pauses?
    - Premature contractions?
    - Are all P waves of the same morphology in a single lead?
    - P before every QRS, and vice versa?
    - PR interval
    - QRS interval
  - QT_C interval
  - QRS axis
    - Evaluate leads I and aVF
  - Hypertrophy (atrial and ventricular)
    - P wave morphology in leads II and V_1 for atria
    - R/S in V_1 and $V_5/_6$ for ventricles

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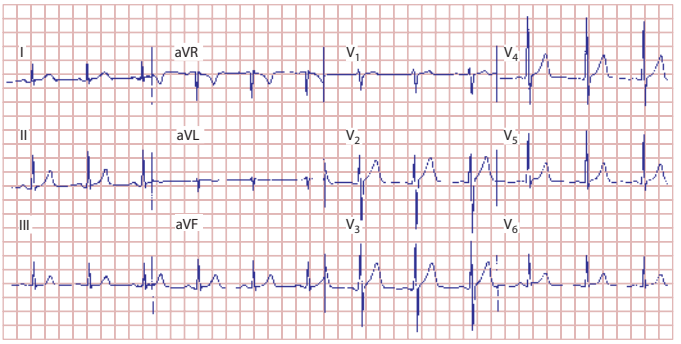

FIGURE 53-2 Normal ECG from a healthy male. Sinus rhythm is present with a heart rate of 75 beats per minute. PR interval is 160 ms; QRS interval (duration) is 80 ms; QT interval is 360 s; QT_c (Framingham formula) is about 390 ms; the mean QRS axis is about +70°. The precordial leads show normal R-wave progression with the transition zone (R wave ≈ S wave) in lead V_3. (Reproduced with permission from Goldberger AL. Electrocardiography, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - Infarction
        - Significant Q waves
        - T wave inversions
        - ST changes (depressions and elevations)
- **Figure 53-2** depicts a normal ECG for a healthy male

RATE

- Count the number of large boxes between the peaks of R waves to measure the following rates
    - 1 = 300 beats/min
    - 2 = 150 beats/min
    - 3 = 100 beats/min
    - 4 = 75 beats/min
    - 5 = 60 beats/min
    - 6 = 50 beats/min
    - 7 = 40 beats/min
- For bradycardia and irregular rhythms
    - Number of cardiac cycles per 6-s strip × 10 = rate
        - For example, 3 cardiac cycles per 6-s rhythm strip is a rate of 30 beats/min

RHYTHM

- Identify the basic rhythm, then scan for
    - Pauses
    - Premature beats
    - Irregularity
    - Intervals
    - Abnormal waves
- P before every QRS
- QRS after every P
- PR interval
- QRS interval
- QT_C interval
- Has the QRS vector shifted outside the normal range?
    - Left axis deviation is observed in a left anterior hemiblock
    - Right axis deviation is observed in a left posterior hemiblock

IRREGULARLY IRREGULAR RHYTHMS

- Sinus arrhythmia
    - Physiologic response to breathing
    - Irregular rhythm that changes with inspiration/expiration (normal variant)

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FIGURE 53-3 Multifocal atrial tachycardia. Rhythm strip obtained from a patient with severe pulmonary disease during an acute illness. Note the irregularity of the rhythm but with distinct P waves. *Arrows* note three distinct P-wave morphologies. (Reproduced with permission from Sauer WH, Romero JE, Zei PC. Common atrial flutter and macroreentrant and multifocal atrial tachycardias, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Wandering pacemaker
  - P waves change shape (> 3 morphologies) with a rate < 100 beats/min
- Multifocal atrial tachycardia (**Fig. 53-3**)
  - P waves change shape (> 3 morphologies) with a rate of > 100 beats/min
- Atrial fibrillation (**Fig. 53-4**)
  - Irregularly irregular ventricular rhythm without discernible P waves

ESCAPE BEATS

- An unhealthy sinoatrial (SA) node may fail to emit a pacing stimulus (sinus block), producing a pause that may produce an escape beat from a normally overdrive-suppressed automaticity focus
- Atrial escape beat
  - A pause that produces a morphologically different P wave than the rest with a normal QRS interval
- Junctional escape beat (**Fig. 53-5**)
  - A pause that produces no P wave with a normal QRS interval
- Ventricular escape beat
  - A pause that produces no P wave with a widened QRS interval and can be unifocal or multifocal

ESCAPE RHYTHMS

- An unhealthy SA node may cease to produce a pacing stimulus (sinus arrest), causing a normally overdrive-suppressed automaticity focus to take over pacing responsibilities
- The same principles as escape beats, but instead of one beat occurring, it turns into the rhythm (multiple escape beats in a row)
  - **Figure 53-6** depicts a junctional escape rhythm

PREMATURE BEATS

- An irritable automaticity focus may suddenly discharge, producing a premature beat
- Premature atrial complex (PAC)
  - A premature beat with a morphologically different P wave than the rest with a normal QRS interval

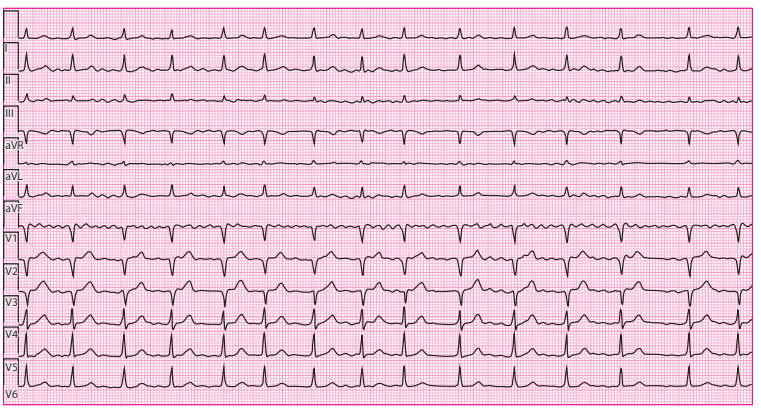

FIGURE 53-4 ECG of an irregularly irregular heart rhythm without discernible P waves of atrial fibrillation. The disorganized atrial activation is best appreciated in lead V_1 for this patient. (Reproduced with permission from Sauer WH, Romero JE, Zei PC. Atrial fibrillation, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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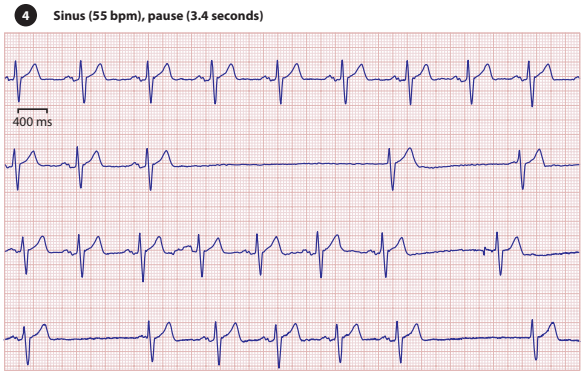

FIGURE 53-5 Sinoatrial exit block. A pause in the heart rhythm is seen that results from a sinus pause. On the second line of the tracing, there is a pause that results from the absence of a sinus beat (absent P wave) and no subsequent QRS. This is followed by a junctional escape beat and eventually recovery of the presence of sinus rhythm P waves. (Reproduced with permission from Sauer WH, Koplan BA. The bradyarrhythmias: Disorders of the sinoatrial node, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Premature junctional complex
  - A premature beat with no P wave and a normal QRS interval
- Premature ventricular complex (PVC) (**Fig. 53-7**)
  - A premature beat with no P wave and a widened QRS interval

TACHYDYSRHYTHMIAS

- Paroxysmal tachycardias (rate of 150–250 beats/min)
  - Includes supraventricular tachycardias
    - Paroxysmal atrial tachycardia (with and without block)
    - Paroxysmal junctional tachycardia
    - Paroxysmal ventricular tachycardia
- Flutter rhythms have an atrial rate of 250–350 beats/min and include
  - Atrial flutter
  - Ventricular flutter
- Fibrillation rhythms have an atrial rate of 350–450 beats/min and include
  - Atrial fibrillation
  - Ventricular fibrillation
- Focal atrial tachycardia (**Fig. 53-8**)
  - An irritable focus discharging at 150–250 beats/min with a P wave visibly different from before
- Atrioventricular (AV) nodal reentry tachycardia (**Fig. 53-9**)
  - A narrow complex tachycardia with retrograde P waves

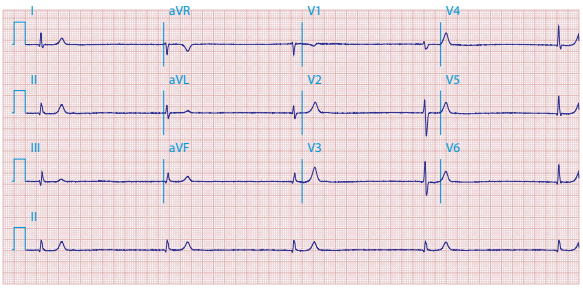

FIGURE 53-6 Marked junctional (escape) bradycardia (25 beats/min). Rate is regular with a flat baseline between narrow QRS complexes, without evident P waves. Patient was taking atenolol, with possible underlying sinus node dysfunction. The serum potassium was borderline elevated at 5.5 mEq/L. (Reproduced with permission from LA Nathanson et al: ECG Wave-Maven: Self-Assessment Program for Students and Clinicians. https://ecg.bidmc.harvard.edu/maven/mavenmain.asp.)

