TORONTO NOTES

2025



COMPREHENSIVE MEDICAL REFERENCE AND REVIEW FOR MCCQE

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and a Review for the Medical Council of Canada Qualifying Exam
(MCCQE)

41st Edition

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NOTE:

Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius' healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

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Preface – From the Editors

Dear Readers,

We are grateful to present *Toronto Notes* 2025 to you. This edition is the product of an exceptional effort from the hundreds of editors and contributors who worked tirelessly with us as we navigated through the year. Together, we have created this milestone 41st edition of Toronto Notes, thus continuing our organization's rich tradition of providing an up-to-date, comprehensive, and concisely written medical resource to our readers.

Forty years ago, *Toronto Notes* began as a humble initiative, with medical students from the University of Toronto collecting and circulating their notes. Four decades later – with annual editions and an ever-expanding vision – *Toronto Notes* has become one of the most trusted medical review texts; it is a resource that is cherished by trainees and physicians throughout Canada and around the world.

The Toronto Notes for Medical Students Inc. is a nonprofit corporation whose mission is to provide a trusted medical resource in order to give back to our community. Keeping in line with our values and community needs, all proceeds from *Toronto Notes* sales are directly donated to support both global and local initiatives. Among other initiatives, we have supported U of T Medicine class activities, student scholarships and bursaries, *Daffdydil*, U of T's annual musical fundraiser for the Canadian Cancer Society, and the entirety of our (over twenty-five) student-led outreach programs that seek to enrich lives in the community, including the *Indigenous Student Mentorship Fund* and the *Black Medical Students' Association of Canada*.

This is why we, and all the members of our U of T team, gladly dedicated so many hours toward this immensely involved project. As our valued reader, we thank you for your honest and vital financial contribution through your purchase of our textbook. Each book sold makes an important difference.

The 2025 edition features substantial content revisions to the text, figures, and graphics of all 32 chapters, following a comprehensive review by our student and faculty editorial team. Up-to-date, evidence-based medicine studies are also summarized in highlighted boxes throughout the text. Once again, our *Ethical, Legal, and Organizational Medicine* chapter has been thoroughly revised, and all chapters reflect the most-updated COVID-19 guidelines. Our editors have also approached each chapter with the new MCCQE objectives on providing anti-oppressive health care, and quality improvement and patient safety in mind. In addition to content updates, the *Toronto Notes* 2025 *Clinical Handbook* has been restructured, and pared down to prioritize high-yield content and Do Not Miss Diagnoses to guide your learning during clerkship rotations.

We sincerely thank each of our 215 student editors and 97 faculty editors, whose meticulous revisions and shared dedication to the bettering of this text has helped make *Toronto Notes* 2025 possible. We have learned so much from leading this team, and are especially grateful to everyone for contributing to *Toronto Notes* even with challenging time commitments and demands. We thank our incredible Associate Editors – Karolina Gaebe, Lyra Halili, Alyssa Li, Huaqi Li, Michelle Lim, Saba Manzoor, Vrati M. Mehra, Farah Qaiser, and Dorrin Zarrin Khat – for their tireless leadership, exceptional organization, and wonderful teamwork. The success of this edition would not be possible without their efforts and we are exceedingly grateful to have worked with them. We also thank our Clinical Handbook Editors – Hardil Bhatt, David Buchan, Mercy Danquah, Rajiv Tanwani, and Timothy Zhang – for their exceptional editorial leadership towards spearheading the work on the 2025 edition. We owe a great deal of gratitude to the Editors-in-Chief of the 2024 edition – Anders Erickson and Jennifer Parker– for their guidance over the past year. We would also like to thank the wonderful BMC illustration team for their work, notably Amy Jiao and Vadym Lytvynov who worked iteratively to embrace the spirit of Toronto Notes through their cover design. Lastly, we thank our longtime partners at Type & Graphics Inc – especially our backbone, Enrica Aguilera and Maria Garcia — for their years of support and excellent work producing *Toronto Notes* 2025. Finally, we thank you for supporting our initiative by purchasing and reading our product. We hope that you will find *Toronto Notes* 2025 to be a useful companion on your medical journey, both now and for years to come.

Sincerely,

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How To Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of *Toronto Notes* allows easy identification of important information.
These items are indicated by icons interspersed throughout the text:

Icon	Icon Name	Significance
	**Key Objectives**	This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.
	**Clinical Pearl**	This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.
	**Memory Aid**	This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids.
	**Clinical Flag**	This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral.
	**Evidence Based Medicine**	This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text.
	**Colour Photo Atlas**	This icon is found next to headings in the text. It indicates topics that correspond with images found in the Colour Photo Atlas available online (www.torontonotes.ca).
	**Radiology Atlas**	This icon is found next to headings in the text. It indicates topics that correspond to images found in the Radiology Atlas available online (www.torontonotes.ca).
	**Online Resources**	This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online (www.torontonotes.ca).

Chapter Divisions

To aid in studying and finding relevant material quickly, many chapters incorporate the following general framework:

Basic Anatomy/Physiology Review

- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

Common Differential Diagnoses

- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

Diagnoses

- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

Common Medications

- a quick reference section for review of medications commonly prescribed

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Common Acronyms and Abbreviations Used in Medicine

The following are common medical acronyms/abbreviations that may be used without definition throughout the Toronto Notes text. These are typically not included in the acronym list at the beginning of each chapter. Please refer back to this list for definitions.

[ ]	concentration
β-hCG	beta human chorionic gonadotropin
ABx	antibiotics
ACE	angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	absolute risk
ASA	acetylsalicylic acid
AST	aspartate transaminase
aSx	asymptomatic
AXR	abdominal x-ray
BID	twice a day (bis in die)
BMI	body mass index
BP	blood pressure
BPM/bpm	beats per minute
C/I	contraindication
C&S	culture and sensitivity
CAD	coronary artery disease
CBC	complete blood count
CC	chief complaint
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
Cr	creatinine
CRH	corticotropin-releasing hormone
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
D&C	dilatation and curettage
dBP	diastolic blood pressure
DDx	differential diagnosis
DM	diabetes mellitus
DNR	do not resuscitate
Dx	diagnosis
ECG	electrocardiogram
ED	emergency department
EEG	electroencephalography
EMG	electromyography
ENT	ears, nose, and throat
ESR	erythrocyte sedimentation rate
EtOH	ethanol/alcohol
FMHx	family medical history
FSH	follicle stimulating hormone
G6PD	glucose-6-phosphate dehydrogenase
GGT	gamma-glutamyl transferase
GH	growth hormone
GHB	gamma hydroxybutyrate
GI	gastrointestinal
GU	genitourinary
Hb	hemoglobin
HIV	human immunodeficiency disease
HR	heart rate
HTN	hypertension
Hx	history
I&D	incision and drainage
ICP	intracranial pressure
ICU	intensive care unit
IM	intramuscular
IV	intravenous
JVP	jugular venous pressure
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LR	likelihood ratio

Common Acronyms and Abbreviations Used in Medicine

MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MDI	metered-dose inhaler
MI	myocardial infarction
MRI	magnetic resonance imaging
MSK	musculoskeletal
N/V	nausea/vomiting
NG	nasogastric
NMDA	N-Methyl-D-aspartate
NPO	nothing by mouth (nil per os)
NSAID	non-steroidal anti-inflammatory drug
OR	operating room
OTC	over-the-counter
PCR	polymerase chain reaction
PE	pulmonary embolism
PMHx	past medical history
PO	oral administration (per os)
POCUS	point-of-care ultrasound
PPI	proton pump inhibitor
PRN	as needed (pro re nata)
QID	four times a day (quater in die)
RBC	red blood cell
RCT	randomized controlled trial
ROS	review of symptoms
Rx	medical prescription
sBP	systolic blood pressure
SC	subcutaneous
SL	sublingual
SLE	systemic lupus erythematosus
SOB	shortness of breath
STAT	urgent or immediately (statum)
STI	sexually transmitted infection
Sx	symptom(s)
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TID	three times a day (ter in die)
TNM	tumour, nodes, and metastases
TRH	thyroid releasing hormone
TSH	thyroid stimulating hormone
Tx	treatment
U/A	urinalysis
U/S	ultrasound
UTI	urinary tract infection
UTox	urine toxicology screen
VDRL	Venereal Disease Research Laboratory test
WBC	white blood cell
wt	weight

Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor

To convert from the SI unit to the conventional unit, **divide** by conversion factor

	Conventional Unit	Conversion Factor	SI Unit
ACTH	pg/mL	0.22	pmol/L
Albumin	g/dL	10	g/L
Bilirubin	mg/dL	17.1	µmol/L
Calcium	mg/dL	0.25	mmol/L
Cholesterol	mg/dL	0.0259	mmol/L
Cortisol	µg/dL	27.59	nmol/L
Creatinine	mg/dL	88.4	µmol/L
Creatinine clearance	mL/min	0.0167	mL/s
Ethanol	mg/dL	0.217	mmol/L
Ferritin	ng/mL	2.247	pmol/L
Glucose	mg/dL	0.0555	mmol/L
HbA1c	%	0.01	proportion of 1.0
Hemaglobin	g/dL	10	g/L
HDL cholesterol	mg/dL	0.0259	mmol/L
Iron, total	µg/dL	0.179	µmol/L
Lactate (lactic acid)	mg/dL	0.111	mmol/L
LDL cholesterol	mg/dL	0.0259	mmol/L
Leukocytes	x 10^3cells/mm ^{3}	1	x 10^9cells/L
Magnesium	mg/dL	0.411	mmol/L
MCV	µm^3	1	fL
Platelets	x 10^3cells/mm ^{3}	1	x 10^9cells/L
Reticulocytes	% of RBCs	0.01	proportion of 1.0
Salicylate	mg/L	0.00724	mmol/L
Testosterone	ng/dL	0.0347	nmol/L
Thyroxine (T_4)	ng/dL	12.87	pmol/L
Total Iron Binding Capacity	µg/dL	0.179	µmol/L
Triiodothyronine (T_3)	pg/dL	0.0154	pmol/L
Triglycerides	mg/dL	0.0113	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Uric acid	mg/dL	59.48	µmol/L

Celsius → Fahrenheit	F = (C x 1.8) + 32
Fahrenheit → Celsius	C = (F – 32) x 0.5555
Kilograms → Pounds	1 kg = 2.2 lbs
Pounds → Ounces	1 lb = 16 oz
Ounces → Grams	1 oz = 28.3 g
Inches → Centimetres	1 in = 2.54 cm

Commonly Measured Laboratory Values

Test	Conventional Units	SI Units
Arterial Blood Gases		
pH	7.35-7.45	7.35-7.45
PCO_2	35-45 mmHg	4.7-6.0 kPa
PO_2	80-105 mmHg	10.6-14 kPa
Serum Electrolytes		
Bicarbonate	22-28 mEq/L	22-28 mmol/L
Calcium	8.4-10.2 mg/dL	2.1-2.5 mmol/L
Chloride	95-106 mEq/L	95-106 mmol/L
Magnesium	1.3-2.1 mEq/L	0.65-1.05 mmol/L
Phosphate	2.7-4.5 mg/dL	0.87-1.45 mmol/L
Potassium	3.5-5.0 mEq/L	3.5-5.0 mmol/L
Sodium	136-145 mEq/L	136-145 mmol/L
Serum Nonelectrolytes		
Albumin	3.5-5.0 g/dL	35-50 g/L
ALP	35-100 U/L	35-100 U/L
ALT	8-20 U/L	8-20 U/L
Amylase	25-125 U/L	25-125 U/L
AST	8-20 U/L	8-20 U/L
Bilirubin (direct)	0-0.3 mg/dL	0-5 µmol/L
Bilirubin (total)	0.1-1.0 mg/dL	2-17 µmol/L
BUN	7-18 mg/dL	2.5-7.1 mmol/L
Cholesterol	<200 mg/dL	<5.2 mmol/L
Creatinine (female)	10-70 U/L	10-70 U/L
Creatinine (male)	25-90 U/L	25-90 U/L
Creatine Kinase – MB fraction	0-12 U/L	0-12 U/L
Ferritin (female)	12-150 ng/mL	12-150 µg/L
Ferritin (male)	15-200 ng/mL	15-200 µg/L
Glucose (fasting)	70-110 mg/dL	3.8-6.1 mmol/L
HbA1c	<6%	<0.06
LDH	100-250 U/L	100-250 U/L
Osmolality	275-300 mOsm/kg	275-300 mOsm/kg
Serum Hormones		
ACTH (0800h)	<60 pg/mL	<13.2 pmol/L
Cortisol (0800h)	5-23 µg/dL	138-635 nmol/L
Prolactin	<20 ng/mL	<20 ng/mL
Testosterone (male, free)	9-30 ng/dL	0.31-1 pmol/L
Thyroxine (T_4)	5-12 ng/dL	64-155 nmol/L
Triiodothyronine (T_3)	115-190 ng/dL	1.8-2.9 nmol/L
TSH	0.5-5 µU/mL	0.5-5 µU/mL
Hematologic Values		
ESR (female)	0-20 mm/h	0-20 mm/h
ESR (male)	0-15 mm/h	0-15 mm/h
Hemoglobin (female)	12.3-15.7 g/dL	123-157 g/L
Hemoglobin (male)	13.5-17.5 g/dL	140-174 g/L
Hematocrit (female)	36-46%	36-46%
Hematocrit (male)	41-53%	41-53%
INR	1.0-1.1	1.0-1.1
Leukocytes	4.5-11 x 10^3cells/mm ^{3}	4.5-11 x 10^9cells/L
MCV	88-100 µm^3	88-100 fL
Platelets	150-400 x 10^3/mm^3	150-400 x 10^9/L
PTT	25-35 s	25-35 s
Reticulocytes	0.5-1.5% of RBC	20-84 x 10^9/L

ELOM Ethical, Legal, and Organizational Medicine

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Acronyms **ELOM2**

Ethical Issues in Health Care **ELOM2**

The Canadian Healthcare System **ELOM2**
Overview of Canadian Healthcare System
Legal Foundation
History of the Canadian Healthcare System and Crown-Indigenous Relations Pursuant to Healthcare
Healthcare Expenditure and Delivery in Canada
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Ethical and Legal Issues in Canadian Medicine **ELOM9**
Introduction to the Principles of Ethics
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Truth-Telling
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Research Ethics
Physician-Industry Relations
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Indigenous Health **ELOM25**
Overview of the History and Impact of Colonialism
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Indigenous Health Coverage and Jurisdictions
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References **ELOM32**

Further information on these topics can be found in the Objectives of the Considerations of the Legal, Ethical, and Organizational Aspects of the Practice of Medicine (CLEO) – which can be downloaded free of charge from the Medical Council of Canada website at http://mcc.ca/wp-content/uploads/CLEO.pdf.