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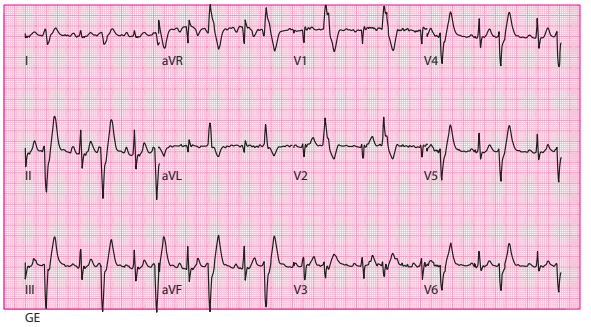

FIGURE 53-7 Ventricular bigeminy with premature ventricular contractions (PVCs) originating from the posteromedial papillary muscle. Twelve-lead ECG showing normal sinus rhythm with ventricular bigeminy. The PVCs have a right bundle branch block configuration in V_1 with superiorly directed axis. The leads V_4–V_6 are negative. The configuration is consistent with a PVC origin in the posteromedial papillary muscle of the left ventricle. (Reproduced with permission from Sauer WH, Tedrow UB. Premature ventricular contractions, nonsustained ventricular tachycardia, and accelerated idioventricular rhythm, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

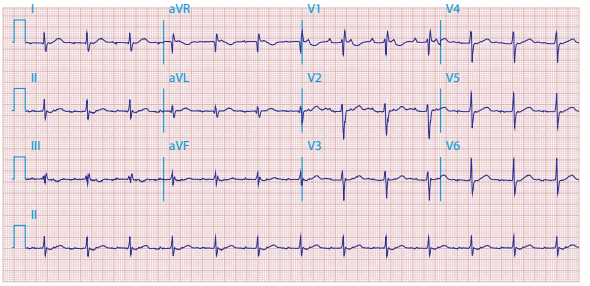

FIGURE 53-8 Atrial tachycardia (focal) with 2:1 conduction (block). The nonsinus P-wave rate at rest is about 150/min, with ventricular (QRS) rate of about 75/min. The nonconducted ("extra") P waves just after the QRS complex are best seen in lead V_1. Note also: incomplete right bundle branch block and borderline QT prolongation. (Reproduced with permission from LA Nathanson et al: ECG Wave-Maven: Self-Assessment Program for Students and Clinicians. http://ecg.bidmc.harvard.edu.)

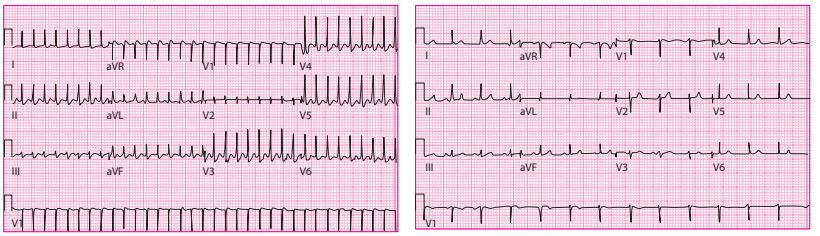

FIGURE 53-9 Atrioventricular nodal reentry tachycardia with retrograde P waves before and after adenosine termination. (Reproduced with permission from Sauer WH, Zei PC. Paroxysmal supraventricular tachycardias, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Wolff-Parkinson-White syndrome (**Fig. 53-10**)
  - When in normal sinus rhythm, a short P-R interval with delta waves and widened QRS complexes are seen and can become orthodromic AV reentry
- Paroxysmal junctional tachycardia
  - An AV junctional focus produces a rapid sequence of QRS-T cycles (no P waves) at 150–250 beats/min
  - QRS interval may be slightly widened

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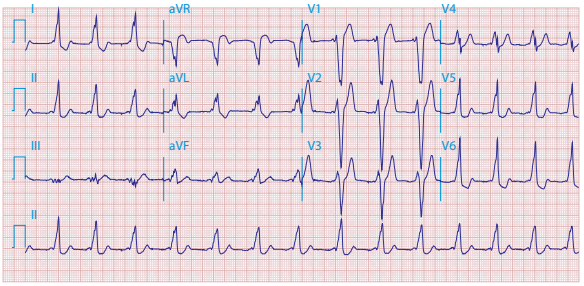

FIGURE 53-10 Wolff-Parkinson-White preexcitation pattern, with classic triad of a short PR, wide QRS, and delta waves. Polarity of the delta waves (slightly positive in leads V_1 and V_2 and most positive in lead II and lateral chest leads) is consistent with a right-sided bypass tract. (Reproduced with permission from LA Nathanson et al: ECG Wave-Maven: Self-Assessment Program for Students and Clinicians. http://ecg.bidmc.harvard.edu.)

- Atrial fibrillation (Fig. 53-4)
  - Multiple atrial foci rapidly discharging produce a jagged baseline of tiny spikes, irregular ventricular rhythm without discernible P waves
  - Treatment: calcium channel or β-blocker; synchronized cardioversion if unstable
- Atrial flutter (**Fig. 53-11**)
  - A continuous (sawtooth) rapid sequence of atrial complexes from a single rapid-firing atrial focus
  - Treatment: calcium channel or β-blocker; synchronized cardioversion if unstable
- Ventricular tachycardia (**Fig. 53-12** A, C, and D)
  - A ventricular focus produces a rapid (150–250 beats/min) sequence of PVC-like wide ventricular complexes
  - QRS interval widened with no P waves
- Ventricular flutter (Fig. 53-12 B and C)
  - A rapid series of smooth sine waves from a single rapid-firing ventricular focus, usually leading to ventricular fibrillation
  - Also can have torsades de pointes
  - Treatment: amiodarone; IV magnesium; unsynchronized shock if unstable
- Ventricular fibrillation (Fig. 53-12 E)
  - Multiple ventricular foci rapidly discharging produce a totally erratic ventricular rhythm without identifiable waves
  - Treatment: amiodarone; unsynchronized shock if unstable

SA AND AV BLOCKS

- Scan PR interval to see if
  - It is prolonged (> 0.2 s)

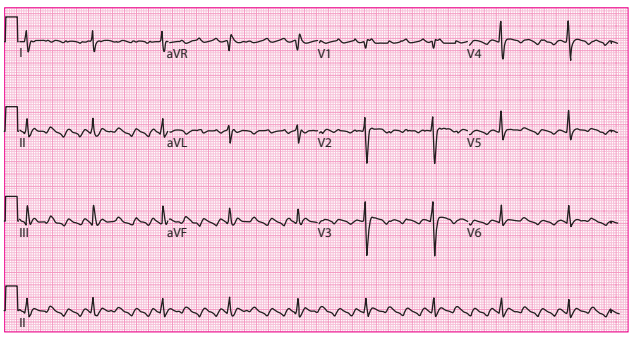

FIGURE 53-11 A 12-lead ECG of typical or common atrial flutter (counterclockwise activation) is shown. Note the sawtooth pattern of atrial activation, with negative flutter (F) waves in inferior limb lead and positive flutter waves in lead V_1, as well as 4:1 atrioventricular conduction during flutter. (Reproduced with permission from Sauer WH et al. Common atrial flutter and macroreentrant and multifocal atrial tachycardias, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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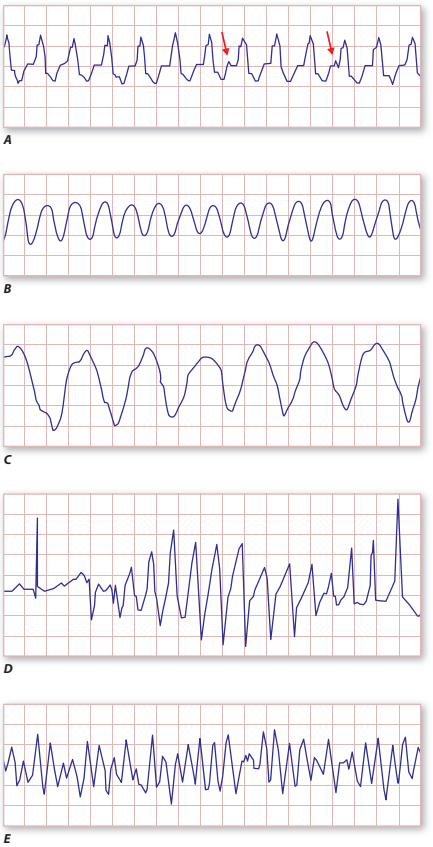

FIGURE 53-12 ***A.*** Monomorphic ventricular tachycardia (VT) with dissociated P waves (*short arrows*). ***B.*** Ventricular flutter. ***C.*** Sinusoidal VT due to electrolyte disturbance or drug effects. ***D.*** Polymorphic VT resulting from prolongation of QT interval (torsades de pointes VT). ***E.*** Ventricular fibrillation. (Reproduced with permission from Sauer WH, Tedrow UB. Approach to ventricular arrhythmias, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

    - The interval is getting longer or is fixed
    - There are missed beats
- Scan QRS interval to see if it is prolonged (> 0.12 s) (bundle branch blocks)
- Evaluate for axis deviation (hemiblock may be present)
- SA block
    - An unhealthy SA node misses one or more cycles (sinus pause)—an escape beat may occur
- First-degree AV block (Fig. 53-13)
    - Prolonged PR interval (> 0.2 s) with no missed beats
- Second-degree type 1 AV block (Mobitz I AV block; Fig. 53-13)
    - PR interval gradually lengthens with each cycle until the last P wave in the series does not produce a QRS
- Second-degree type 2 AV block (Mobitz II AV block; Fig. 53-13)
    - PR intervals remain constant, but some P waves do not produce a QRS response
    - Treatment: pacemaker
- Third-degree AV block (complete heart block; Fig. 53-13)
    - The P wave and QRS have no correlation
    - If QRS is narrow and ventricular rate is 40–60 beats/min, then it is a junctional focus
    - If QRS widened and rate is 20–40 beats/min, then it is a ventricular focus
    - Treatment: pacemaker
- Right and left bundle branch blocks (Fig. 53-14)
    - Right bundle branch block (RBBB)
        - Widened QRS with broad S waves in leads I and $V_5/_6$ and a R,R' in $V_1/_2$

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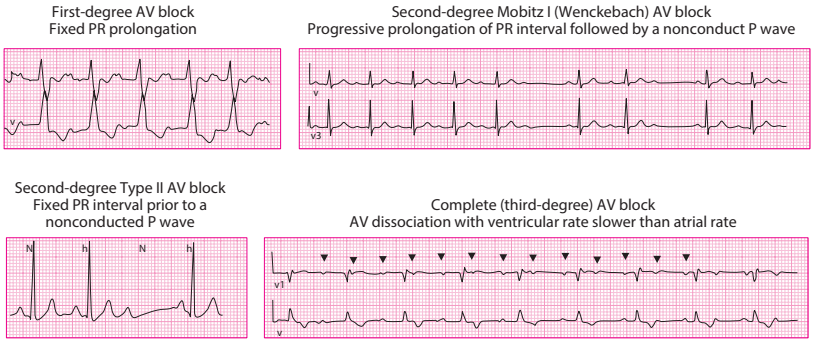

FIGURE 53-13 Types of atrioventricular (AV) block. The *upper left* figure displays fixed prolongation of the PR interval. The *upper right* figure demonstrates Mobitz I block (Wenckebach AV block) manifested as progressive prolongation of the PR interval followed by a nonconducted P wave ("dropped beat"). The *lower left* figure displays AV block with P wave with no QRS complex and no associated PR prolongation prior to the dropped beat (Mobitz type II AV block). The *lower right* figure demonstrates complete heart block manifested as dissociation between P waves and QRS complexes (AV dissociation). (Reproduced with permission from Sauer WH, Koplan BA. The bradyarrhythmias: Disorders of the atrioventricular node, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

- Left bundle branch block (LBBB)
  - Widened QRS with broad deep S wave in $V_{1}/_{2}$ and a R,R' in $V_{5}/_{6}$
- Hemiblocks (Fig. 53-14)
  - RBBB with left anterior hemiblock
    - RBBB with left axis deviation
  - RBBB with left posterior hemiblock
    - RBBB with right axis deviation

QT_c INTERVAL

- A variety of formulas has been proposed for computing a rate-corrected QT interval, termed QT_C, but without formal consensus

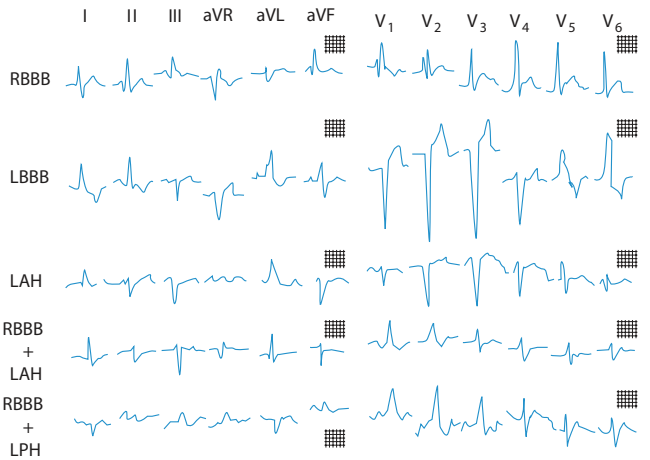

FIGURE 53-14 Intraventricular conduction abnormalities. Illustrated are right bundle branch block (RBBB); left bundle branch block (LBBB); left anterior hemiblock (LAH); right bundle branch block with left anterior hemiblock (RBBB + LAH); and right bundle branch block with left posterior hemiblock (RBBB + LPH). (Reproduced with permission from Jameson JL et al. Electrocardiography, in *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). New York, McGraw-Hill Education, 2020.)

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- The following upper normal limits (based visually on the longest QT) have been proposed
  - QT_C of 460 ms in women
  - QT_C of 450 ms in men
- Lower limits are less well defined
- Prolonged QT_C etiologies
  - Congenital
  - Hypokalemia
  - Hypocalcemia
  - Medications (e.g., class IA and class III antiarrhythmics, tricyclics)
- Short QT_C etiologies
  - Hypercalcemia
  - Inherited short QT syndromes
  - Acidosis
  - Hyperthermia

QRS AXIS

- Is the QRS positive or negative in leads I and aVF (Fig. 53-15)?
  - Positive in I and aVF → normal axis
  - Positive in I and negative in aVF → left axis deviation
  - Negative in I and positive in aVF → right axis deviation
  - Negative in I and aVF → extreme right axis deviation

HYPERTROPHY

ATRIAL HYPERTROPHY

- Assess lead V_1 to look for a large, diphasic P wave (Fig. 53-16)
- Assess lead II for P wave morphology changes
- Right atrial hypertrophy
  - V_1 has a large, diphasic P wave with a tall initial component; lead II looks similar
- Left atrial hypertrophy
  - V_1 has a large, diphasic P wave with a wide terminal component; lead II is notched

VENTRICULAR HYPERTROPHY

- Examine the R and S in leads V_1, V_5, V_6, as well as right or left axis deviation (Fig. 53-17)
- Right ventricular hypertrophy
  - R wave > S in V_1 but the R wave gets progressively smaller from V_1–V_6
  - S wave persists in V_5/$_6$
  - Right axis deviation with a slightly widened QRS

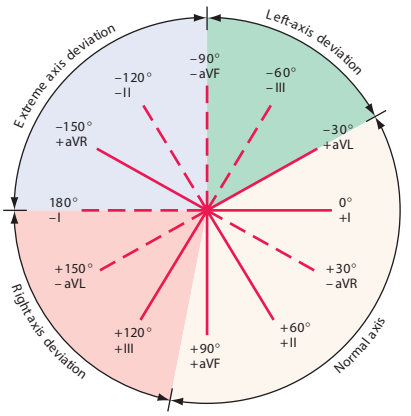

FIGURE 53-15 Electrocardiographic lead systems: The hexaxial frontal plane reference system to estimate electrical axis. Determine leads in which QRS deflections are maximum and minimum. For example, a maximum positive QRS in I which is isoelectric in aVF is oriented to 0°. Normal axis ranges from −30° to +90°. An axis > +90° is right-axis deviation and < 30° is left-axis deviation. (Reproduced with permission from Jameson JL et al. Electrocardiography, in *Harrison's Manual of Medicine,* 20th ed, JL Jameson et al (eds). New York, McGraw Hill Education, 2020.)

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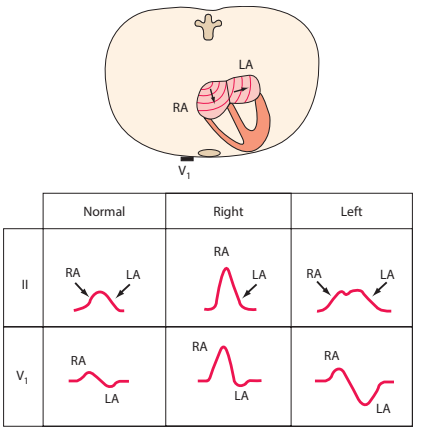

FIGURE 53-16 Right atrial (RA) overload may cause tall, peaked P waves in the limb or precordial leads. Left atrial (LA) abnormality may cause broad, often notched P waves in the limb leads and a biphasic P wave in lead V_1 with a prominent negative component representing delayed depolarization of the LA. (Reproduced with permission from MK Park, WG Guntheroth: *How to Read Pediatric ECGs*, 4th ed. St. Louis, Mosby/Elsevier, 2006.)

- Left ventricular hypertrophy
  - Amplitude of S in V_1 + amplitude of R in V_5 is > 35 mm
  - Left axis deviation with slightly widened QRS
  - Inverted T wave slants downward gradually but up rapidly (not symmetrically)

INFARCTION

- Assess for
  - T wave inversion (ischemia)
  - ST depression or elevation (injury)
  - Q waves (necrosis)
  - Changes in contiguous leads (**Table 53-1**)
- These changes evolve over time (**Fig. 53-18**)

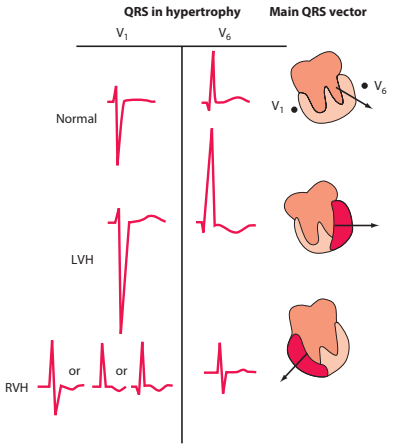

FIGURE 53-17 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V_1. T-wave inversions may be present in right precordial leads. (Reproduced with permission from Goldberger AL. Electrocardiography, in *Harrison's Principles of Internal Medicine,* 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.)