There are three main types of law in Canada: criminal, civil, and administrative. The penalties for violating each are, in general, as follows: criminal – fine or incarceration; civil – monetary damages paid to the wronged party; and administrative – sanctions by the regulator (such as a suspension by the College of Physicians and Surgeons). All three types of law can be engaged by a single act. For example, a physician that inappropriately touches a patient can be liable for criminal (sexual assault), civil (monetary damages paid to the patient for the civil wrong of sexual assault), and administrative (fines and sanctions up to and including loss of ability to practice medicine for sexual abuse) penalties.

Canadian law applicable to medical practice varies between jurisdictions and changes over time.

Criminal law is nationwide, but civil and administrative law varies between provinces and territories. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.

Acronyms

AE	adverse event	CPSO	College of Physicians and Surgeons of Ontario	LMCC	Licentiate of the Medical Council of Canada	PIPEDA	Personal Information Protection and Electronic Documents Act
ART	assisted reproductive technologies	EMR	electronic medical record	MAID	Medical Assistance in Dying	POA	Power of Attorney
CFMS	Canadian Federation of Medical Students	FMEQ	Fédération médicale étudiante du Québec	MCC	Medical Council of Canada	PTMA	Provincial/Territorial Medical Association
CFPC	College of Family Physicians of Canada	FRCPC	Fellow of the Royal College of Physicians of Canada	OECD	Organization for Economic Co-operation and Development	RCPSC	Royal College of Physicians and Surgeons of Canada
CIHR	Canadian Institutes of Health Research	FRCSC	Fellow of the Royal College of Surgeons of Canada	OMA	Ontario Medical Association	RDoC	Resident Doctors of Canada
CMA	Canadian Medical Association	GA	gestational age	OTC	over the counter	SDM	substitute decision-maker
CME	continuing medical education	GDP	gross domestic product	PHO	Provincial House staff Organization	TRC	Truth and Reconciliation Commission
CMPA	Canadian Medical Protective Association	HCCA	Health Care Consent Act	PHIPA	Personal Health Information Protection Act		
		IVF	in vitro fertilization				

The practice of medicine and ethics are inherently linked. As the complexity of medicine evolves, so do the principles that we use to guide ethical decision-making in clinical practice. Traditionally, four fundamental principles: Beneficence, Nonmaleficence, Autonomy, and Justice have been the basis of clinical ethics. In recognition of this complexity and the importance of relationships within the practice of medicine, the CMA Code of Ethics recommends the use of a broader array of ethical principles. Ethical issues are usually identifiable by the presence of a moral dilemma and are navigated by carefully considering all factors involved and selecting the best possible option. Understanding how to navigate ethical dilemmas is extremely important, as they present at all levels of medical training and practice. These dilemmas can be approached by first identifying the ethical issue and then by using ethics frameworks. Having early ethical training allows one to develop the necessary skills to navigate various morally ambiguous scenarios that arise in the practice of medicine. Although medical ethics is an ever-evolving discipline, this chapter seeks to provide an overview of relevant frameworks and a basic guide to knowing how to best act in the face of ethical dilemmas.

Ethical Issues in Health Care

Managing Controversial and Ethical Issues in Practice

- use an Ethics Framework. Many hospitals have adopted the IDEA framework or versions of it.
- determine the ethical issue or question eg. is it ethical to allow patient X to refuse life saving treatment?
- discuss the issue(s) in a manner that is as objective and non-judgmental as possible (separate facts from assumptions that may carry health care provider' bias)
- involve all relevant interprofessional colleagues who are involved in the care of the patient (or the issue if it is an organisational ethics issue)
- consider what hospital, university, regulatory college policies and laws are applicable to the case
- be mindful that everyone involved in the case (patients, family members and healthcare providers) all bring their own values and lived experiences to the issue at hand
- identify if any options are outside of the physician's moral boundaries (e.g. something to which the physician has a conscientious objection) and refer to another physician, if appropriate
- consult with a bioethicist and/or the appropriate ethics committees or boards



IDEA Framework Tool
Identify the facts
Determine the relevant ethical principles
Explore the options
Act on your decision and evaluate



Intentions and Impact Tool
1. What is the intention of an action?
2. What is the impact of an action?

The Canadian Healthcare System

Overview of Canadian Healthcare System

- one federal, three territorial, and ten provincial systems
- major complexities in establishment of Canadian health policy include geographical diversity, socioeconomic divisions, and international pressures
- financed by both the public (70%) and private (30%) sectors
- each provincial/territorial plan must cover all medically necessary health services and remain in compliance with the Canada Health Act in order to receive federal transfers
- provincial/territorial governments may choose to offer and fund supplementary services not covered under the *Canada Health Act*, such as prescription drugs and vision care
- non-insured health services and fees are either covered by private insurance or by the individual
- workers' compensation funds cover treatment for work-related injuries and diseases

Table 1. Division of Government Responsibilities in Healthcare

Federal Government	Provincial Government
Healthcare services for Indigenous peoples (Status First Nations peoples and Inuit only, Non-Insured Health Benefits (NIHB)), federal government employees (RCMP and armed forces), immigrants, and civil aviation personnel	Establishment, maintenance, and management of hospitals, asylums, charities, and charitable institutions (*Constitution Act*, 1867)
Marine hospitals and quarantine (Constitution Act, 1867)	Licensing of physicians, nurses, and other health professionals
Investigations into public health	Determining the standards for licensing all hospitals
Regulation of food and drugs	Administering provincial medical insurance plans
Inspection of medical devices	Financing healthcare facilities
Administration of healthcare insurance	Delivery of certain public health services
General information services related to health conditions and practices	
Role in health derives from constitutional responsibility over criminal law, spending powers, and legislation for 'peace, order, and good government.' Examples include *Canada Health Act, Food and Drugs Act, Controlled Substances Act*, and *Canada Health Transfer Act*)	

Principles of the Canada Health Act

1. Public Administration: provincial/territorial health insurance programs must be administered on a not-for-profit basis by public authorities
2. Comprehensiveness: provincial/territorial health insurance programs must cover all medically necessary diagnostic, physician, and hospital services
3. Universality: all eligible residents must be entitled to healthcare services (including status First Nations peoples and Inuit; note that non-status First Nations and Métis are included under all eligible residents)
4. Portability: emergency health services must be available to Canadians who are outside their home province, paid for by the home province
5. Accessibility: provincial/territorial plans must ensure reasonable access to medically necessary hospital and physician services without financial or other barriers

The federal government can reduce its contributions to provinces that violate the key principles of the *Canada Health Act*

Legal Foundation

- the legal foundation of the Canadian health system is based on:
  - five constitutional documents:
    1. Royal Proclamation (1763): the foundation for the rights of Indigenous peoples in Canada; sets out the sovereignty of Indigenous peoples in Canada
    2. *Constitution Act* (1867): deals primarily with the jurisdictional power between federal and provincial governments
    3. Treaty 6 (1876): included the Medicine Chest Clause, which addresses Indigenous sovereignty in healthcare delivery and equitable access to all forms of medicine
    4. Dreaver vs. King court ruling (1935): provided the legal precedence for Non-Insured Health Benefits
    5. The Canadian Charter of Rights and Freedoms (1982): does not guarantee a right to healthcare; but, if the government decides to finance healthcare, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physicians' mobility rights, etc.)
  - two statutes:
    1. *Canada Health Act* (1984): outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
    2. *Canada Health and Social Transfer Act* (1996): federal government gives provinces a single grant for healthcare, social programs, and post-secondary education; division of resources at provinces' discretion

History of the Canadian Healthcare System and Crown-Indigenous Relations Pursuant to Healthcare

1534 Europeans first arrive in Canada
- settlers find healthy inhabitants with complex societies, cultures, and belief systems
- Indigenous peoples' have specific knowledge of local environment and medicines
  - early instance of medical practice occurs when local Indigenous nation (Haudenosaunee) used cedar as a source of vitamin C to treat scurvy experienced by European settlers

1763 *Royal Proclamation*
- identifies Indian Country that was under British sovereignty but Indigenous possession
- sets out guidelines for European settlement of Indigenous territories in what is now North America; statements include: Aboriginal title (a legal term for ancestral land rights) has existed and continues to exist, and that all land would be considered Aboriginal land unless ceded by treaty
  - forbids settlers from claiming land from the Indigenous occupants, unless it was first bought by the Crown and then sold to the settlers
  - only the Crown can buy land from First Nations

1764 *Treaty of Niagara*
- the treaty is signed with 24 Indigenous Nations represented
- Indigenous peoples and the Crown agree to co-exist and build their relationship on Turtle Island

1867 *British North America Act* (now *Constitution Act* 1867)
- establishes Canada as a confederacy
- "establishment, maintenance, and management of hospitals" under provincial jurisdiction
- gives the federal government control over lands reserved for "Indians"

1870 *Manitoba Act*
- Métis land is protected and they are given an additional 1.4 million acres for their descendants
- this act was subsequently ignored and infringed upon as this land was given freely to incoming settlers

1871-1921 *Numbered Treaties*
- transfer large tracts of Indigenous land to the Crown with various promises made to Indigenous Peoples
- Treaty 6 explicitly includes medicine, while others contain agreements related to social factors affecting health

1876 *Indian Act*
- reinforces the federal government's exclusive jurisdiction over Indians and lands reserved for Indians
- gives complete control of "Indian bands," status, and reserves to the Canadian government
- enfranchisement (the process of terminating one's legal Indian Status, identity, and ancestral rights in order to gain full Canadian citizenship) becomes legally compulsory in many situations (such as becoming a physician)
- denies women equal citizenship status
- denies the right to vote
- outlaws the practice of Indigenous culture and spirituality
- imposes band councils and "Indian agents"
- restricts First Nations peoples from leaving reserves without the Indian agent's permission

1884-1996 Residential Schools and Indian Hospitals
- legislated genocide (see Public Health and Preventive Medicine, PH5)

1885 Execution of Métis leader Louis Riel
- leader of the North-West Rebellion against the Federal government due to infringement on Métis ancestral lands, rights, and way of life

1939 Court Decision *Reference Re Eskimo* rules that the federal government has similar responsibility for Inuit people as Indigenous Peoples
- following this decision the government developed policies that enforced assimilation and benefited governmental goals, with disregard for Inuit wellbeing. This leads to extensive harm, some of which are noted below:
  - coercive relocation to isolated and sedentary communities away from ancestral lands, ending seasonally dynamic way of life
  - sled dogs were killed, which discontinued the Inuit traditional way of life and forced them to rely on government supplies
  - discs, to be worn around the neck, were issued with numbers in lieu of Inuit surnames and to ease bureaucratic workload

1965 *Royal Commission on Health Services* (Hall Commission) recommends federal leadership and financial support with provincial government operation

1966 *National Medical Care Insurance Act*
- federal government's first legislation with the goal of free access to healthcare
- federal government to pay half of medicare costs in any province with insurance plans that meet criteria of being universal, publicly administered, portable, and comprehensive
- Indian Health Services budget is reduced under the guise of equality and social and legal integration. Individuals can only receive support for healthcare services if they prove they are Indigenous, have been refused funds from their band, and can not obtain provincial health services. Financial limits are set to prevent "overuse" of services. This creates further barriers to accessing healthcare, while reducing barriers for non-Indigenous peoples

1984 *Canada Health Act* is passed by federal government
- replaces *Medical Care Act* (1966) and *Hospital Insurance and Diagnostic Services Act* (1957)
- provides federal funds to provinces with universal hospital insurance
- maintains federal government contribution at 50% on average, with poorer provinces receiving more funds

ALGrawany

- medical insurance must be "comprehensive, portable, universal, and publicly administered"
- bans extra-billing by new fifth criterion: accessibility

1985 *Bill C-31*
- the *Indian Act* forced Indigenous women who married non-Indigenous men to lose their Indian status
- *Bill C-31* attempted to stop the involuntary enfranchisement of Indigenous women (and their children) who married non-Indigenous men
- *Bill C-31* in 2011 and later cases ensured that eligible grandchildren of women who lost status could regain it

1990 Oka Crisis
- land dispute over ancestral Kanienkehaka (Mohawk) territory
- brought about the Royal Commission on Aboriginal Peoples (1996)

1996 *Canada Health and Social Transfer Act* passed by federal government
- federal government gives provinces a single grant for healthcare, social programs, and post-secondary education; division of resources at provinces' discretion

1996 Royal Commission on Aboriginal Peoples
- established in the wake of the Oka Crisis. The Commission's Report, the product of extensive research and community consultation, was a broad survey of historical and contemporary relations between Aboriginal and non-Aboriginal peoples in Canada
- recommendations made on how to repair the relationship between Indigenous peoples and Canada

2001 *Kirby and Romanow Commissions* appointed
- *Kirby Commission* (final report, October 2002)
- examines history of the healthcare system in Canada, pressures and constraints of current healthcare system, role of federal government, and healthcare systems in foreign jurisdictions

Romanow Commission (final report, November 2002)
- dialogue with Canadians on the future of Canada's public healthcare system

2004 *First Ministers' Meeting on the Future of Health Care* produces a 10 year plan
- priorities include reductions in waiting times, development of a national pharmacare plan, and primary care reform

2005 *Chaoulli v. Québec,* Supreme Court of Canada decision
- rules that Québec's banning of private insurance is unconstitutional under the Québec Charter of Rights since patients cannot access the relevant services under the public system in a timely manner

2007 *Jordan's Principle*
- Jordan Anderson was a First Nations child from Norway House Cree Nation born with complex medical needs
- he spent two unnecessary years in hospital because provincial and federal governments could not decide who was responsible for paying for the home-based care that Jordan needed to be discharged. Consequently, he died in hospital at age 5 without ever going home
- *Jordan's Principle* is a legal obligation that promises that First Nations children will get prompt and equitable access to healthcare and that payments (federal/provincial/local) will be determined later
- in 2016, the Canadian Human Rights Tribunal found that the Canadian government was racially discriminating against First Nations children and their families for its failure to properly implement Jordan's Principle. The Tribunal issued legally binding orders that Canada has an obligation to fulfill

2011 First progress report by the Health Council reviews progress toward 2004 First Ministers' 10 year plan
- significant reductions in wait times for specific healthcare areas (such as cancer care, joint replacements, and sight restoration), but may have inadvertently caused increased wait times for other services
- despite large investments into EMRs, Canada continues to have low uptake, ranking last in the Commonwealth Fund International Health Policy survey, with only 37% use among primary care physicians
- minimal progress in creating a national strategy for equitable access to pharmaceuticals; however, there has been some success in increasing pharmacists' scope of practice, reducing generic drug costs, and implementing drug information systems

- increases funding to provinces at 6% per annum until the 2016-2017 fiscal year; from then onwards, increases tied to nominal GDP at a minimum of 3% per annum

2012 Second progress report by the Health Council reviews progress towards 2004 First Ministers' 10 year plan
- funding is sufficient; however, more innovation is needed including incentivizing through models of remuneration
- 46 recommendations are made to address the lack of progress

2014 Expiry of 10 Year Health Care Funding Agreement between federal and provincial governments
- *Canadian Doctors for Refugee Care v. Canada*, the Federal Court of Canada rules that the federal government could not significantly reduce/eliminate healthcare services for refugee claimants, as to do so would constitute "cruel and unusual treatment" contrary to the Charter of Rights and Freedoms

2015 Negotiations underway for a new Health Accord with a $3 billion investment over four years to homecare and mental health services by the elected Liberal government

2015 The Truth and Reconciliation Commission releases 94 "calls to action" (or recommendations) to further reconciliation between Canada and Indigenous peoples
- the full list of calls to action can be found here: https://www2.gov.bc.ca/assets/gov/british-columbians-our-governments/indigenous-people/aboriginal-peoples-documents/calls_to_action_english2.pdf, while health-specific calls and subsequent government actions can be found here: https://www.rcaanc-cirnac.gc.ca/eng/1524499024614/1557512659251
- the seven calls to action included under health are the following:
  - we call upon the federal, provincial, territorial, and Aboriginal governments to acknowledge that the current state of Aboriginal health in Canada is a direct result of previous Canadian government policies, including residential schools, and to recognize and implement the health-care rights of Aboriginal people as identified in international law, constitutional law, and under the Treaties
  - we call upon the federal government, in consultation with Aboriginal peoples, to establish measurable goals to identify and close the gaps in health outcomes between Aboriginal and non-Aboriginal communities, and to publish annual progress reports and assess longterm trends. Such efforts would focus on indicators such as: infant mortality, maternal health, suicide, mental health, addictions, life expectancy, birth rates, infant and child health issues, chronic diseases, illness and injury incidence, and the availability of appropriate health services
  - in order to address the jurisdictional disputes concerning Aboriginal people who do not reside on reserves, we call upon the federal government to recognize, respect, and address the distinct health needs of the Métis, Inuit, and off-reserve Aboriginal peoples
  - we call upon the federal government to provide sustainable funding for existing and new Aboriginal healing centres to address the physical, mental, emotional, and spiritual harms caused by residential schools, and to ensure that the funding of healing centres in Nunavut and the Northwest Territories is a priority
  - we call upon those who can effect change within the Canadian health-care system to recognize the value of Aboriginal healing practices and use them in the treatment of Aboriginal patients in collaboration with Aboriginal healers and Elders where requested by Aboriginal patients
  - we call upon all levels of government to: i. Increase the number of Aboriginal professionals working in the health-care field. ii. Ensure the retention of Aboriginal health-care providers in Aboriginal communities. iii. Provide cultural competency training for all healthcare professionals
  - we call upon medical and nursing schools in Canada to require all students to take a course dealing with Aboriginal health issues, including the history and legacy of residential schools, the United Nations Declaration on the Rights of Indigenous Peoples, Treaties and Aboriginal rights, and Indigenous teachings and practices. This will require skills-based training in intercultural competency, conflict resolution, human rights, and anti-racism

2016 Canada's Minister of Indigenous Affairs announces their full support for the *United Nations Declaration on the Rights of Indigenous Peoples*
- document describes individual and collective rights of Indigenous peoples and provides guidance about how to maintain a relationship with Indigenous peoples based on equality, partnership, good faith, and mutual respect

2017 New 10 year Canada Health Accord is reached with a $11.5 billion federal investment over 10 years to homecare and mental health services and a 3% annual rise in the Canada Health Transfer (from 6% in the previous agreement)

2019 Missing and Murdered Indigenous Women and Girls Inquiry Final Report and Calls for Justice
- reveals that persistent and deliberate human and Indigenous rights violations and abuses amount to genocide and are the root cause behind Canada's staggering rates of violence against Indigenous women, girls, and 2SLGBTQQIA+ people
- the report calls for transformative legal and social changes to resolve the crisis that has devastated Indigenous communities across the country

2019 The federal government announces the creation of a national drug agency. It will negotiate prices on behalf of Canada's drug plans, assess the efficacy of prescription drugs, and develop a nationalformulary
- this commitment is later confirmed in the 2022 Federal Budget

Healthcare Expenditure and Delivery in Canada

- the projected total healthcare expenditure in 2022 was expected to reach $331 billion, or $8563 per person. Health spending was expected to comprise 12.2% of Canada's GDP that year

Sources of Healthcare Funding

- public sector covers services offered on either a fee for service, capitation, or Alternate Payment Plan (APP) in physicians' offices and in hospitals
  - fee-for-service is a payment model where services are unbundled and paid for separately. This can serve as an incentive for physicians to provide more services because payment is dependent on the quantity of services provided
  - in Ontario, each service has a corresponding billing code defined by the Ministry of Health in the Physician Services Agreement under the *Health Insurance Act*
  - capitation is a physician remuneration payment model determined by the number of patients rostered that is used in Primary Care models
  - APP is a mutual agreement between a physician (or group of physicians) and their provincial health authority. The agreement outlines the physician's salary, incentives, and various after-hour bonuses
- public sector does not cover services provided by privately practicing health professionals (e.g. dentists, chiropractors, optometrists, massage therapists, osteopaths, physiotherapists, podiatrists, psychologists, private duty nurses, and naturopaths), prescription drugs, OTC drugs, personal health supplies, and use of residential care facilities

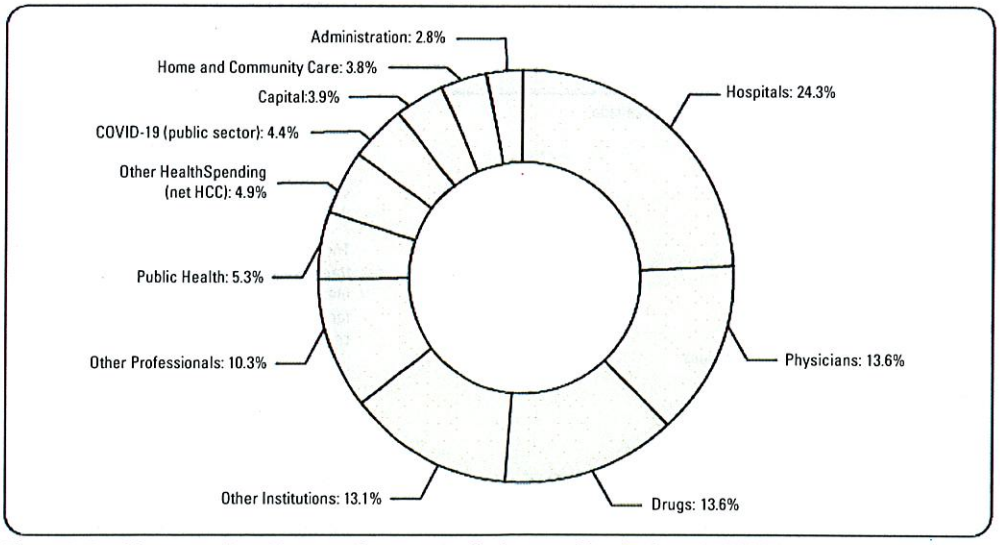


Figure 1. Total forecasted health expenditure per capita by use of funds, Canada 2022 (dollars and percentage share)
Share of total health expenditures by spending category, where Hsopitals, Physicians, and Drugs account for the largest shares of health spending
Source: National Health Expenditure Database, Canadian Institute for Health Information. Reprinted with permission of CIHI

Delivery of Healthcare

- hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities
- other countries have different systems of healthcare delivery, for example:
  - the United States has a mix of public and private funding, as well as private for-profit and private not-for-profit delivery
  - the United Kingdom has primarily public funding and delivery

Physician Licensure and Certification

Table 2. Key Physician Certification and Licensing Bodies in Canada (and Ontario)

Certifying Body	Description
MCC	Certifies physicians with the LMCC. LMCC acquired by passing the MCC Qualifying Examination Parts I and II
RCPSC	Certifies residents who complete an accredited residency program and pass the appropriate exam
	Voluntary membership of the RCPSC is designated FRCPC or FRCSC
CFPC	Certifies residents who complete an accredited family medicine residency program and pass the Certification Examination in Family Medicine
Licensing Body	13 provincial medical regulatory (licensing) authorities
	All postgraduate residents and all practicing physicians must hold an educational or practice license from the licensing body in the province in which they study or practice
CPSO	Membership to the provincial licensing authority is mandatory
	Licensing authority functions include:
	Provide non-transferable licensure to physicians
	Maintaining ethical, legal, and competency standards and developing policies to guide physicians
	Investigating complaints against physicians
	Disciplining physicians guilty of professional misconduct or incompetence
Certifying Body	At times of license investiture and renewal, physicians must disclose if they have a condition (such as substance use disorders, or other illnesses) that may impact their ability to practice safely

- physician certification is governed nationally, while the medical profession in Canada self-regulates under the authority of provincial legislation
- self-regulation is based on the premise that due to the advanced education and training involved in the practice of medicine, the lay person is not in a position to accurately judge the standards of the profession; the self-regulating colleges have a mandate to regulate the profession in the public interest
- the RCPSC and CFPC are responsible for monitoring ongoing CME and professional development
- certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities

Role of Professional Associations

Table 3. Key Professional Associations

Association	Description
CMA	Provides leadership to physicians and advocates for access to high quality care in Canada
	Represents physician and population concerns at the national level
	Membership is voluntary
PTMAs (such as the OMA)	Negotiates fee and benefit schedules with provincial governments
	Represents the economic and professional interests of physicians
	Membership is voluntary
	Provide physician health support
CMPA	Physician-run organization that protects the integrity of member physicians
	Provides legal defense against allegations of malpractice or negligence
	Provides risk management and educational programs
	Membership is voluntary but all physicians must have some form of liability insurance
RDoC and PHO	Upholds economic and professional interests of residents across Canada
	Facilitates discussion amongst PHOs regarding policy and advocacy items
CFMS and FMÉQ	Medical students are represented at their universities by student bodies, which collectively form the CFMS or FMÉQ
	FMÉQ membership includes that of francophone medical schools



Advocacy and Diversity

Similar to how the FMÉQ represents the interests of francophone medical schools and the CFMS represents those nation-wide, other professional associations serve and advocate on behalf of different communities

These associations may serve traditionally underrepresented groups, underserved communities, communities facing structural barriers, and/or communities with unique health needs

Some examples of professional associations that physicians or medical students may join are: Gay, Lesbian, Bisexual and Transgender (GLBT) Medical Students of Canada; the Black Medical Students Association of Canada; Black Physicians Association of Ontario (BPAO); Muslim Medical Association of Canada and the Indigenous Physicians Association of Canada (IPAC); Indigenous Medical/Dental Students Association (IMDSA, Alberta)

Ethical and Legal Issues in Canadian Medicine

Introduction to the Principles of Ethics

- ethics involve thinking about what the best course of action may be in a specific case, including:
  1. principles and values that help us consider what might be morally permissible and/or impermissible in specific circumstances
  2. rights, duties, and obligations of individuals and groups
- as a self-regulated profession, ethical and professional practice is guided by a shared code of conduct (the CMA code of ethics), and by our provincial licensing bodies (through policies)
- the physician-patient relationship significantly depends on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- a fiduciary duty is a legal duty to act in another party's interest. Profit from the fiduciary relationship must be strictly accounted for with any improper profit (monetary or otherwise) resulting in sanctions against the physician and potential compensation to the patient, even if no physical harm has befallen the patient



Autonomy vs. Competence vs. Capacity
Autonomy: the right that patients have to make decisions according to their values, beliefs, and preferences
Competence: the ability to make a specific decision for oneself as determined legally by the courts
Capacity: the ability to make a specific decision for oneself as determined by the clinicians proposing the specific treatment

Table 4. The Four Principles Approach to Medical Ethics

Principle	Definition
Autonomy	Recognizes an individual's right to make their own decisions in their own way(s) based on their wishes, beliefs, values, and preferences
	It may not be possible for a person to make a fully autonomous decision and/or to have an autonomous decision honoured in some circumstances. For instance, if an autonomous request for a medical intervention is deemed clinically inappropriate from the physician's perspective, then the physician need not offer it
	Autonomy is not synonymous with capacity
Beneficence	Obligation to provide benefit to the patient, based on what is considered to be their best interests. Consideration of best interests should consider the patient's values, beliefs, and preferences, so far as these are known. Best interests extend beyond solely medical considerations
	May be limited by the principle of Autonomy (such as when differences exist between patient and clinician's conception of best interests)
	Paramount in situations where consent/choice is not possible
Non-Maleficence	Obligation to avoid causing harm; primum non nocere ("First, do no harm")
	A limiting principle of the Beneficence principle
Justice	Fair distribution of benefits and harms within a community, regardless of geography, income, or other social factors
	Concept of fairness: Is the patient receiving what they deserve – their fair share? Are they treated the same as equally situated patients? (equity) How does one set of treatment decisions impact others? (equality)
	Equality and equity are different notions of justice. Equality involves providing the distribution of resources to all people irrespective of differing needs, and equity involves distributing resources in a way that considers differing needs (such as circumstance and social context). Both concepts raise different considerations
	Basic human rights, such as freedom from persecution and the right to have one's interests considered and respected

Note: The four principles approach (i.e. principlism) is just one approach to medical ethics. There exist many other ethical principles that are also relevant to medicine (e.g. transparency, trust, etc.)