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TABLE 53-1 Location of Infarction and Its Corresponding Coronary Anatomy

AFFECTED LEADS	INFARCT LOCATION	LIKELY CORONARY ARTERY INVOLVED
II, III, aVF	Inferior wall MI	Right coronary artery
V_1–V_2	Septal MI	Left anterior descending artery
V_3–V_4	Anterior wall MI	Left anterior descending artery
V_1–V_4	Anteroseptal wall MI	Left anterior descending artery
I, aVL, V_5-V_6	Lateral wall MI	Circumflex artery
Prominent R in V_1	Posterior wall MI	Right coronary artery or circumflex artery
ST elevation in V_1 and right-sided V_4 with anterior wall MI	Right ventricular MI	Right coronary artery

Q WAVES

- *Necrosis* of myocardial tissue
- Significant Q waves are 1 mm wide, or one-third the amplitude (or more) of the QRS
- Ignore lead aVR when assessing for Q waves
- Old infarct Q waves remain for a lifetime

ST-SEGMENT DEPRESSION & ELEVATION

- *Injury* of myocardial tissue
- ST elevation with significant Q waves indicates an acute or recent infarct
- Returns to baseline with time

T WAVE INVERSIONS

- *Ischemia* of myocardial tissue
- Inverted T waves of ischemia are symmetric
- Normally, the T wave is upright when the QRS is upright, and inverted when the QRS is downward

ISCHEMIA IN THE SETTING OF A NEW LBBB

- In patients with LBBB and chest pain, use *Sgarbossa's criteria* to evaluate whether patient has had an MI
  - Sgarbossa's criteria have a 90% specificity for a STEMI if at least 3 points of the criteria are met:
    - Concordant ST elevation ≥ 1 mm in leads with a positive QRS complex (5 points)
    - Concordant ST depression ≥ 1 mm in leads V_1–V_3 (3 points)
    - ST elevation ≥ 5 mm in a lead with a negative QRS complex (2 points)

ANATOMY OF INFARCTION

- Know which contiguous leads correspond to coronary anatomy (Table 53-1)

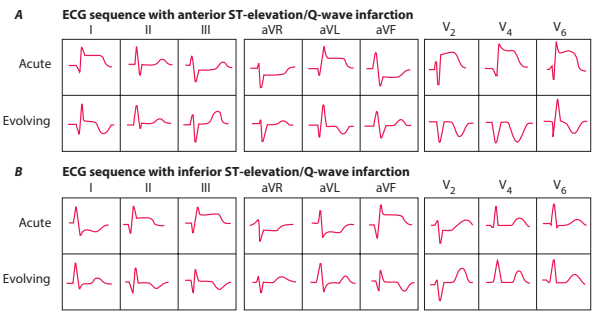

FIGURE 53-18 Sequence of depolarization and repolarization changes with acute and evolving anterior (*A*) and (*B*) inferior ST-elevation/Q-wave infarctions. With anterior infarcts, ST elevation in leads I and aVL and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterolateral) infarcts may be associated with reciprocal ST depressions in leads V_1 to V_3. (Reproduced with permission from AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 10th ed. Philadelphia, Elsevier, 2024.)

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CASE ANSWERS

1. The rhythm is irregularly irregular without discernible P waves prior to each QRS. The rate is tachycardic, estimated at 168 beats/min. There are no dropped beats or premature beats.
2. There is artificial drift of the baseline on this ECG, and nonspecific ST-T wave changes. There are no specific findings of myocardial ischemia on this ECG.
3. This ECG with an irregularly irregular rhythm without discernible P waves is diagnostic of atrial fibrillation. This patient currently has an uncontrolled rate for atrial fibrillation, which is termed *atrial fibrillation with rapid ventricular response*.

FURTHER READING

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54 Alcohol Withdrawal

CLINICAL VIGNETTE

A 43-year-old man presents to the ED with nausea and vomiting, tremor of the hands, and headaches. He states the symptoms have been progressively worsening over the past 24 h, since he stopped drinking alcohol. His alcohol consumption increased from 1–2 beers daily over the past 5 years to a pint of vodka daily since he lost his job 2 months ago. He has felt depressed and hopeless and is seeking help to stop alcohol consumption. He denies any other drug use and takes no prescribed medications. There is no history of delirium tremens or alcohol-withdrawal seizures. He currently denies any visual or auditory hallucinations. On exam, he is afebrile, the heart rate is 116 beats/min, respiratory rate is 18 breaths/min, BP is 164/88 mm Hg, and Spo_2 is 96% on room air. He appears anxious and diaphoretic and occasionally has angry outbursts in response to questions. Tremors of the hands and tongue are present. The pupils are equal, normal in size, and reactive to light. There is no jaundice, caput medusa, palmar erythema, or spider angiomata. The CMP reveals potassium 3.0 mEq/L, HCO_3^- 16 mEq/L, BUN 22 mg/dL, SCr 1.0 mg/dL, glucose 120 mg/dL, and AST/ALT 280 U/L and 95 U/L, respectively. A CBC, ECG, and CXR are within normal limits. The patient is administered 1 L of LR and PO thiamine.

GUIDING QUESTIONS

1. What clinical scoring system can assess the severity of this patient's alcohol withdrawal?
2. What clinical monitoring and precautions should this patient have while admitted?
3. What are the two main management strategies used in alcohol withdrawal?

GENERAL INFORMATION

- Sudden decrease in alcohol intake can produce withdrawal symptoms when a patient who has drunk large amounts for a prolonged period suddenly stops
- Alcohol withdrawal can be a *life-threatening condition* when not recognized or treated appropriately
- Symptoms usually begin 5–10 h after decreasing alcohol intake, peak on day 2 or 3, and improve by day 4 or 5
- Symptoms of alcohol withdrawal are due to withdrawal of alcohol, a CNS depressant, mimicking CNS overactivity
- Mild symptoms may persist for 4–6 months as a protracted abstinence syndrome
- About 2% of individuals with alcohol use disorder experience a withdrawal seizure
    - The risk increases in the context of older age, concomitant medical problems, misuse of additional drugs, and higher alcohol quantities
- Steps in evaluating a patient with alcohol withdrawal
    - A thorough history and physical exam
        - Include a thorough history of prior withdrawals, quantity of alcohol consumption, and timing of last drink for severity risk assessment
    - Evaluation of liver impairment, GI bleeding, cardiac dysrhythmias, infection, and glucose or electrolyte abnormalities
    - Assess willingness to stop alcohol consumption
        - Inquire about interest in naltrexone (an opioid antagonist) and referrals to long-term addiction treatment services upon discharge (possibly including inpatient detox programs)

CLINICAL FEATURES

- *Minor withdrawal symptoms* (6–48 h after alcohol cessation) are due to CNS hyperactivity and include
    - Insomnia
    - Tremulousness
    - Mild anxiety
    - GI upset and anorexia
    - Headache
    - Diaphoresis
    - Palpitations

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- *Alcoholic hallucinosis* refers to hallucinations developing within 12–24 h (or even earlier) of alcohol abstinence
  - Typically resolve within 24–48 h
  - This is a separate clinical entity from delirium tremens despite both involving hallucinations
- *Withdrawal-associated seizures* are generalized tonic-clonic convulsions that usually occur within 12–48 h after the last alcoholic drink
  - Withdrawal seizures can occur earlier than the 12- to 48-h mark
- *Delirium tremens* (DTs) is defined by hallucinations, disorientation, tachycardia, hypertension, hyperthermia, agitation, and diaphoresis in the setting of acute reduction or abstinence from alcohol
  - DTs typically begin between 48 and 96 h after the last drink and last 1–5 days
  - Typically, all patients in whom DTs develop have minor withdrawal symptoms prior to onset
- *Severe alcohol withdrawal* is often associated with fluid and electrolyte abnormalities, including the following
  - Metabolic acidosis (including anion gap metabolic acidosis from lactic acidosis)
  - Hypokalemia
  - Hypophosphatemia
  - Hypovolemia
  - Hypomagnesemia
- Differential diagnosis of alcohol withdrawal
  - Withdrawal from other sedatives (e.g., benzodiazepines, opioids)
  - Drug intoxication (e.g., cocaine, amphetamines)
  - Delirium due to a medical illness (e.g., hypoxemia, hypercapnia, hepatic encephalopathy, acute liver failure, thiamine deficiency, sepsis, bacteremia)
  - Anxiety disorder
  - Hallucinosis due to other causes (e.g., schizophrenia, amphetamine psychosis)
  - Seizure due to other causes (e.g., hypoglycemia, epilepsy)
  - CNS infection or bleed
  - GI bleeding

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL–REVISED (CIWA-Ar) SCALE

- A scoring system to monitor the signs and symptoms of alcohol withdrawal
- Helpful in all treatment strategies of alcohol withdrawal
  - Especially useful when using a symptom-triggered management strategy (see Management section)
- High initial scores and worsening scores over time indicate severe withdrawal with the need to escalate management and monitoring
- 10 categories are scored from 0-7 except the category of orientation, which is scored 0-4 (**Fig. 54-1**)
  - Bedside nurses usually assess and record the score, but any clinician can perform
- Score interpretation
  - < 10: very mild withdrawal
  - 10–15: mild withdrawal
  - 16–20: modest withdrawal
  - > 20: severe withdrawal

MANAGEMENT

BASIC PRINCIPLES OF INPATIENT ALCOHOL WITHDRAWAL TREATMENT

- Multivitamin with folate supplementation if able to tolerate PO
- Thiamine supplementation, either PO or IV
  - If concerned for Wernicke's encephalopathy, administer high-dose IV thiamine
- Administer glucose (with oral diet or via fluids) after thiamine has been administered
- Isotonic IV fluids as needed
- Vitals q4h if CIWA < 10, otherwise q1h
- Replete electrolytes, including magnesium, phosphorus, and potassium, when necessary
- Cardiac monitoring, continuous pulse oximetry, and fall/seizure/aspiration precautions
- Addiction service consult (if available at your institution)
- Medications used in alcohol withdrawal treatment
  - Benzodiazepines (e.g., lorazepam, oxazepam, diazepam, chlordiazepoxide)
    - Benzodiazepines have the most supportive data for alcohol withdrawal, including high levels of safety and low cost
  - Barbiturates (e.g., phenobarbital) are agents used to suppress CNS hyperactivity
- Most hospital systems have "alcohol withdrawal order sets," where CIWA monitoring and either front-loading and/or symptom-triggered medications can be ordered (use your institution's protocol)

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Patient: _____ **Date:** _____ **Time:** _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for 1 minute: _____ **Blood pressure:** _____

NAUSEA AND VOMITING — Ask "Do you feel sick to your stomach? Have you vomited?" Observation.