CMA Code of Ethics and Professionalism

- the CMA developed a Code of Ethics and Professionalism that provides standards of ethical practice to guide Canadian physicians, which covers virtues that should be exemplified by an ethical physician, fundamental commitments of the medical profession, professional responsibilities, and the relation of the physician to themselves, colleagues, and society
- the Code of Ethics and Professionalism is:
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - informs ethical decision-making, especially where existing guidelines are insufficient or values and principles come into tension
  - not exhaustive; it is intended to provide standards of ethical practice that can be interpreted and applied in particular situations
  - founded on other principles including the Hippocratic Oath, developments in human rights, and recent bioethical discussions
- CMA policy statements address specific ethical issues/topics not mentioned by the code (e.g. abortion, transplantation, and medical assistance in dying)



The CMA Code of Ethics and Professionalism is a quasi-legal standard for physicians; if the law sets a minimal moral standard for physicians, the Code seeks to augments these standards

Table 5. CMA Code of Ethics and Professionalism

A. Virtues exemplified by the ethical physician	
Compassion Honesty Humility	Integrity Prudence
B. Fundamental commitments of the medical profession	
Commitment to the well-being of the patient Commitment to respect for persons Commitment to justice Commitment to professional integrity and competence	Commitment to professional excellence Commitment to self-care and peer support Commitment to inquiry and reflection
C. Professional responsibilities	
Physicians and patients	Patient-physician relationship Decision-making
Physicians and the practice of medicine	Patient privacy and the duty of confidentiality Managing and minimizing conflicts of interest
Physicians and self	Awareness of wellness services and promote health among self Seek support for professional and personal problems Cultivate safe training and working environments
Physicians and colleagues	Treating colleagues with respect and dignity Take responsibility for actions towards colleagues
Physicians and society	Commitment to high quality healthcare services Recognition of the social determinants of health Supporting equitable access to healthcare resources, and building collaborative relationships with marginalized groups

Confidentiality

Overview of Confidentiality

- start from the foundational assumption that all information given by the patient is both confidential (meaning it cannot be disclosed to others) and privileged (meaning it cannot be used in court), then determine whether exceptions to this exist
- the legal and ethical basis for maintaining confidentiality is that personal health information and private details of a patient's life are often required for accurate diagnosis and care of patients. As part of maintaining a therapeutic relationship, patients must trust their physician to keep this information confidential (see *Privacy of Medical Records, ELOM11*)
- privacy is a right of patients (which they may forgo), while confidentiality is a duty of physicians (which they must respect barring patient consent or requirements of the law)
- if confidentiality is inappropriately breached by a physician, that physician can be sanctioned by the hospital, court, or regulatory authority
- based on the ethical principle of autonomy, patients have the right to control their own health information and they may choose what aspects they want to disclose to their physicians
- confidentiality may be ethically and legally breached in certain circumstances (see below)
- while physician-patient privilege exists, it is limited in comparison to solicitor-client privilege. During conversations with patients about confidentiality, physicians should avoid promising absolute confidentiality or privilege, as it cannot be guaranteed by law
- legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting court cases in the common law

Legal Aspects of Confidentiality
Advice should always be sought from provincial licensing authorities, provincial/territorial privacy commissioner's offices, and/or legal counsel when in doubt

CMA Code of Ethics and Professionalism
"Fulfill your duty of confidentiality to the patient by keeping identifiable patient information confidential; collecting, using, and disclosing only as much health information as necessary to benefit the patient; and sharing information only to benefit the patient and within the patient's circle of care. Exceptions include situations where the informed consent of the patient has been obtained for disclosure or as provided for by law"

Statutory Reporting Obligations

- legislation has defined specific instances where public interest overrides the patient's right to confidentiality; varies by province, but may include:
  1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children's Aid Society)
  2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see Geriatric Medicine, GM14)
  3. communicable diseases – report to local public health authority (see Public Health and Preventive Medicine, PH31)
  4. improper conduct of other physicians or health professionals – report to College or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
  5. vital statistics must be reported; reporting varies by province (e.g. in Ontario, births are required to be reported within 30 d to the Office of Registrar General or local municipality; death certificates must be completed by a physician then forwarded to municipal authorities)
  6. reporting to coroners (see *Physician Responsibilities Regarding Death, ELOM21*)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn

- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of patients for clinical assessment), informing the police, and/or warning the potential victim(s) if a patient expresses an intent to harm
- Canadian courts have not expressly imposed a mandatory duty to report, however, the CMA Code of Ethics and some provincial/territorial regulatory authorities may oblige physicians to report (mandatory reporting rather than permissive)
- concerns of breaching confidentiality should not prevent the physician from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where:
    1. there is an imminent risk
    2. to an identifiable person or group
    3. of serious bodily harm or death

Disclosure for Legal Proceedings

- disclosure of health records can be compelled by a court order, warrant, or subpoena

Privacy of Medical Records

- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the Canadian Charter of Rights and Freedoms, and the physician's fiduciary duty
- the federal government created the PIPEDA in 2000 which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, and private labs)
- PIPEDA has been superseded by provincial legislation in many provinces, such as the Ontario *Personal Health Information Protection Act*, which applies more specifically to health information

Duties of Physicians with Regard to the Privacy of Health Information

- inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
- obtain the patient's expressed consent to disclose information to third parties
    - under Ontario privacy legislation, the patient's expressed consent need not be obtained to share information between healthcare team members involved in the "circle of care." However, the patient may withdraw consent for this sharing of information and may put parts of the chart in a "lock box"
    - physicians have a professional obligation to facilitate timely transmission of the patient's medical record to third parties (with the patient's consent), such as for insurance claims. Failure to do so has resulted in sanctions by regulatory bodies
    - while patients have a right of access to their medical records, physicians can charge a "reasonable fee" commensurate with the time and material used in providing copies/access
- provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
- provide secure storage of information and implement measures to limit access to patient records
- ensure proper destruction of information that is no longer necessary
- regarding taking pictures or videos of patients, findings, or procedures, in addition to patient consent and privacy laws, trespassing laws apply in some provinces
- in addition to Ontario legislation and case law, the CPSO policy sets out professional expectations of physicians regarding the handling of personal health information. This includes regulations regarding express or implied consent, incapacity, lock boxes, disclosure under exceptional circumstances, mandatory reporting, ministry audits, subpoenas, court orders, and police, as well as electronic records and voice messaging communication: https://www.cpso.on.ca/Physicians/Policies-Guidance/Policies/Protecting-Personal-Health-Information
- it is the physician's responsibility to ensure appropriate security provisions with respect to electronic records and communications
    - with the advent of digital records, there have been increasing issues with healthcare providers that are not part of a patient's circle of care accessing medical records inappropriately (e.g. out of curiosity or for profit). All staff and learners should be aware that most EMRs log which healthcare providers view records and automatically flag files for further review in certain cases (e.g. same surname, VIP patients, or audit of access to records). Regular audits are completed specifically to look for unauthorised access to records. This includes accessing personal health information of friends and family.

Consequences of a Breach of Privacy

- PHIPA outlines which privacy breaches must be reported to the Information and Privacy Commissioner of Ontario
- to underscore the importance of maintaining confidentiality and privacy the fines for breaches was increased in 2020
- an individual who commits a breach may be fined up to $200000 or a year in prison or both. An institution can be fined up to $1000000
- beyond financial implications, breaches in confidentiality and privacy erode the trust of the patient involved and greater society's trust of the profession



Ontario's Medical Expert Panel on Duty to Warn
CMAJ 1998;158(11):1473-1479
There should be a duty to inform when a patient reveals that they intend to do serious harm to another person(s) and it is more likely than not that the threat will be carried out

Where a threat is directed at a person or group and there is a specific plan that is concrete and capable of commission and the method for carrying it out is available to the threatener, the physician should immediately notify the police and, in appropriate circumstances, the potential victim. The report should include the threat, the situation, the physician's opinion, and the information upon which it is based

While Canadian courts have not expressly imposed a mandatory "duty to warn" on physicians to alert third parties of a danger posed by a patient, Canadian supreme court decisions have held that a physician is permitted to warn (permissive vs. mandatory)



CMA Code of Ethics and Professionalism
Protect the health information of your patients

Provide information reasonable in the circumstances to patients about the reasons for the collection, use, and disclosure of their health information

Be aware of your patients' rights with respect to the collection, use, disclosure, and access to their health information; ensure that such information is recorded accurately



Lock Boxes
The term "lock boxes" applies to situations where the patient has expressly restricted their physician from disclosing specific aspects of their health information to others, even those involved in the patient's circle of care. Note that the Personal Health Information Protection Act (PHIPA) provisions denote that patients may not prevent physicians from disclosing personal health information permitted/required by the law



Reasons to Breach Confidentiality
Child abuse
Fitness to drive
Communicable disease
Coroner report
Duty to inform/warn

Consent and Capacity

Ethical Principles Underlying Consent and Capacity from the Ontario Health Care Consent Act

- consent is the autonomous authorization of a medical intervention by a patient or their substitute decision-maker
- informed consent is a process, not a transaction or a signature on a page
- informed refusal is equivalent in principle and approach
- if a patient is deemed incapable of consenting to a proposed medical intervention, then it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
- there is a duty to discover, if possible, what the patient would have wanted when capable
- central to determining best interests is understanding and taking into account the patient's values, beliefs, and preferences, including any relevant cultural and/or religious considerations and the patient's interpretation of those considerations
- more recently expressed wishes take priority over remote ones
- patient wishes may be expressed verbally or in written form
- patients found incapable of making a specific decision should still be involved in the decision-making process as much as possible. If a patient found incapable expresses a willingness to pursue the proposed treatment/intervention, then this is known as assent (rather than 'consent,' which requires capacity)
- agreement or disagreement with medical advice does not determine findings of capacity/incapacity
- however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed. Steer clear from the tendency to define what reasonable person standards may be. If appropriate, look to discern patterns of justification offered by patients and their individual values and beliefs, which may be influenced by social context, such as culture and/or religion
- laws pertaining to consent and capacity may vary by province/territory and readers are encouraged to consult provincial/territorial guidelines

Four Basic Requirements of Valid Consent

1. Voluntary

- consent must be given free of coercion or pressure (e.g. from family members who might exert 'undue influence,' from members of the clinical team)
- the physician must not deliberately mislead the patient about the proposed treatment
- the physician must engage in self-reflection prior to entering the conversation regarding their position of power and privilege as well as take measures to mitigate the power differential within the relationship
- consent is continuous and a patient may change their mind at any point

2. Capable

- the patient must be able to understand and appreciate the nature and effect of their condition as well as of the proposed treatment or decision

3. Specific

- the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (e.g. the patient must be informed if students will be involved in providing the treatment)

4. Informed

- sufficient information and time must be provided to allow the patient to make choices in accordance with their wishes, including:
  - the nature of the treatment or investigation proposed and its expected effects
  - all significant risks and special or unusual risks
  - disclose common adverse events and all serious risks (e.g. death), even if remote
  - alternative treatments or investigations and their anticipated effects and significant risks
  - the consequences of declining treatment
  - answers to any questions the patient may have
- the reasonable person test – the physician must provide all information that would be needed "by a reasonable person in the patient's position" to be able to make a decision
- it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information, including overcoming language barriers, or communication challenges
- physicians have a duty to inform the patient of all legitimate therapeutic options and must not withhold information based on conscientious objections (e.g. not discussing the option of emergency contraception)



Health Care Consent Act
Obtaining valid consent before carrying out medical, therapeutic, and diagnostic procedures has long been recognized as an elementary step in fulfilling the physician's obligations to the patient Capacity is an essential component of valid consent, and obtaining valid consent is a policy of the CMA and other professional bodies



4 Basic Elements of Consent
Voluntary
Capable
Specific
Informed

ALGrawany

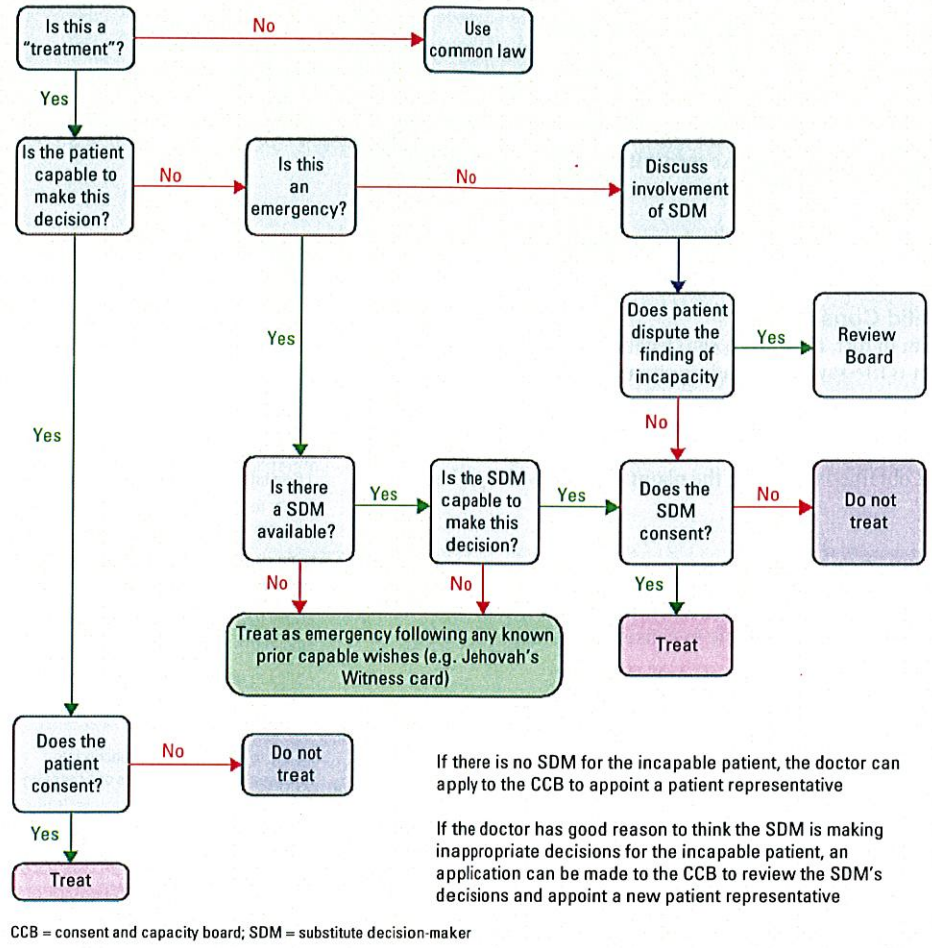


Figure 2. Ontario consent flowchart
Adapted by Hébert P from Sunnybrook Health Sciences Centre Consent Guidelines

Obtaining Legal Consent

- consent of the patient must be obtained before any medical intervention is provided; consent can be:
  - verbal or written, although written is usually preferred
  - a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent
  - most important component is what the patient understands and appreciates, not what the signed consent form states
  - implied (e.g. a patient holding out their arm for an immunization) or expressed
  - consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm, and the patient is not informed of and/or capable of considering these harms
  - if consent has been withdrawn during a procedure, the physician must stop treatment unless stopping the procedure would threaten the patient's life
  - in obtaining consent to continue the procedure, the physician need only re-explain the procedure and risks if there has been a material change in circumstances since obtaining consent originally. If there has been no material change in circumstances, simple assent to continue is sufficient (*Ciarlariello v. Schachter*)
- HCCA of Ontario (1996) covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)

Exceptions to Consent

1. Emergencies

- treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their SDM
- emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah's Witness card)
- if patient is incapable, the physician must document reasons for incapacity and why the situation is emergent
- patients have a right to challenge a finding of incapacity as it removes their decision-making ability
- if a SDM is not available, the physician can treat without consent until the SDM is available or the situation is no longer emergent

2. Legislation
- mental health legislation allows for:
  - the detention of patients without their consent
  - psychiatric outpatients may be required to adhere to a care plan in accordance with community treatment orders
- Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases

3. Special Situations
- public health emergencies (e.g. an epidemic or communicable disease treatment)
- warrant for information by police

Consequences of Failure to Obtain Valid Consent
- treatment without consent is battery (a claim in tort, meaning a civil legal matter, as opposed to a criminal legal matter), even if the treatment is life-saving (excluding situations outlined in Exceptions to Consent)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also a claim in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Overview of Capacity
- capacity is the ability to:
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
- capacity is specific for each decision (e.g. a person may be capable to consent to having a CXR, but not for a bronchoscopy)
- capacity can change over time (e.g. temporary incapacity secondary to delirium)
- most Canadian jurisdictions distinguish capacity to make healthcare decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
- a person is presumed capable unless there is good evidence to the contrary
- capable patients are entitled to make their own decisions
- capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny

Assessment of Capacity
- the person undergoing the assessment of capacity must be informed that they will be assessed
- capacity assessments must be conducted by the clinician providing treatment and, if appropriate, in consultation with other healthcare professionals (e.g. another physician or interprofessional healthcare provider)
- clinical capacity assessment may include specific capacity assessment (i.e. capacity specific to the decision at hand):
  1. effective disclosure of information and evaluation of patient's reason for decision
  2. understanding of:
     - the condition
     - the nature of the proposed treatment
     - alternatives to the treatment
     - the consequences of accepting and rejecting the treatment
     - the risks and benefits of the various options
  3. for the appreciation needed for decision-making capacity, a person must:
     - acknowledge the symptoms that affect them
     - be able to assess how the various options would affect them
     - be able to reach a decision, and make a choice, not based primarily upon delusional belief
- general impressions
- input from psychiatrists, neurologists, etc. for any underlying mental health or neurological condition that may affect insight or decision-making
- employ "Aid to Capacity Evaluation" or any other capacity assessment tool/guideline
- a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board (CCB)), or the courts; the patient has the right to a hearing before the CCB
- if found incapable by the Consent and Capacity Review Board, patient must receive notice of their ability to pursue judicial review (and essentially appeal the determination)

Treatment of the Incapable Patient in a Non-Emergent Situation
- obtain informed consent from SDM
- important to distinguish the cause of incapacity (mental illness vs other) to determine appropriate legislation. The Mental Health Act only covers detention and treatment of patients with specific conditions
- an incapable patient can only be detained against their will to receive treatment if they meet criteria for certification under the Mental Health Act (see Psychiatry, PS61); in such a situation:
  - document assessment in chart
  - notify patient of assessment using appropriate Mental Health form(s) under the Mental Health Act (Form 42 or Form 30 in Ontario)
  - notify Rights Advisor



Aid to Capacity Evaluation
J Gen Intern Med 1999;14(1):27-34

Ability to understand the medical problem

Ability to understand the proposed treatment

Ability to understand the alternatives (if any) to the proposed treatment

Ability to understand the option of refusing treatment or of it being withheld or withdrawn

Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment

Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment

Ability to make a decision that is not substantially based on delusions or depression



Capacity Assessment Criteria in Ontario
Test for understanding: can the patient explain the information you have given them in their own words?
Test for appreciation: can they explain how that information relates to them personally?
Refer to: JAMA The Rational Clinical Examination "Does This Patient Have Medical Decision-Making Capacity?



Incapable Patient
Note: Capacity is treatment-specific and time-specific. An incapable patient is only incapable for the specific treatment at the specific time
If not already present, perform a formal capacity assessment and thoroughly document
Identify if the patient has an SDM or who has their POA and locate it, if applicable
Check the patient's chart for any Mental Health Forms (e.g. Form 1) or any forms they may have on their person (e.g. Form 42)

Pediatric and Adolescent Patients

- no age of consent in all provinces and territories except Québec; Québec has a specific age of consent, but common law and case law deem underage legal minors capable, allowing these individuals to make their own choices
- consent depends on patient's decision-making capacity and must pass the same understand and appreciate test
- infants and young children are assumed to lack mature decision-making capacity for consent but they should still be involved in decision-making processes when appropriate (i.e. be provided with information appropriate to their comprehension level)
- preferably, assent should still be obtained from patient, even if not capable of giving consent
- in the event that the physician believes the SDM is not acting in the child's best interests, an appeal must be made to the local child welfare authorities
- under most circumstances, parents have the right of access to the child's medical record. If the child is able to consent to a treatment, they are also the one to determine who has access to their medical records related to that treatment

There is no age of consent in Ontario
Capacity is determined the ability to understand and appreciate test

Substitute Decision-Makers

- Substitute decision-makers (SDMs) is the person (or persons) who is legally permitted to make healthcare decisions on behalf of an incapable person
- The person who may fulfil this role is outlined in the Health Care Consent Act (HCCA) in Ontario (please check relevant legislation for other provinces)
- In Ontario, the automatic SDM is the closest living relative by blood, marriage or adoption. SDM's can be appointed through a legal process that supercede these automatic ones (Court Appointed Guardian, Attorney for Personal Care and Representative appointed by the Consent and Capacity Board) A full list of the hierarchy can be found in the HCCA
- SDMs must adhere to the following principles when giving informed consent on behalf of an incapable patient:
  - act in accordance with any wishes that the person expressed when capable
  - if wishes unknown, act in the patient's best interest, taking the following into account:
    1. values and beliefs held by the patient while capable
    2. whether well-being is likely to improve with vs. without treatment
    3. whether the expected benefit(s) outweighs the risk of harm
    4. whether a less intrusive treatment would be as beneficial as the one proposed
- the final decision of the SDM may and should be challenged by the physician if the physician believes the SDM is not abiding by the above principles

Most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:

Legally appointed guardian

Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see *Powers of Attorney*)

Representative appointed by the Consent and Capacity Board

Spouse or common law partner

Child (age 16 or older) and parent (unless the parent has only a right of access)

Parent with only a right of access

Sibling

Other relative(s)

Public guardian and trustee

POWERS OF ATTORNEY

- all Guardians and Attorneys have fiduciary duties for the dependent person

Definitions

- **Power of Attorney for Personal Care**
  - a legal document in which one person gives another the authority to make personal care decisions (healthcare, nutrition, shelter, clothing, hygiene, and safety) on their behalf if they become a person with mental incapacity. An Attorney for Personal Care is a substitute decision-maker and they are the third highest on the SDM hierarchy above automatic SDMs
- **Guardian of the Person**
  - someone who is appointed by the court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care. The Guardian is a substitute decision-maker and they are the highest on the SDM hierarchy above automatic SDMs
- **Continuing Power of Attorney for Property**
  - legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions.
- **Guardian of Property**
  - someone who is appointed by the Public Guardian and Trustee or the courts to look after an incapable person's property or finances
- **Public Guardian and Trustee**
  - acts as a SDM of last resort on behalf of a person with a mental incapacity who do not have another individual to act on their behalf

Other Types of Capacity Not Covered by the HCCA

Testamentary (ability to make a will)

Fitness (ability to stand trial)

Financial (ability to manage property – Form 21 of the Mental Health Act)

Personal (ability to care for oneself on a daily basis)

Substitute consent for a procedure whose primary purpose is research, sterilization for non-therapeutic purposes, or removal of organs or tissue for transplantation (does not apply to those already declared dead)

Negligence

Ethical Basis

- the physician-patient relationship is primarily based on trust, which is recognized in the concept of fiduciary duty, the responsibility to act in the patient's best interest
- negligence or malpractice is a form of failure on the part of the physician in fulfilling their fiduciary duty in providing appropriate care and leading to harm of the patient (and/or abuse of patient's trust)

Legal Basis

- physicians are legally liable to their patients for causing harm (tort) through a failure to meet the standard of care applicable under the circumstances

- standard/duty of care is defined as one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, specialization, and standing
- liability arises from physicians' common law duty of care to their patients in the physician/patient relationship (or in Québec, from the Civil Code provisions regarding general civil liability)
- action(s) in negligence (or civil liability) against a physician must be launched by a patient within a specific prescribed period required by the respective province in which the actions occurred

Truth-Telling

Ethical Basis

- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed and autonomous decisions about healthcare and their lives

Legal Basis

- required for valid patient consent (see *Consent and Capacity, ELOM12*)
- goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent based on misleading information and/or insufficient information can be seen as negligent and/or coercive

Evidence about Truth-Telling

- it is a patient's right to have the option of knowing about any clinical condition(s)/diagnoses that they may have
- most patients want to be provided with information regarding their health
- although some patients may want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth-telling improves trust, adherence, and health outcomes
- informed patients are more satisfied with their care and most often receive news about their health better than expected
- potential negative consequences of truth-telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability
- healthcare providers must be cautious to not apply their own personal values concerning the risk and benefits of truth telling.

CPSO Policy on Truth-Telling
Physicians should provide patients with whatever information that will, from the patient's perspective, have a bearing on medical decision-making and communicate that information in a way that is comprehensible to the patient

Medical Error

- medical error may be defined as 'preventable adverse events (AEs)' caused by the patient's medical care and not the patient's underlying illness; some errors may be identified before they harm the patient, so not all errors are truly 'adverse'
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient's decision-maker(s) and reported to the appropriate health authorities
- physicians must disclose to patients the occurrence of AEs or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - negligence is a legal determination
  - error is not equal to negligence
- disclosure allows the injured patient to seek appropriate corrective treatment promptly if possible
- physicians should avoid simple attributions as to the cause and sole responsibility of others or oneself
- physicians should offer apologies or empathic expressions of regret (e.g. "I wish things had turned out differently") as these may help to maintain and/or rebuild trust and are not admissions of guilt or liability
- Apology Acts across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence

Errors of care are compatible with non-negligent care if they are ones that a reasonably cautious and skilled physician could make (i.e. mistakes can be made due to 'honest error')

Adverse Event
An unintended injury or complication from health care management resulting in disability, death, or prolonged hospital stay

Breaking Bad News

- 'bad news' may be any information that reveals conditions or illnesses threatening the patient's sense of well-being; different patients may classify 'bad news' in different ways
- disclosing medical information in a poor or insensitive manner may be as harmful as non-disclosure
  - caution patients in advance of serious tests and about the possibility of bad findings
  - give time for patient to reflect upon the situation prior to disclosing such news
  - give warnings of impending bad news by reviewing prior discussions
  - provide time for the patient to ask questions
  - adequate supports and strategies should always be provided following the disclosure of difficult news
- **SPIKES** protocol was developed to facilitate "breaking bad news" in a conscientious and effective manner
  - **S**etting, **P**erceptions, **I**nvitation, **K**nowledge, **E**mpathy, **S**trategy (see Palliative Medicine, PM6)
  - other tools such as the Serious Illness Conversation Guide or Vital Talk can also assist with conversations with patients with serious illness

Examples of Warning of Impending Bad News
Remember to clarify (invite) the level of knowledge desired by the patient
"I have something difficult to tell you..."
"Unfortunately, the results are not what we were hoping for..."
"This may come as a shock to you, but the tests indicate..."
"There is no easy way for me to tell you this, so I will tell you straight away that you have a serious problem..."