0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES — Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.

0 none
1 very mild itching, pins and needles, burning, or numbness
2 mild itching, pins and needles, burning, or numbness
3 moderate itching, pins and needles, burning, or numbness
4 moderately severe hallucinations (formications)
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

TREMOR — Arms extended and fingers spread apart. Observation.

0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

AUDITORY DISTURBANCES — Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.

0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe auditory hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

PAROXYSMAL SWEATS — Observation.

0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

VISUAL DISTURBANCES — Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.

0 not present
1 very mild photosensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe visual hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

ANXIETY — Ask "Do you feel nervous?" Observation.

0 no anxiety, at ease
1 mildly anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 severely anxious, equivalent…

HEADACHE, FULLNESS IN HEAD — Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.

0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

AGITATION — Observation.

0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM — Ask "What is today's date?… Who am I?". Serial additions: "Please count up by 5's — 0, 5, 10…"

0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for date and place or person

Total **CIWA-Ar** Score _____

Rater's Initials _____

Maximum Possible Score 67

This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 8 (or 10, according to some experts) do not usually need additional medication for withdrawal.

FIGURE 54-1 Alcohol withdrawal assessment (CIWA-Ar) scale. (Reproduced from Sullivan JT et al. Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale [CIWA-Ar]. Br J Addict. 1989;84:1353. This scale is not copyrighted and may be used freely.)

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SYMPTOM-TRIGGERED THERAPY

- The *recommended approach for most patients to treat alcohol withdrawal* when pharmacotherapy is indicated
- Involves providing medications only when a patient is symptomatic
  - Symptomatic is determined by CIWA-Ar scoring
- Regular (e.g., q1–4h) CIWA-Ar scores are recorded, and if scores reach a certain threshold—such as a score ≥ 8—a benzodiazepine is administered; typical agents include
  - Lorazepam 2–4 mg PO or IV *or*
  - Diazepam 5–10 mg IV
- If the CIWA-Ar score reaches a higher threshold (e.g., ≥ 15)
  - Higher doses of benzodiazepines and more frequent monitoring may be necessary
- Giving benzodiazepines only when needed is supported by randomized and observational studies
  - Symptom-triggered therapy achieves equivalent or superior clinical endpoints while requiring lower total doses of sedatives and shorter periods of hospitalization

FRONT-LOADING THERAPY

- Appropriate for patients who are at the highest risk for experiencing dangerous complications (e.g., withdrawal seizures or DTs)
- Consists of administering higher initial doses of benzodiazepines or barbiturates to prevent worsening of symptoms or achieve rapid control of symptoms (i.e., appropriate levels of sedation)
  - Benzodiazepines
    - Lorazepam 2–4 mg IV q15–20 min *or*
    - Diazepam 5–10 mg IV q5–10 min
  - Barbiturates
    - IV load of phenobarbital 130–260 mg with repeat doses q15–20 min
    - Monotherapy with phenobarbital is not recommended given a lack of evidence, and one study found it was not superior to benzodiazepines in preventing ICU or hospital admission
- If choosing this strategy, consult with your pharmacist and the ICU team

REFRACTORY DELIRIUM TREMENS DESPITE BENZODIAZEPINES

- Barbiturates (e.g., phenobarbital) can be very effective in these patients when given with a benzodiazepine
- Phenobarbital and benzodiazepines work synergistically
  - Barbiturates increase the duration of the GABA chloride channel opening
  - Benzodiazepines increase the frequency of the GABA chloride channel opening

ADJUNCTIVE MEDICATIONS

- Gabapentin 300 mg tid can reduce alcohol cravings
- However, carbamazepine, gabapentin, and valproate lack convincing evidence that these medications help patients with DTs or severe alcohol withdrawal symptoms

TRANSITIONING TO THE OUTPATIENT SETTING

- All patients should be educated about alcohol cessation
- Addiction treatment teams are useful for continuity of care in managing the patient post-discharge
- Naltrexone may shorten subsequent relapses; options of administration include
  - Naltrexone 50–150 mg PO daily
  - Naltrexone 380 mg intramuscular injection once per month
- Acamprosate 2 g/d divided into three doses inhibits NMDA receptors and decreases mild symptoms and protracted withdrawals
- The combination of naltrexone and acamprosate is well tolerated, and efficacy might be superior to that of either drug alone

CASE ANSWERS

1. The Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA-Ar) Scale is measured frequently in patients with alcohol withdrawal to assess severity and response to treatment. It has 10 categories that are scored (Fig. 54-1), resulting in a total score that is trended over time. The higher the score, the greater the alcohol withdrawal severity.
2. Patients with alcohol withdrawal may have dysrhythmias, seizures, aspiration, and lab abnormalities. Continuous telemetry (for at least 24 h), seizure precautions (pads on the side of the hospital bed), aspiration precautions, and frequent lab monitoring (especially potassium, magnesium, and phosphate) are indicated until the withdrawals begin to improve and the patient is eating regularly.

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3. Symptom-triggered and front-loading therapy are the two main management strategies for alcohol withdrawal. Both use benzodiazepines as the main pharmacologic intervention. Barbiturates as monotherapy are not recommended for front-loading therapy but can be used in conjunction with benzodiazepines in patients with benzodiazepine-refractory delirium tremens and severe alcohol withdrawal.

FURTHER READING

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55 Acid-Base Disorders

CLINICAL VIGNETTE

A 42-year-old woman is evaluated in the hospital 5 days after admission for nausea and vomiting due to a partial small bowel obstruction. Medical history includes diverticulitis and a partial colectomy 2 years ago. A nasogastric tube on continuous suction was initiated on hospital day 1, and she has been NPO since admission. On exam, she is afebrile, BP is 98/66 mm Hg, heart rate is 98 beats/min, and respiratory rate is 18 breaths/min. There is decreased skin turgor and a delayed capillary refill time. An ABG on room air reveals a pH of 7.48, Pao_2 80 mm Hg, $Paco_2$ 47 mm Hg, and HCO_3^- 32 mEq/L. A BMP reveals a sodium of 137 mEq/L, potassium 2.9 mEq/L, chloride 97 mEq/L, and HCO_3^- 31 mEq/L.

GUIDING QUESTIONS

1. What is the primary acid-base disorder present in this patient?
2. What additional test would you order to help diagnosis and management?

NORMAL ACID-BASE HOMEOSTASIS

- Systemic arterial pH is maintained between 7.35 and 7.45 by extracellular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms
- The control of arterial CO_2 tension ($Paco_2$) by the CNS and respiratory system and the control of plasma bicarbonate by the kidneys stabilize the arterial pH by excretion or retention of acid or alkali
- The metabolic and respiratory components that regulate systemic pH are described by the Henderson-Hasselbalch equation and solved for pH when the solubility of CO_2 is considered (dissolved CO_2 in mEq/L = 0.03 × $Paco_2$ in mm Hg) at a pK' of 6.1
    - $pH = pK' + \log_{10} \frac{[HCO_3^-]}{PCO_2}$
- Under most circumstances, CO_2 production and excretion are matched
    - The usual steady-state $Paco_2$ is maintained at ~ 40 mm Hg
    - Underexcretion of CO_2 produces hypercapnia
    - Overexcretion of CO_2 causes hypocapnia
    - Nevertheless, production and excretion are again matched at a new steady-state $Paco_2$
    - Therefore, the $Paco_2$ is regulated primarily by neural respiratory factors and is not subject to regulation by the rate of CO_2 production
- Hypercapnia is usually the result of hypoventilation rather than of increased CO_2 production
- Increases or decreases in $Paco_2$ represent derangements of neural respiratory control or are due to compensatory changes in response to a primary alteration in the plasma $[HCO_3^-]$
- Compensatory mechanisms
    - Primary respiratory disturbances (primary changes in $Paco_2$) invoke compensatory metabolic responses (secondary changes in $[HCO_3^-]$)
    - Primary metabolic disturbances elicit predictable compensatory respiratory responses (secondary changes in $Paco_2$)

APPROACH TO ACID-BASE DISORDERS

- Steps in acid-base analysis
    - Obtain an ABG and venous electrolytes simultaneously
    - What is the pH?
        - Acidemia or alkalemia?
    - What is the primary disorder present?
        - Metabolic or respiratory?
    - Is there appropriate compensation?
    - Is the respiratory compensation acute or chronic?
    - If the disorder is primarily a metabolic acidosis, is there an elevated anion gap (AG)?
        - If there is an AG, what is the delta–delta ratio (delta AG/delta bicarbonate)?
            - The delta–delta ratio helps determine if there are other metabolic disorders present
    - What is the differential diagnosis for the acid-base disorder present?