Arguments Against Truth-Telling

- may go against certain cultural norms and expectations
- may lead to patient harm, but only in extreme, rare situations
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

Reproductive Technologies

- people of all gender identities may access reproductive technologies
- the words "maternal, mother, and woman" may refer to gender diverse individuals

Overview of Pregnancy Considerations

- medico-legally, the maternal body and the fetal body are considered one. In general, the individual who is pregnant and the fetus's interests align unless otherwise indicated via appropriate consent processes, maternal health takes precedence

Ethical Issues and Arguments

- principle of reproductive autonomy:
  - pregnant individuals have the right to reproductive choice (e.g. to make decisions that align with their personal values, interests, and beliefs)
  - coercion of an individual to accept medical advice is an unacceptable infringement of their personal autonomy. It is important to empower individuals to make informed decisions about their medical care in relation to pregnancy. This involves providing the individual with information about any relevant benefits and risks in relation to recommendations, giving them time to ask questions and reflect upon the recommendation(s), etc. A fine, but important, line exists between making a strong recommendation and coercing an individual into consenting to a medical recommendation, the latter of which must be avoided. A recommendation is, precisely, a recommendation (not forced)
  - Canada's colonial history includes a legacy of infringement of reproductive rights. It is important to be mindful of one's own inherent power and privilege when engaging in conversations
  - biases: it is important to be cognizant of one's potential biases in relation to reproductive decision-making. Ensuring that one's personal values and preferences do not unduly influence a patient's decision-making process is of the utmost importance in order to enable autonomous decision-making

Legal Issues and Arguments

- the law protects a gestating individual's right to life, liberty, and security of person. Key aspects of the gestating individual's rights include:
  - an individual with capacity (recognizing that capacity is decision- and time-specific) has the right to consent or refuse to consent to any medical recommendations irrespective of whether or not they are gestating. It is up to the treatment-proposing clinician to ensure that all relevant information related to a medical recommendation (e.g. risks, benefits) is provided to help ensure informed decision-making
  - the fetus does not have legal rights until it is born alive and with complete delivery
  - a pregnant person with comorbid substance use disorder cannot be detained and treated to protect the fetus (*Winnipeg Child and Family Services (Northwest Area) v. G. (D.F.), [1997] 3 S.C.R. 925*)
  - a fetus is not a "human being" within the meaning of the Criminal Code of Canada, thus medical negligence during delivery resulting in the death of a fetus that has not been born alive does not *constitute* criminal negligence causing death (manslaughter) and cannot attract criminal penalties (*R v Sullivan*)

Assisted Human Reproduction Act (2004) Principles

- The Parliament of Canada recognizes and declares that
  - (a) the health and well-being of children born through the application of assisted human reproductive technologies must be given priority in all decisions respecting their use;
  - (b) the benefits of assisted human reproductive technologies and related research for individuals, for families and for society in general can be most effectively secured by taking appropriate measures for the protection and promotion of human health, safety, dignity and rights in the use of these technologies and in related research;
  - (c) while all persons are affected by these technologies, women more than men are directly and significantly affected by their application and the health and well-being of women must be protected in the application of these technologies;
  - (d) the principle of free and informed consent must be promoted and applied as a fundamental condition of the use of human reproductive technologies;
  - (e) persons who seek to undergo assisted reproduction procedures must not be discriminated against, including on the basis of their sexual orientation or marital status;
  - (f) trade in the reproductive capabilities of women and men and the exploitation of children, women and men for commercial ends raise health and ethical concerns that justify their prohibition; and
  - (g) human individuality and diversity, and the integrity of the human genome, must be preserved and protected



The Tri-Council Policy Statement

1. Genetic treatment aimed at altering germ cells is prohibited in Canada and elsewhere
2. Embryo research is permitted up to 14 d post-fertilization
3. Embryos created for reproductive purposes that are no longer required may be used
4. Gamete providers must give free and informed consent for research use
5. No commercial transactions in the creation and use of the embryos are permitted
6. Creation of embryos solely for research purposes is prohibited
7. Human cloning is strictly prohibited
8. Risks of coercion must be minimized (i.e. the fertility treatment team may not be pressured to generate more embryos than necessary)
9. One may only discuss the option of using fetal tissue for research after the patient makes a free and informed choice to have a therapeutic abortion
10. Physicians responsible for fertility treatment may not be part of a stem cell research team

Assisted Reproductive Therapies

- includes non-coital insemination, hormonal ovarian stimulation, and IVF
- some commonly referenced, ethically complex topics related to assisted reproductive therapies (ART) include, but are not limited to:
  - donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
  - preimplantation genetic testing for diagnosis before pregnancy
  - use of new techniques without patients appreciating their experimental nature
  - moral status of embryo
  - access to ART
  - private vs. public funding of ART
  - social justice factors influencing one's access to and/or experiences with ART (e.g. same-sex couples having an opportunity to access welcoming, morally safe 2SLGBTQQIA+ spaces to receive care)
  - the 'commercialization' of reproduction (e.g. surrogates)

Fetal Tissue

- pluripotent stem cells can currently be derived from human embryonic and fetal tissue
- use of stem cells in research is reviewed by the Stem Cell Oversight Committee as part of the CIHR
- potential uses of stem cells in research:
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown in vitro to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson's disease)
  - genetic treatment aimed at altering somatic cells (e.g. myocardial or immunological cells) is acceptable and ongoing

Induced Abortion

- CMA definition of induced abortion: the active termination of a pregnancy before fetal viability (fetus >500 g or >20 wk GA)
- full CMA policy on induced abortion can be accessed here: https://www.cmaj.ca/content/139/12/1176a
- after a CMAJ publication in 2006, several letters to the editor were published, questioning the CMA's position on induced abortion. In response, the CMA published clarification of their stance. This clarification can be accessed here: Clarification of the CMA's position concerning induced abortion | CMAJ (a)

Ethical and Legal Concerns and Arguments

- in Canada, there is no criminal prohibition regarding abortion
- termination of pregnancy is a medical and personal decision to be made in consultation with a healthcare provider, alongside anyone else the patient wishes
- there exist various reasons as to why a person may inquire about and choose to pursue termination of pregnancy
- termination of pregnancy is a value-laden and moralized topic. Healthcare providers, even those who conscientiously object to termination of pregnancy, ought to treat all patients requesting such termination with dignity, respect, and in a person-centred manner. It is of particular importance to be cognizant of one's own biases when caring for patients who want to receive a medical treatment that does not accord with one's personal belief system and preferences
- if a medical practitioner does not provide termination of pregnancy, an effective referral to a willing and available provider must be made without delay. From an ethics perspective, it is important to demonstrate continued trustworthiness and support, recognizing that trusting one's providers can influence health outcomes
- 2nd and 3rd trimester abortions are legal in Canada, but are usually, though not exclusively, pursued when there are risks to the person's health, if the fetus died in utero, and/or if the fetus has a known major irreversible condition which may subject them to poor health outcomes upon birth (e.g. anencephaly). In any of these cases, however, it is the choice of the pregnant individual as to whether or not they will maintain or terminate pregnancy

Prenatal/Antenatal Genetic Testing

- uses:
  1. to confirm a clinical diagnosis
  2. to detect genetic predisposition to a disease
  3. genetic testing/learning of predispositions may allow for preventative steps to be taken and help the person prepare for the future
  4. gives parents the option to terminate a pregnancy or begin early treatment if/as applicable
  - ethical dilemmas may arise because of the sensitive nature of genetic information; important ethical complexities and considerations related to genetic testing may include:
    - the individual and familial implications (e.g. how will learning about information confirmed via genetic testing influence one's family dynamic?)
    - its pertinence to future disease
    - its ability to identify disorders for which there are no effective treatments or preventive steps (e.g. should a person know if they/their fetus is genetically predisposed to an incurable disease? Would the potential harms of knowing this information potentially outweigh the benefits?)

- its ability to identify the sex of the fetus, which may or may not be desired and/or relevant information to one's decision-making
- obtaining truly informed consent is difficult due to the complexity of genetic information and the inability to know precisely what will/will not occur as a result of such testing (e.g. people may receive unexpected and unwanted genetic information after consenting to the testing)
- related to the above, consent to genetic testing and consent to disclosure of all genetic information that results from the test may be distinct
- some patients may want to be informed of genetic test results in particular ways (e.g. with a support person present). In the case of delivering complex information, genetic counselling may be recommended
- duty to maintain confidentiality vs. duty to warn family members (e.g. if a patient's sister is likely predisposed to the same genetic condition as your patient, what are your responsibilities to the sister, if any?)
- risk of psychological harm
- risk of experiencing unjust social discrimination if such genetic information is disclosed to certain parties

Legal Aspects

- as of 2017, the Genetic Non-Discrimination Act exists
- genetic testing requires informed consent
- physicians are obligated to inform patients that prenatal testing exists and is available
- in some specific circumstances, a physician may be able to breach confidentiality in order to warn family members about a condition if harm can possibly be prevented via treatment or prevention. In general, the patient's consent is required, unless the harm to be avoided is sufficiently serious to rise to the level of imminent risk of serious bodily harm or death (i.e. not a chronic condition, but an acute life-threatening condition). It is recommended to consult with legal counsel and bioethics if complexities arise in regard to breach of confidentiality/duty to warn

End-of-Life Care

Overview of Palliative and End-of-Life Care

- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, and loved ones
  - palliative care is an approach that improves the quality of life of patients facing life-threatening illness, through the prevention and relief of suffering, including treating pain, physical, psychosocial, and spiritual concerns
  - *early* palliative care leads to improved quality of life and mood, fewer aggressive end-of-life treatments, and extended median survival time compared to patients receiving standard care
- appropriate for any patient at any stage of a serious or life-limiting illness
- may occur in a hospital, hospice, in the community, or at home
- often involves an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care
- palliative sedation: the use of sedative medications for patients that are terminally ill to relieve suffering and manage symptoms
- withdrawing or withholding life sustaining interventions (e.g. artificial ventilation or nutrition) that are keeping the patient alive but no longer wanted or indicated



Palliative Care – Not the Same as Medical Assistance in Dying
Palliative care is an approach designed to improve symptoms and quality of life for the duration of a person's life, but unlike Medical Assistance in Dying, it does not aim directly at or intend to end the person's life. Many palliative care physicians are incorporating MAID into their practice, though some may conscientiously object

Medical Assistance in Dying

- medical assistance in dying: the administering or prescribing for self-administration, by a medical practitioner or nurse practitioner, of a substance, at the request of a person, that causes their death

Common Ethical Arguments/Opinions

- criminally prohibiting medical assistance in dying may influence some individuals to end their own lives and/or to endure intolerable suffering until their natural death occurs
- patient has the right to make autonomous choices about the time of their own death
- belief that there is no ethical difference between the acts of euthanasia/assisted suicide and forgoing life-sustaining treatments
- belief that these acts benefit terminally ill patients by relieving suffering
- belief that patient autonomy has limits and that one cannot and/or should not be allowed to make an autonomous request to end one's life
- death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death
- an argument presented in the Carter case (see below) suggested permitting MAID will detract support for palliative care, since with proper palliative care, the number of requests for MAID would decrease. This argument was rejected in *Carter v. Canada*, as it was deemed unacceptable to make people suffer intolerably to potentially improve and/or increase support for palliative care

Legal Aspect

- in the *Carter v. Canada* decision of February 2015, the criminal prohibition on assistance in suicide was ruled unconstitutional to the extent that they prohibit physician-assisted death for a competent adult person who (1) clearly consents to the termination of life and (2) has a grievous and irremediable medical condition that causes enduring suffering that is intolerable to the individual in the circumstances of his or her condition
- Bill C-14 (June 17, 2016) legalized MAID by amending the Criminal Code to create exemptions permitting medical practitioners to provide MAID, specified the eligibility criteria, safeguards, and required documentation and authorization from the Minister of Health, as well as new offences for failure to comply with the new regulations. As the Bill C-14 criteria are narrower than the Carter decision, there are ongoing constitutional challenges to the MAID framework as it currently stands
- Bill C-39 (March 9, 2023) temporarily postpones MAID eligibility for persons suffering solely from mental illness to March 17, 2025