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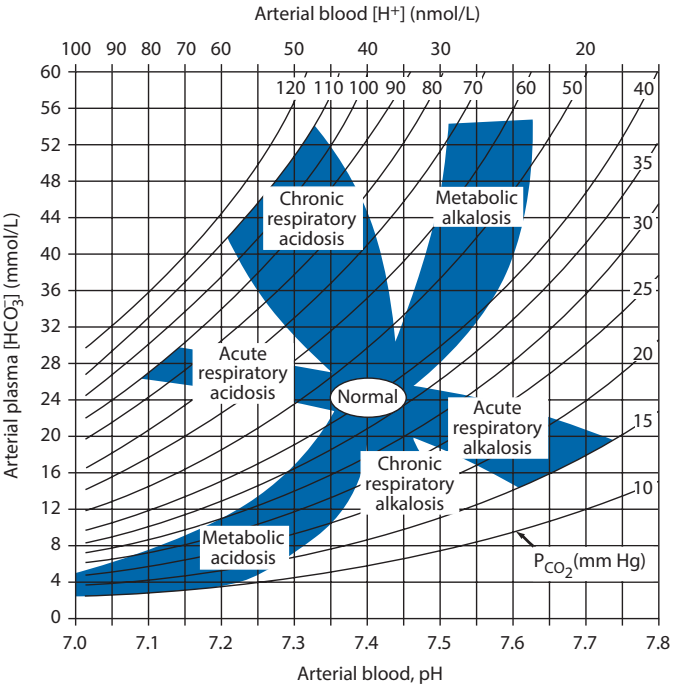

FIGURE 55-1 Acid-base nomogram. Shown are the 90% confidence limits (range of values) of the normal respiratory and metabolic compensations for primary acid-base disturbances. (Reproduced with permission from LL Hamm and TD DuBose Jr, in *Brenner and Rector's The Kidney,* 11th ed. Alan S.L. Yu, et al (eds). Philadelphia, Elsevier, 2020.)

- Normal values
  - pH: 7.35–7.45
  - $Paco_2$: 35–45 mm Hg
  - HCO_3^-: 22–26 mEq/L
  - Anion gap: 10–14 mEq/L
  - Albumin: 4 mg/dL
- Figure 55-1 describes the acid-base nomogram (normal respiratory and metabolic compensations for primary acid-base disturbances)
- *Determine the primary acid-base disorder from the pH and $Paco_2/HCO_3^-$ levels* (Table 55-1)
- *Is the respiratory compensation acute or chronic?* (Table 55-2)
  - Winter's formula
    - For metabolic acidosis, calculate the expected $Paco_2$
      - $Paco_2 = 1.5 \times (HCO_3^-) + 8 \pm 2$
      - If serum $Paco_2$ is greater than expected $Paco_2$, an additional respiratory acidosis is present
    - For metabolic alkalosis, calculate the expected $Paco_2$
      - $Paco_2 = [HCO_3^-] + 15$
      - If serum $Paco_2$ is lower than expected $Paco_2$, an additional respiratory alkalosis is present

TABLE 55-1 pH and $Paco_2/HCO_3^-$ Levels and Their Corresponding Acid-Base Disorders

pH	$Paco_2$ OR HCO_3^-	PRIMARY DISORDER
< 7.35	High CO_2	Respiratory acidosis
< 7.35	Low HCO_3^-	Metabolic acidosis
> 7.45	Low CO_2	Respiratory alkalosis
> 7.45	High HCO_3^-	Metabolic alkalosis

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TABLE 55-2 Prediction of Compensatory Responses to Simple Acid-Base Disturbances and Pattern of Changes

DISORDER	PREDICTION OF COMPENSATION	RANGE OF VALUES		
		pH	HCO_3^-	$Paco_2$
Metabolic acidosis	$Paco_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ *or* $Paco_2$ will ↓ 1.25 mm Hg per mmol/L ↓ in $[HCO_3^-]$ *or* $Paco_2 = [HCO_3^-] + 15$	Low	Low	Low
Metabolic alkalosis	$Paco_2$ will ↑ 0.75 mm Hg per mmol/L ↑ in $[HCO_3^-]$ *or* $Paco_2$ will ↑ 6 mm Hg per 10 mmol/L ↑ in $[HCO_3^-]$ *or* $Paco_2 = [HCO_3^-] + 15$	High	High	High
Respiratory alkalosis		High	Low	Low
Acute	$[HCO_3^-]$ will ↓ 0.2 mmol/L per mm Hg ↓ in $Paco_2$			
Chronic	$[HCO_3^-]$ will ↓ 0.4 mmol/L per mm Hg ↓ in Pco_2			
Respiratory acidosis		Low	High	High
Acute	$[HCO_3^-]$ will ↑ 0.1 mmol/L per mm Hg ↑ in Pco_2			
Chronic	$[HCO_3^-]$ will ↑ 0.4 mmol/L per mm Hg ↑ in Pco_2			

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- *If there is primarily a metabolic acidosis, is there an elevated anion gap (AG)?*
  - $AG = Na^+ - (Cl^- + HCO_3^-)$
  - Normal AG is 12 ± 2 mEq/L
  - Corrected AG for albumin = AG + 2.54 × (4 – serum albumin)
- *If there is an elevated AG, what is the delta–delta ratio?*
  - Delta–delta ratio: calculate to help determine the presence of an additional metabolic disorder
    - Delta–delta ratio = (measured AG – 12)/(24 – measured HCO_3^-)
    - If the ratio is < 0.5 to 1, there may be the presence of a concurrent normal-AG metabolic acidosis
    - If the ratio is between 1 and 2, this generally confirms the primary high-AG metabolic acidosis
    - If the ratio is > 2, there may be the presence of a concurrent metabolic alkalosis

DIFFERENTIAL DIAGNOSIS & WORKUP OF ACID-BASE DISORDERS

ANION-GAP METABOLIC ACIDOSIS

- Differential diagnosis
  - Lactic acidosis
  - Ketoacidosis (diabetic, alcoholic, and starvation)
  - Ethylene glycol
  - Methanol
  - Salicylates
  - Propylene glycol
  - Paraldehyde
  - Isoniazid, iron toxicity
  - Pyroglutamic acid (5-oxoproline)
  - Kidney failure (acute and chronic [uremia])
  - Rhabdomyolysis
- Initial diagnostic tests to consider depending on the clinical context
  - Lactic acid
  - Urine ketones and β-hydroxybutyrate
  - Serum and urine osmolality
  - BMP and serum albumin
  - Creatine kinase

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NON-ANION-GAP METABOLIC ACIDOSIS

- Table 55-3 describes the differential diagnosis of non-anion-gap metabolic acidosis
- Initial diagnostic tests to consider depending on the clinical context
  - BMP (chloride should be high) and serum albumin
  - Urine studies including pH, calcium, ammonium, sodium, chloride, and potassium

TABLE 55-3 Causes of Non-Anion-Gap Metabolic Acidosis

I. GI bicarbonate loss
   a. Diarrhea
   b. External pancreatic or small-bowel drainage/fistula
   c. Diversion of ureter: ureterosigmoidostomy, jejunal loop, ileal loop
   d. Drugs
      i. Calcium chloride (acidifying agent)
      ii. Magnesium sulfate (diarrhea)
      iii. Cholestyramine (bile acid diarrhea)

II. Renal acidosis
   a. Hypokalemia
      i. Proximal RTA (type 2 RTA)
         Drug-induced: acetazolamide, topiramate
         Inherited: (a) autosomal recessive missense mutation of *SLCA4* (encodes for basolateral NBCe1) (accompanied by ocular abnormalities); (b) autosomal dominant mutation of *NHE3* (apical Na^+/H^+ exchanger) (rare; associated with short stature)
      ii. Distal (classic) RTA (type 1 RTA)
         Drug-induced: amphotericin B, ifosfamide
         Inherited: defect of *ATP6V1B1* (encodes for basolateral HCO_3^-/Cl^- exchanger of distal tubule and collecting duct)
   b. Hyperkalemia
      i. Generalized distal nephron dysfunction (type 4 RTA)
         1. Selective aldosterone deficiency
         2. Mineralocorticoid resistance (PHA I, autosomal dominant)
         3. Voltage defect (PHA I, autosomal recessive, and PHA II)
         4. Hyporeninemic hypoaldosteronism
         5. Tubulointerstitial disease
   c. Normokalemia
      i. Progressive CKD

III. Drug-induced hyperkalemia (with CKD)
   a. Potassium-sparing diuretics (amiloride, triamterene, spironolactone, eplerenone)
   b. Trimethoprim
   c. Pentamidine
   d. ACE-Is and ARBs
   e. NSAIDs
   f. Calcineurin inhibitors
   g. Heparin in critically ill patients

IV. Other
   a. Acid loads (ammonium chloride, IV hyperalimentation [uncommon])
   b. Loss of potential bicarbonate: ketosis with ketone excretion
   c. Expansion acidosis (rapid saline administration)
   d. Hippurate
   e. Cation exchange resins

PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis.
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- Serum and urine osmolality
- Serum renin and aldosterone

METABOLIC ALKALOSIS

- Table 55-4 describes the differential diagnosis of metabolic alkalosis
- Assess the patient's extracellular fluid volume (measure recumbent and upright BP and pulse)

TABLE 55-4 Causes of Metabolic Alkalosis

I. Exogenous HCO_3^- loads
   a. Acute alkali administration
   b. Milk-alkali syndrome

II. Effective ECFV depletion, normal or low BP (with orthostasis), K^+ deficiency, and secondary hyperreninemic hyperaldosteronism
   a. GI origin
      i. Vomiting
      ii. Gastric aspiration
      iii. Congenital chloridorrhea
      iv. Gastrocystoplasty
      v. Villous adenoma
   b. Renal origin
      i. Diuretic use (thiazides and loop diuretics)
      ii. Posthypercapnic state
      iii. Hypercalcemia/hypoparathyroidism
      iv. Recovery from lactic acidosis or ketoacidosis
      v. Nonreabsorbable anion administration (e.g., IV penicillin, carbenicillin)
      vi. Mg^{2+} deficiency
      vii. K^+ depletion
      viii. Bartter's syndrome (loss-of-function mutations of transporters and ion channels in TALH)
      ix. Gitelman's syndrome (loss-of-function mutation of Na^+-Cl^- cotransporter in DCT and collecting duct)

III. ECFV expansion, hypertension, K^+ deficiency, and mineralocorticoid excess
   a. High renin
      i. Renal artery stenosis
      ii. Accelerated hypertension
      iii. Renin-secreting tumor
      iv. Estrogen therapy
   b. Low renin
      i. Primary aldosteronism
         1. Adenoma
         2. Hyperplasia
         3. Carcinoma
      ii. Adrenal enzyme defects
         1. 11β-Hydroxylase deficiency
         2. 17α-Hydroxylase deficiency
      iii. Cushing's syndrome or disease
      iv. Other
         1. Licorice
         2. Carbenoxolone
         3. Chewer's tobacco

IV. Gain-of-function mutation of sodium channel in DCT (ENaC) with ECFV expansion, hypertension, K^+ deficiency, and hyporeninemic-hypoaldosteronism
   a. Liddle's syndrome

DCT, distal convoluted tubule; ECFV, extracellular fluid volume; TALH, thick ascending limb of Henle's loop.
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TABLE 55-5 Respiratory Acid-Base Disorders

I. Alkalosis
- a. CNS stimulation
  - i. Pain
  - ii. Anxiety
  - iii. Fever
  - iv. Cerebrovascular accident
  - v. Meningitis, encephalitis
  - vi. Tumor
  - vii. Trauma
- b. Hypoxemia or tissue hypoxia
  - i. High-altitude acclimatization
  - ii. Pneumonia, pulmonary edema
  - iii. Aspiration
  - iv. Severe anemia
- c. Drugs or hormones
  - i. Pregnancy, progesterone
  - ii. Salicylates
  - iii. HF
- d. Stimulation of chest receptors
  - i. Hemothorax
  - ii. Flail chest
  - iii. HF
  - iv. PE
- e. Miscellaneous
  - i. Septicemia
  - ii. Hepatic failure
  - iii. Mechanical hyperventilation
  - iv. Heat exposure
  - v. Recovery from metabolic acidosis

II. Acidosis
- a. Central
  - i. Drugs (anesthetics, morphine, sedatives)
  - ii. Stroke
  - iii. Infection
- b. Airway
  - i. Obstruction
  - ii. Asthma
- c. Parenchyma
  - i. Emphysema
  - ii. Pneumoconiosis
  - iii. Bronchitis
  - iv. ARDS
  - v. Barotrauma
- d. Neuromuscular
  - i. Poliomyelitis
  - ii. Kyphoscoliosis
  - iii. Myasthenia
  - iv. Muscular dystrophies
- e. Miscellaneous
  - i. Obesity
  - ii. Hypoventilation
  - iii. Permissive hypercapnia

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- Initial diagnostic tests to consider depending on the clinical context
  - Calculate the urinary chloride value to differentiate saline responsive and saline resistant
    - Saline responsive: low urine chloride (< 15 mEq/L)
  - Urine sodium, potassium, and chloride
  - BMP (metabolic alkalosis is often accompanied by hypokalemia and hypochloremia)
  - Magnesium
  - Serum renin and aldosterone

RESPIRATORY ALKALOSIS

- Table 55-5 describes the differential diagnosis of respiratory alkalosis
- A detailed history and physical exam typically identifies the cause
- Initial diagnostic tests to consider depending on the clinical context
  - BMP (potassium and chloride are often reduced)
  - CXR

RESPIRATORY ACIDOSIS

- Table 55-5 describes the differential diagnosis of respiratory acidosis
- Initial diagnostic tests to consider depending on the clinical context
  - A detailed history and physical exam typically identifies the cause
  - Pulmonary function tests (outpatient), arterial $Paco_2$ and O_2 saturation (via ABG)
  - CBC
  - CXR

CASE ANSWERS

1. This patient has a partial small bowel obstruction managed with a nasogastric tube on continuous suction and signs of intravascular volume depletion. With the high pH and high HCO_3^-, the primary acid-base disorder present is a metabolic alkalosis. This is caused by losing acid from the stomach during nasogastric tube suction. Additionally, there is not an additional metabolic alkalosis present, as the measured $Paco_2$ (47 mm Hg) is not lower than the expected $Paco_2$ (HCO_3^- + 15). lower than expected.
2. A urinary chloride will help determine if the metabolic alkalosis is saline responsive or resistant. A urinary chloride < 15 mEq/L, in the setting of low intravascular volume, indicates the patient has a saline-responsive metabolic alkalosis. IV NS with potassium supplementation is the most appropriate initial treatment.

FURTHER READING

- DuBose TD Jr. Acidosis and alkalosis, in *Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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56 Electrolyte Repletion

CLINICAL VIGNETTE

A 23-year-old woman with anorexia nervosa presents to the ED with dyspnea and leg swelling. She states that the symptoms have progressively worsened over the last week, and her dyspnea worsens when she is lying flat. She has started to eat more and has gained 7 kg in the last 2 weeks. Her BMI was 12 a month ago. On exam, she is afebrile, heart rate is 108 beats/min, respiratory rate is 20 breaths/min, BP is 98/64 mm Hg, and Spo_2 is 92% on room air. JVD and 2+ bilateral pitting edema of the lower extremities are present. Lab data reveal a sodium of 132 mEq/L, potassium 2.4 mEq/L, SCr 1.4 mg/dL, BUN 28 mg/dL, phosphate 0.7 mEq/L, magnesium 1.4 mEq/L, and the BNP is elevated. A CXR reveals bilateral small pleural effusions and pulmonary edema.

GUIDING QUESTIONS

1. What underlying syndrome does this patient have?
2. How would you replete this patient's electrolyte abnormalities?

HYPOKALEMIA

- *Always identify the underlying etiology and manage appropriately* (Table 56-1)
- *Replete magnesium first*
  - Potassium levels depend on adequate magnesium levels
- The goal is for the serum potassium to be ≥ 4.0 mEq/L
- PO or IV potassium
  - Oral
    - Mainstay of therapy
    - Has a quicker onset but is shorter acting than IV potassium
  - IV
    - Slow infusion and more expensive than PO
    - Should be limited to patients unable to use the enteral route or in patients with severe complications (e.g., paralysis, dysrhythmia)
- 10 mEq PO or IV potassium chloride increases the serum potassium by 0.1 mEq/L in patients with serum potassium 3.0–4.0 mEq/L
  - As the serum potassium level is further reduced, total body stores are proportionately even lower
  - 15 mEq/L of potassium chloride increases the serum potassium by 0.1 mEq/L in patients with serum potassium 2.5–3.0 mEq/L
  - 20 mEq/L of potassium chloride increases the serum potassium by 0.1 mEq/L in patients with serum potassium 2.0–2.5 mEq/L
- IV potassium chloride can cause a burning sensation in the veins
  - IV potassium can be infused at only 10 mEq/h through a peripheral IV
  - Through a central line, 20 mEq/h can be administered
- Oral potassium chloride powder tastes unpleasant but can be administered with orange juice (also has potassium)
- Oral potassium chloride pills can be hard to swallow
- IV and PO potassium can be administered at the same time with appropriate monitoring
- You may be treating conditions (e.g., HF) with medications (e.g., diuretics) that cause potassium wasting
  - Therefore, higher amounts of potassium repletion may be necessary in these settings

HYPOMAGNESEMIA

- *Always identify the underlying etiology and manage appropriately* (Table 56-2)
- The goal is for the serum magnesium to be ≥ 2.0 mEq/L
  - Higher levels may decrease dysrhythmias and improve mortality after myocardial ischemia
- Repletion
  - Magnesium sulfate 4 g IV infusion × 1 (for magnesium levels < 1.4 mEq/L)
  - Magnesium sulfate 6–8 g IV infusion × 1 (for magnesium levels < 1.0 mEq/L)
  - Magnesium oxide (400 mg PO bid) is adequate for patients with chronically low magnesium
    - A side effect of oral magnesium is diarrhea

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TABLE 56-1 Causes of Hypokalemia

Decreased potassium intake
Potassium shift into the cell
Alkalosis
β-Adrenergic agonists
Insulin release (postprandial, exogenous, insulinoma)
Hypokalemic periodic paralysis
Renal potassium loss with metabolic acidosis
Proximal and distal RTAs
Toluene inhalation (glue sniffing)
Renal potassium loss with metabolic alkalosis
Normal/low BP
Vomiting
Magnesium deficiency
Loop/thiazide diuretics
Bartter's syndrome
Gitelman's syndrome
High BP
Elevated renin and aldosterone
Malignant hypertension
Renin-producing tumor
Renal artery stenosis
Depressed renin and elevated aldosterone
Adrenal adenoma
Glucocorticoid-remediable aldosteronism
Adrenal hyperplasia
Depressed renin and aldosterone
Cushing's syndrome
Black licorice
Apparent mineralocorticoid excess
Liddle's syndrome
Increased GI losses
Diarrhea
Laxative abuse