Bill C-14 Criteria for MAID

- patient is eligible for publicly-funded health services in Canada
- at least 18 yr, and has capacity for clear and freely given consent
- grievous and irremediable medical condition: in an advanced state of irreversible decline in capability
- suffering intolerable to the patient, not relieved under conditions they consider acceptable
- recent update eliminated criteria of "reasonable foreseeability of natural death"
- MAID process:
  1. eligibility criteria satisfied
  2. patient signs and dates a written request for MAID
  3. two independent witnesses sign the written request. Witnesses must be 18 y/o, understand the nature of MAID, and must not a) benefit (financially or otherwise) from the death, b) be an owner or operator of the healthcare facility where the patient is receiving care, c) be directly involved in the provision of health or personal care of the patient
  4. healthcare provider must inform the patient that they can withdraw their consent at any time
  5. two independent assessors (physician or nurse practitioner) must provide written confirmation that eligibility criteria are met
  6. 10 clear days must elapse between the request and the day on which MAID is provided, unless both healthcare providers agree that a shorter period is appropriate due to the patient's imminent death or loss of capacity
  7. as per the new MAID legislation (updated in 2021), a patient may request MAID even if death is not reasonably foreseeable. For a patient whose death is not reasonably foreseeable, their eligibility assessment must be a minimum of 90 days unless the assessments are completed sooner and the patient is at immediate risk of losing the capacity to consent.
  8. throughout the 10 or 90 day period and immediately before providing MAID, the healthcare provider must give the individual an opportunity to withdraw the request and ensure that the patient gives express consent to receive MAID
     - contravention of this process is an offence punishable by up to 5 yr in prison
  9. as of changes to the legislation in 2021, a patient may waive the requirement for giving final consent just before MAID is administered only if: (1) the patient's death is reasonably foreseeable and (2) while the patient has decision-making capacity the patient is:
     (a) assessed and approved for MAID
     (b) advised that they are at risk of losing capacity to provide final consent and
     (c) the patient makes a written arrangement with their health care provider where they consent in advance to receive MAID on a chosen date if they (i.e. the patient) no longer has capacity to consent on that date

Usage of Palliative and End-of-Life Care

- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from MAID as it is seen as allowing the underlying disease to take its 'natural course,' but this distinction may be more theoretical than real
- consent for withdrawal of life-support must be sought from the capable patient, or in case of incapable patient the SDMs, as per the Health Care Consent Act and Substitute Decisions Act, and as re-affirmed by the ruling in Cuthbertson v. Rasouli in 2013, as palliative care would be instituted and consent for that would require SDM consent
- refusals of care by the patient that may lead to death as well as requests for a hastened death, ought to be carefully explored by the physician to rule out any 'reversible factors' (e.g. poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice
- Government of Canada – Services and Information for End-of-Life Care:
  - https://www.canada.ca/en/health-canada/topics/end-life-care.html
  - options and decision making at end of life: palliative care, Do Not Resuscitate orders, refusal or withdrawal of treatment, refusal of food and drink, palliative sedation, MAID
  - decisions at end of life: capacity for informed consent, SDM, advanced care planning (written plan, will, or medical directive) often established through a family meeting



MAID: Ethically Appropriate Actions

Respect capable decisions to forgo available treatment options and/or palliative care options

Provide appropriate palliative measures with patient consent

Try to assess reasons for MAID requests to see if there are 'reversible factors' that are directly and unduly influencing one's desire to receive MAID (e.g. depression, pain, loneliness, anxiety) that can be treated



Exploring the Experience of Supporting a Loved One through a Medically Assisted Death in Canada

Can Fam Physician. 2018;64(9):e387-e393

Purpose: To explore the experience of family and close friends of patients seeking MAID in Canada.

Methods: Primary support givers of clinic patients seeking MAID were identified during consultations for an assisted death evaluation. The identified support givers were then invited to participate in the study, and those interested were asked to contact interviewers. Semi-structured interviews were conducted, transcribed, coded, and subjected to content analysis to elucidate common themes.

Results: 18 support people for patients seeking MAID were interviewed. All participants were supportive of their loved one's wishes for MAID and provided emotional and practical support in preparation for the procedure. Some participants reported feeling opposed, however, changed their minds after seeing the suffering their loved ones had to endure. The time before the procedure involved saying goodbye and ceremonial rituals. Those interviewed after the procedure found the death peaceful and reported that it offered advantages compared with natural death in their loved one's individual circumstances.

Conclusion: Participants were supportive of their loved one's wishes for assistance in death to end suffering and found the process to be peaceful overall.

Physician Responsibilities Regarding Death

- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence
  - Coroner's Act, 1990 (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy
  - suddenly and unexpectedly
  - from disease which was not treated by a legally qualified medical practitioner
  - from any cause other than disease
  - under suspicious circumstances
  - death from MAID
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
  - the identity of the deceased
  - where and when the death occurred
  - the medical cause of death
  - the means of death (i.e. natural, accidental, suicide, homicide, or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility
- while the Supreme Court of Canada noted that nothing in the Carter v. Canada decision compelled a physician to participate in MAID, the College of Physicians and Surgeons of Ontario mandatory referral policy, which has been upheld by the courts, requires physicians in Ontario to provide an effective referral if the physician conscientiously objects to MAID
  - the impact of MAID on religious institutions' obligation towards patients is not yet clear

Notify coroner if death occurs due to:
Violence, negligence, misconduct
Pregnancy
Sudden or unexpected causes
Disease not treated
Cause other than disease
Suspicious circumstances
MAID

Physician Competence and Professional Conduct

CanMEDS Competencies (Ethical/Policy Statement)

- a framework of professional competencies established by the Medical Council of Canada (MCC) as objectives for the MCC Qualifying Exam
- further information on Medical Council of Canada objectives can be found at www.mcc.ca

Legal Considerations

- physicians' conduct and competence are legally regulated to protect patients and society via mandatory membership to provincial governing bodies (e.g. the CPSO)
- physicians are legally required to maintain a license with the appropriate authority, and are thus legally bound to outlined policies on matters of conduct within their medical practice
- the ultimate constraint on physician behaviour with regards to unprofessionalism is 'conduct unbecoming a physician,' such as inappropriate behaviour with colleagues, conflicts of interest, untruthfulness, unethical billing practices, and sexual impropriety with patients

CPSO Policy: Treating Self and Family Members
Physicians will not diagnose or treat themselves or family members except for minor conditions or in emergencies, and only if no other physician is readily available

Common Policies on Physician Conduct

- physicians must ensure that patients have knowledge of/access to on-call coverage and are never abandoned
  - physicians are required to comply with the law, including human rights laws
- sexual conduct with patients, even when consented to by the patient can lead to accusations of battery and professional misconduct by the provincial governing body. Important notes on this topic include:
  - inappropriate sexual conduct includes intercourse, undue touching, inappropriate and unrelated references to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
  - in specific situations, physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
  - physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
  - in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety (as per CPSO Policy on Boundary Violations)
- physicians must maintain adequate records for each patient, which include:
  - demonstration that care has been continuous and comprehensive
  - minimal standards for record-keeping, including readability, diagnosis, differential diagnosis, appropriate tests and referrals, and a coherent patient record, including drugs, a cumulative patient profile, and all aspects of charting that are required for safe patient care (full standards available at www.cpso.on.ca). Another physician should be able to take over the safe care of the patient based on the record
  - records stored for 10 yr in most jurisdictions, though this ought to be verified with one's provincial governing bodies
  - although the medical record is the property of the physician or an institution:
    - the patient or the patient's delegate must be allowed full access to information in the medical record

CPSO Policy: Ending the Physician-Patient Relationship
Discontinuing services that are needed is an act of professional misconduct
Exceptions include patient request, alternative services arranged, or adequate notice has been given

CMA Code of Ethics
Report any unprofessional conduct by colleagues to the appropriate authority

CanMEDS Competencies
- Communicator

Collaborator
Health Advocate
Leader
Professional
Scholar
Medical Expert

- the patient or delegate must obtain access within a reasonable period of time, usually upon a written request
- the physician can charge a reasonable fee for this service

- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain hospital records

Research Ethics

- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  - study participants are protected
  - study participants are treated in accordance with relevant research ethics norms, including but not limited to: respect for persons, concern for welfare, and justice
  - clinical research is conducted to serve the interests of the participants and/or society as a whole
- the protection of research participants is of the utmost importance when conducting clinical research
- a Research Ethics Board (REB) is responsible for reviewing and approving proposed human research. REB approval is required prior to commencing a research study involving humans
- an ethical dilemma arises for physician researchers when their obligation to patients as their physician comes into conflict with research obligations and/or incentives as a researcher. Physicians pursuing research should not be the primary point of contact responsible for recruiting and consenting their own patients due to the possibility of therapeutic misconception and/or feelings of undue influence/ lack of voluntariness
- REB offices located within hospitals may have requirements about who can/cannot recruit and/or consent patients for their possible participation in research
- the Human Research Standards Organization (HRSO) develops and publishes national standards for those interested in overseeing, conducting, and/or participating in human research activities in Canada. All published national standards can be accessed here: https://www.hrso-onrh.org
- in order to become aware of all relevant research ethics principles and norms, of which there are many (the above-mentioned principles and norms are far from an exhaustive list), it is recommended that you read Declaration of Helsinki, the Belmont Report, and complete the Tri-Council Policy Statement: Ethical Conduct on Research Involving Human Subjects (TCPS2) online training. The TCPS 2 (2022) can be accessed here: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2022) (ethics.gc.ca)

Ethics on Research with Indigenous People

- the Ownership, Control, Access, and Possession (OCAP) principles are "a set of standards that establish important ground rules about how Indigenous peoples' data should be collected, protected, used, or shared"
- OCAP principles are:
  - control: Indigenous peoples, their communities, and representatives have the right to control all aspects of "research and information management processes that impact them"
  - access: "Indigenous peoples must have access to information and data about themselves and their communities regardless of where it is held"
  - possession: Indigenous peoples are stewards of the data. As they possess the data, it is within their jurisdiction and control
- researchers working with Indigenous communities are expected to uphold OCAP principles in their research
- First Nations, Inuit, and Métis (FNIM) communities are self-determining, and as such, may have their own version of OCAP. Investigators should respect each community's autonomy with respect to research, data collection, analysis, interpretation, and knowledge transfer
- Chapter 9 of the TCPS2 discusses and provides considerations regarding research involving FNIM Peoples of Canada. This chapter can be accessed here: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2022) – Chapter 9: Research Involving the First Nations, Inuit and Métis Peoples of Canada (ethics.gc.ca)

The First Nations Principles of OCAP® [Internet]. Akwesasne (ON): First Nations Information Governance Centre (FNIGC); 2020 [cited 2020 Apr 12]. Available from: www.FNIGC.ca/OCAP. OCAP® is a registered trademark of the First Nations Information Governance Centre (FNIGC)

Guiding Principles for Research Ethics
There are a number of principles that are important to research ethics – the three listed are primary ones that are typically cited, but this list is non-exhaustive.

Respect for persons: informed consent

Beneficence: harm vs. benefit

Justice: avoid exploitation/unjustified exclusion criteria

Informed Consent for Research

- Purpose of study
- Expectations of the research participant
- Name and probability of harm and benefits
  - Whether and/or how participants can withdraw their consent to participate
  - Confidentiality (e.g. how will it be maintained? Are participants going to be deidentified and anonymized?)
  - Privacy (e.g. for how long will participants' data be stored?)
- Nature of physician's participation including compensation

Proposals for research must be submitted to a Research Ethics Board (REB)

ALGrawany

Physician-Industry Relations

- healthcare delivery in Canada involves collaboration between physicians and the pharmaceutical and healthcare supply industries in the areas of research, education, and clinical evaluation packages (e.g. product samples)
- however, unlike physicians, pharmaceutical and healthcare supply industries do not have a fiduciary duty to patients and are profit-driven. There exists a motive for pharmaceutical companies, which extends beyond your responsibility as a physician
  - literature is clear that our decision-making is influenced by items such as gifts provided by the pharmaceutical and healthcare supply industries (e.g. pens with brand names inscribed, free lunch and learn sessions)
  - accepting such offers (e.g. saying "yes" to a lunch and learn session being offered by a pharmaceutical company, personal injury law firm, etc.) can directly influence physician practices and beliefs in favour of such promoted products. This influence can result in, for instance, the prescription of medications for reasons other than their efficacy and safety profile, recommending particular law firms to patients (which is outside of one's scope)
  - ultimately, there is a reason as to why the pharmaceutical and healthcare supply industries spend money to build relationships (namely, to influence decision-making in favour of the company)
  - the dissemination of free product samples by pharmaceutical companies is associated with increased patient preference for new drugs that are often more expensive, thus incurring a greater long-term cost for patients and the healthcare system
  - new pharmaceutical products are not always more effective than previous standard of care and may have less robust safety evidence by virtue of being new
- physicians must ensure that their participation in any collaborative efforts with pharmaceutical and healthcare supply industries is in keeping with their duties to their patients and society; however, physicians often struggle to properly identify situations in which a conflict of interest is present. It is recommended that clinicians who want support in identifying and navigating potential conflicts of interest gain bioethics support
- gifts or free products from the pharmaceutical industry are usually inappropriate:
  - sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance
  - physicians receiving such sponsorship must disclose this at presentations and/or in written articles; it is important to note, however, that the disclosure of conflicts does not eliminate the potential influence that the conflict may have on physician behaviours



CMA and CPSO Guidelines for Ethically Appropriate Physician-Industry Relations

The primary goal should be the advancement of the health of Canadians

Relationships should be guided by the CMA Code of Ethics

The physician's primary obligation is to the patient

Physicians should avoid any self-interest in their prescribing and referral practices

Physicians should always maintain professional autonomy, independence, and commitment to the scientific method

Resource Allocation

- **definition**: the distribution of any resource to programs and people (e.g. goods and services)
- if healthcare resources are clinically indicated, physicians must make such resources available to patients in a manner that takes into consideration equity, potential biases, and possible discriminatory motivation of offering/not offering such resources
  - a person's and/or society's need for and benefit of certain resources are morally relevant criteria for determining allocation, particularly if resources are scarce
  - gender identity, sex, sexual orientation, religion, level of education, socioeconomic status, or age alone are morally irrelevant criteria in and of themselves (i.e. one must not prevent a patient from accessing a scarce resource exclusively on the basis of age)
  - factors determining whether and/or how resources ought to be allocated must be balanced against each other and weighed on a case-by-case, situation-by-situation basis. For instance, there may be some cases where one's age is relevant to determining how much a patient is expected to/not to benefit from a particular resource, but in other cases, age may be entirely irrelevant
- ethical dilemmas that may arise when deciding how best to allocate scarce resources:
  - favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
  - aggregation problem: providing modest benefits to many individuals vs. significant benefits to few individuals
  - decision-making framework considerations: when to rely on a fair democratic process to arrive at a decision, what does a 'fair' process look like?