RTA, renal tubular acidosis.
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HYPOCALCEMIA

- *Always identify the underlying etiology and manage appropriately* (Table 56-3)
- Generally, only severe or symptomatic hypocalcemia needs repletion
- The goal is for the serum calcium to be 7.5–8.5 mg/dL or the ionized calcium > 3.0 mg/dL
- Corrected calcium = serum calcium – 0.8 × (normal albumin – serum albumin)
- Repletion
  - Symptomatic hypocalcemia
    - Calcium gluconate 10–15 mg/kg added to 1 L of D_5W and infused over 4–6 h
      - Monitor the serum calcium frequently (q4–6h)
  - Asymptomatic hypocalcemia
    - Oral calcium (1–2 g of elemental calcium) and vitamin D preparation

HYPOPHOSPHATEMIA

- *Always identify the underlying etiology and manage appropriately* (Table 56-4)
- The goal is for the serum phosphate to be ≥ 3.4 mg/dL

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TABLE 56-2 Causes of Hypomagnesemia

I. Impaired intestinal absorption
  A. Hypomagnesemia with secondary hypocalcemia (*TRPM6* mutations)
  B. Malabsorption syndromes
  C. Vitamin D deficiency
  D. Proton pump inhibitors
II. Increased intestinal losses
  A. Protracted vomiting/diarrhea
  B. Intestinal drainage, fistulas
III. Impaired renal tubular reabsorption
  A. Genetic magnesium-wasting syndromes
    1. Gitelman's syndrome
    2. Bartter's syndrome
    3. Claudin 16 or 19 mutations
    4. Potassium channel mutations (Kv1.1, Kir4.1)
    5. Na^+,K^+-ATPase γ-subunit mutations (FXYD2)
  B. Acquired renal disease
    1. Tubulointerstitial disease
    2. Postobstruction, ATN (diuretic phase)
    3. Kidney transplantation
  C. Drugs and toxins
    1. Ethanol
    2. Diuretics (loop, thiazide, osmotic)
    3. Cisplatin
    4. Pentamidine, foscarnet
    5. Cyclosporine
    6. Aminoglycosides, amphotericin B
    7. Cetuximab
  D. Other
    1. Extracellular fluid volume expansion
    2. Hyperaldosteronism
    3. SIAD
    4. Diabetes mellitus
    5. Hypercalcemia
    6. Phosphate depletion
    7. Metabolic acidosis
    8. Hyperthyroidism
IV. Rapid shifts from extracellular fluid
  A. Intracellular redistribution
    1. Recovery from diabetic ketoacidosis
    2. Refeeding syndrome
    3. Correction of respiratory acidosis
    4. Catecholamines
  B. Accelerated bone formation
    1. Post-parathyroidectomy
    2. Treatment of vitamin D deficiency
    3. Osteoblastic metastases
  C. Other
    1. Pancreatitis, burns, excessive sweating
    2. Pregnancy (third trimester) and lactation

ATN, acute tubular necrosis.
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TABLE 56-3 Causes of Hypocalcemia
Low Parathyroid Hormone Levels (Hypoparathyroidism)
Parathyroid agenesis
Isolated (genetic: autosomal recessive *GCM2* loss of function; X-linked mutations)
Syndromic (e.g., DiGeorge's, HDR, Kearns-Sayre)
Parathyroid destruction
Surgical
Autoimmune (genetic, e.g., APS-1; or acquired, including immune checkpoint inhibitors)
Radiation
Iron or copper overload (hemochromatosis, transfusion-dependent thalassemia, Wilson's disease)
Infiltration by metastases or systemic diseases (sarcoid, IgG_4-related disease, Riedel's struma)
Reduced bioactive PTH secretion
Hypomagnesemia (genetic, drug-induced, anti–claudin-16 antibodies)
Severe hypermagnesemia (e.g., obstetric magnesium infusions)
Autosomal dominant hypocalcemia (CaSR activating mutations)
Autoimmune (CaSR activating antibodies; immune checkpoint inhibitor therapy)
Familial isolated hypoparathyroidism (rare *PTH* gene mutations)
High Parathyroid Hormone Levels (Secondary Hyperparathyroidism)
Vitamin D deficiency or impaired $1,25(OH)_2D$ production/action
Nutritional vitamin D deficiency (poor intake or absorption)
CKD [phosphate retention, impaired 1,25(OH)2D production]
Excessive IV phosphate infusion
Vitamin D resistance, including receptor defects
Intrinsic small intestine disorders with chronic calcium malabsorption
Roux-en-Y bariatric surgery, other causes of short bowel syndrome
Celiac disease, Crohn's disease (often with concomitant vitamin D deficiency)
Parathyroid hormone resistance
Pseudohypoparathyroidism (*GNAS* mutations or imprinting defects)
Congenital PTH receptor mutation syndromes
PTH receptor blocking autoantibodies
Drugs
Alcohol (both acute and chronic ingestion)
Calcium chelators (including citrate from massive blood transfusion or FFP)
Inhibitors of bone resorption (bisphosphonates, denosumab, plicamycin)
Increased vitamin D catabolism (phenytoin, phenobarbital)
Phosphate-containing enemas (excessive or with kidney disease)
Miscellaneous causes
Acute pancreatitis
Acute rhabdomyolysis
Hungry bone syndrome after parathyroidectomy
Osteoblastic metastases with marked stimulation of bone formation (prostate cancer)
Respiratory or metabolic alkalosis (increased calcium binding to albumin)
Refeeding syndrome and its management
Pseudohypocalcemia (e.g., low serum albumin with malnutrition, nephrotic syndrome, cirrhosis; gadoversetamide MRI contrast)

APS-1, autoimmune polyglandular syndrome type 1; CaSR, calcium sensing receptor; FFP, fresh frozen plasma; HDR, hypoparathyroidism, sensorineural deafness, and renal disease; MEN, multiple endocrine neoplasia.
Reproduced with permission from F. Richard Bringhurst; Henry M. Kronenberg; Eva S. Liu; Marc N. Wein. Bone and Mineral Metabolism in *Health and Disease, in Harrison's Principles of Internal Medicine*, 22nd ed, D Longo et al (eds). New York, McGraw Hill, 2025.

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TABLE 56-4 Causes of Hypophosphatemia

Decreased intestinal absorption
Starvation
Absorption blocked by oral antacids or phosphate binders
Parenteral alimentation with inadequate phosphate content
Malabsorption syndrome, small bowel bypass
Vitamin D–deficient and vitamin D–resistant osteomalacia
Increased urinary excretion
Hyperparathyroidism (primary or secondary)
Hyperthyroidism
Inadequately controlled diabetes mellitus
Renal tubular defects with excessive phosphaturia (congenital, Fanconi's syndrome induced by monoclonal gammopathy, heavy metal poisoning), alcohol use disorder
Hypokalemic nephropathy
Hypophosphatemic rickets
Phosphaturic medications: IV iron, acetazolamide, tenofovir
Phosphatonins of oncogenic osteomalacia (e.g., FGF23 production)
Transcellular shift of phosphorus
Acute respiratory alkalosis
Increased insulin secretion (i.e., during refeeding)
Anabolic steroids, estrogen, oral contraceptives, β-adrenergic agonists, xanthine derivatives
Hungry bone syndrome
Salicylate poisoning
Other
Electrolyte abnormalities
Hypercalcemia
Hypomagnesemia
Metabolic alkalosis
Abnormal losses followed by inadequate repletion
Diabetes mellitus with acidosis, particularly during aggressive therapy
Recovery from starvation or prolonged catabolic state
Alcohol use disorder, particularly during restoration of nutrition; associated with hypomagnesemia
Recovery from severe burns

FGF23, fibroblast growth factor 23.
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- Aggressive repletion is recommended in patients with refeeding syndrome
- Repletion
  - Symptomatic hypophosphatemia or serum phosphate < 1.0 mg/dL
    - IV phosphate 0.4 mmol/kg (max 50 mmol) over 6 h, then replete with PO phosphate as below
  - Asymptomatic hypophosphatemia and serum phosphate 1.0–1.5 mg/dL
    - PO phosphate 1.3 mmol/kg in three to four divided doses over 24 h
  - Asymptomatic hypophosphatemia and serum phosphate > 1.5–2.0 mg/dL
    - PO phosphate 1 mmol/kg in three to four divided doses over 24 h

CASE ANSWERS

1. This patient with anorexia nervosa is presenting with a rapid weight gain in the setting of a major risk factor for the development of refeeding syndrome (starting BMI of < 14). With the symptoms of dyspnea, orthopnea, peripheral edema, an elevated BNP, and a CXR with pulmonary edema, refeeding syndrome is likely with the complication of HF.
2. The magnesium, potassium, and phosphate should be aggressively repleted in this patient with refeeding syndrome. IV repletion is initially indicated until levels are normalized and complications of refeeding syndrome

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are improving. After IV doses restore levels to normal, frequent monitoring of electrolytes is indicated with PO repletion as needed while nutrition is reinitiated.

a. Magnesium repletion: 4 g IV × 1 with repeat magnesium level and repeat dosing as needed
b. Potassium repletion: 40 mEq/L IV over 4 h with repeat levels and repeat dosing as needed
c. Phosphate repletion: 0.4 mmol/kg (max 50 mmol) over 6 h with repeat phosphate level and repeat dosing as needed

FURTHER READING

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