Choosing Wisely Canada is the national voice for reducing unnecessary tests and treatments in healthcare. Refer to https://choosingwiselycanada.org/recommendations/ for a comprehensive list of recommendations to assist in decision making as healthcare stewards

Guidelines for Appropriately Allocating Resources

- protect and promote the welfare and best interests of patients
- enable informed, autonomous, and voluntary decision-making
- choose interventions known to be beneficial based on evidence of efficacy
- seek the test(s) or treatment(s) that will be most likely to accomplish the diagnostic or therapeutic goal with minimal expected harms
- advocate for one's patients, but do not manipulate the system to gain unfair advantage
- resolve conflicting claims for scarce resources justly and equitably, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures. Consult with external resources (e.g. bioethics team) to help reduce potential biases in decision-making processes
- if appropriate, sensitively inform patients of the impact of cost constraints on care/the healthcare system
- seek resolution of unacceptable shortages at the level of hospital management or government

Conscientious Objection

Patients Refusing Treatment

- in accordance with the principle of autonomy, it is generally acceptable for capable patients to make an informed decision to refuse medical interventions, although exceptions may occur
- it is important to determine justification for refusal of recommended treatment, to ensure decision-making is informed, etc., particularly if the risks of such refusal are significant
- if SDMs make decisions that are not in the best interests (or, if known, previously expressed wishes) of an incapable child, physicians may have grounds for administering treatment, depending on the acuity of the clinical situation. It is best to consult with Legal Counsel, Bioethics, and one's College if you are considering the administration of treatment without consent since applications to gain this permission (via the Consent and Capacity Board in Ontario, for instance) may be essential
  - in high-acuity scenarios (e.g. refusing blood transfusion based on religious grounds for a child in hemorrhagic shock), physicians have a stronger obligation to act in the child's best interests
  - in lower acuity scenarios (e.g. refusing childhood immunization in a developed nation), there is a stronger obligation to respect the autonomy of the decision-makers

Physicians Refusing to Provide Treatment

- it is the case that with justification provided, physicians may refuse to provide a desired treatment (e.g. a treatment that is not clinically indicated and may cause harm) and/or discharge/discontinue relationships with patients (e.g. if there is no therapeutic relationship or trust due to a series of conflicts), but must ensure these patients can access services elsewhere by way of referring the patient to an available and willing practitioner

Implicit Bias

- implicit bias involves: implicit attitudes, thoughts, and/or feelings that may exist outside of conscious awareness and are therefore difficult to acknowledge and control
  - there exist various types of (implicit) biases (e.g. related to age, race, sex, sexual orientation, gender identity, and socioeconomic circumstances among many other factors)
  - negative attitudes towards certain patients based on implicit biases may contribute to disparities in quality of healthcare received
  - these negative attitudes caused by implicit biases reflect constant pervasive exposure to stereotypical portrayals of members of different "social groups"
- bias and stereotypes can be lethal
  - on September 21, 2008, Brian Sinclair, an Indigenous man, presented to a Winnipeg emergency department with a blocked catheter. His presence was not recorded by triage
  - while he waited in the emergency department waiting room, he lost consciousness, but was not checked on by healthcare staff
  - after being in the waiting room for 34 h, he passed away without having received any medical attention
  - later, an inquest found that healthcare staff thought he was intoxicated or homeless
  - a Manitoba court stated that Brian Sinclair's race, and consequently the stereotypes staff held leading to the assumption that he was intoxicated, were relevant factors in his tragic and preventable death

Suggestions for Noticing Implicit Bias

- before a clinical encounter, physicians are advised to check-in with themselves
- physicians may want to ask themselves:
  - how are they feeling?
  - what are they worried about?
  - what do they notice in their body?
  - what is their intention for the interaction?
  - what do they need to feel more grounded and supported before going into the clinical space?
  - how can they leave some of their assumptions and fears in the hall, instead of bringing them into the examination room?



Working with Vaccine-Hesitant Parents: An Update
Canadian Paediatric Society 2018

1. Understanding the health provider's key role in parental decision-making and not dismissing vaccine refusers from practice
2. Using presumptive and motivational interviewing techniques to identify specific vaccine concerns
3. Using effective and clear language to present evidence for disease risks and vaccine benefits fairly and accurately
4. Managing pain during immunization
5. Reinforcing the importance of parental responsibility for community protection

Clinical Informatics and Ethical Considerations

Key Terms

Health Informatics
- is the study of information design and use in healthcare

Clinical Informatics
- is the application of health informatics knowledge in the clinical setting to promote quality care. It has three domains: collection of longitudinal personal health information for direct patient care, exchange of health information between services and locations, and aggregation of health data for analysis using analytics, artificial intelligence, and machine learning

Digital Health
- is the use of information technology and electronic communication tools, services, and processes to deliver healthcare services

Overview of Digital Health Technologies

Table 6. Overview of Digital Health Technologies and Relevant Ethical Considerations

Digital Health Technologies	Definitions	Ethical Considerations
EMR (Electronic Medical Record)	System of electronically stored patient health information in a digital format	Impact of threats to healthcare information Privacy and confidentiality Security breaches System implementation Data entry inaccuracies
EHR (Electronic Health Record)	Digital collection of medical information (e.g. patient's health history, allergies, immunizations, treatment plans	
LIS (Laboratory Information System)	Computer software that processes, stores, and manages data from all stages of medical processes and tests	
PACS (Picture Archiving and Communication System)	Computer software providing storage and access to images from multiple modalities	

Indigenous Health

Overview of the History and Impact of Colonialism

- the Indigenous health crisis that exists today is a result of many factors, including the impact of colonial laws, oppression, and genocide
- Indigenous health is deeply connected to the land and freedom that have been systematically stolen from its people
- physicians can consider how oppressive legislation plays a role in precluding many Indigenous patients from experiencing health
- you might find this timeline outlining "Key Moments in Indigenous History" helpful: http://education.historicacanada.ca/files/426/Key_Moments_in_Indigenous_History_Timeline.pdf

- long before the arrival of European newcomers, Indigenous peoples lived on and cared for Turtle Island (now known as North America). This history is richly steeped in culture, relationships, and a holistic worldview. The Indigenous peoples had a flourishing trade, complex social and legal systems, and scientific knowledge about astronomy, ecology, agriculture, and medicine. Despite hundreds of years of adversity, Indigenous peoples and their rich cultures persist and thrive today – an indication of the resilience and tenacity of Indigenous peoples and communities

- upon European arrival, Indigenous and non-Indigenous people formed friendships based on mutual respect. These relationships were formalized through treaties. Treaties provided a framework for relationships and the sharing of Indigenous lands in a peaceful and respectful way

- one example of how treaties were documented and enacted was through wampum belts. Wampum belts are intricate visual displays made from clam shells. These belts serve as a living record of agreements. The two-row wampum belt is particularly important for understanding the relationship between Indigenous peoples and Europeans

- in 1613, Kanienkehaka (Mohawk) peoples noticed that settlers were using and living on their traditional lands. The Haudenosaunee Confederation met and discussed how they could live and work together peacefully on the land. Through these discussions, they learned much about one another and the two-row wampum was created: "In one row is a ship with our White Brothers' ways; in the other a canoe with our ways. Each will travel down the river of life side by side. Neither will attempt to steer the other's vessel." This wampum represented three principles: friendship, peace, and the concept of forever
- soon after these treaties were forged, greed and colonial policies began to erode these relationships.
- the treaties and the rights they established with Indigenous peoples became an inconvenience to the expanding European empire, and consequently, they began to be ignored, as they continue to be today
- the Doctrine of Discovery was the piece of colonial law that let European explorers 'discover' lands previously occupied for thousands of years. This doctrine arose from a series of statements from the Pope, which morally and legally justified the dispossession of lands from their Indigenous inhabitants (Terra Nullius)
- this justification is based erroneously on the supposed 'inferiority' of Indigenous peoples to their 'superior' European counterparts. This allowed monarchs to exploit North American land and resources regardless of its original caretakers and use the power of this doctrine to extinguish Indigenous rights. This doctrine continues to have devastating impacts on Indigenous peoples in Canada

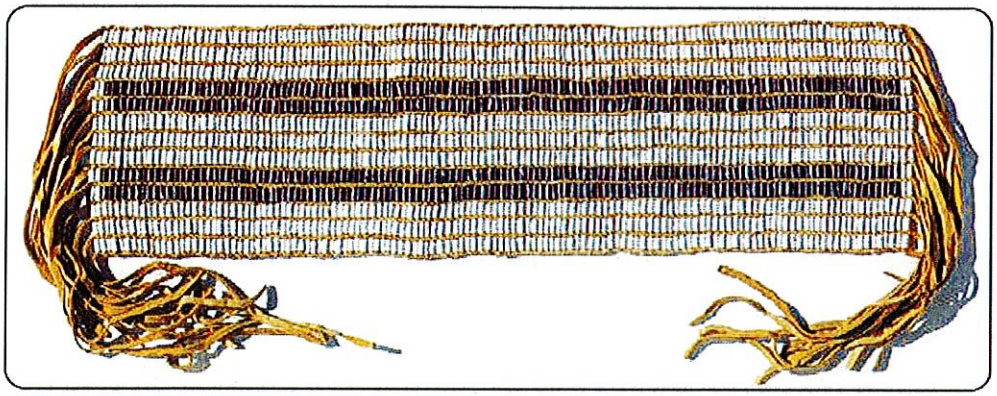


Figure 3. Image of a two row wampum belt. It represents friendship, peace, and the concept of forever
Bonaparte D. The Two Row Wampum Belt: An Akwesasne Tradition of the Vessel and Canoe [Internet]. [place unknown]: The People's Voice. 2005 Aug 5 [cited 2020 Apr 16]. Available from: http://www.wampumchronicles.com/tworowwampumbelt.html

- in 1763, King George III issued the *Royal Proclamation* that delineated the process of British settlement of Indigenous lands. This proclamation gave ownership of North America to King George III; however, it stated that Indigenous title existed and would continue to exist. Therefore, any land would belong to the Indigenous people unless otherwise noted and agreed upon in a treaty. This prevented European settlers from taking possession of land that was occupied by Indigenous peoples, unless already purchased by the Crown
- this document unequivocally recognizes Indigenous rights, title, and self-determination. To this day, no law has overruled the Royal Proclamation; therefore, it is still valid according to Canadian law. Additionally, the notion of Indigenous rights is protected in section 25 of the Constitution Act. Although Indigenous rights cannot be legally diminished or extinguished, the Canadian government frequently disregards this fact

- in 1764, the year following the *Royal Proclamation*, the *Treaty of Niagara* would lay the foundation for the relationship between the Crown and First Nations and their coexistence on Turtle Island. At this instance, the Silver Covenant Chain of Friendship was affirmed and both Indigenous and British sovereignty were recognized. The Treaty of Niagara established a multinational familial relationship between the Crown and the Indigenous nations
- over 2000 Indigenous dignitaries, representatives of 24 Indigenous nations across Turtle Island, were present, and the 24-nation wampum belt was created. This wampum represents the relationship between the Indigenous nations and the Crown

- the *British North America (BNA) Act* of 1867 (later renamed the *Constitution Act*, 1982) gave the Canadian government control over "Indians" (notably excluding Inuit and Métis peoples). This act included New Brunswick, Nova Scotia, Ontario, and Québec as a new self-governing federation. This laid the foundation for Canada's laws and governance and the rights of those living in the territory now defined as Canada. The BNA Act stated that the federal government had jurisdiction over "Indians and lands reserved for Indians." Indigenous peoples were not involved in conversations or proceedings associated with the passing of this act

- in 1857, *An Act for the Gradual Civilization of the Indian Tribes in Canada* passed and later absorbed under the larger umbrella of the *Indian Act*
- "it is desirable to encourage the progress of Civilization among the Indian Tribes in this Province, and the gradual removal of all legal distinctions between them and Her Majesty's other Canadian Subjects, and to facilitate the acquisition of property and of the rights accompanying it, by such Individual Members of the said Tribes as shall be found to desire such encouragement and to have deserved it"

- this act encouraged the voluntary enfranchisement of Indigenous people. Enfranchisement is the legal process of exterminating one's "Indian" status and ancestral rights in order to gain Canadian citizenship. Later, involuntary enfranchisement would be enforced. This would extinguish the status of any Indigenous person who served in the armed forces, received a university degree, or became a professional (e.g. lawyer, engineer, physician)

- this act depicts the deliberate intentions of Canadian parliament to erase Indigenous culture and diversity from Canada. Other assimilatory programs such as residential schools, the Sixties Scoop, and Indian hospitals have been implemented over various time periods since Confederation. These policies have created irreparable harm, and much of the poverty and current physical and mental health crises facing Indigenous communities today can be traced back to these colonial injustices, as well as ongoing colonialist policies
- a strong understanding of these historical factors can equip physicians to provide better care and cultivate a more empathetic physician-patient relationship

- the *Indian Act* (1876) allows the Canadian government to obtain complete control over First Nations, status, and reserves. It precluded equal political and economic participation and actually made cultural and spiritual practices illegal

- the *Indian Act* still exists today but has morphed significantly since its establishment. This act has taken total political control, imposed foreign governmental structures (band councils), and eliminated the rights of Indigenous peoples to practice their sacred cultural and spiritual beliefs. Indian agents were government workers who enforced these laws and were given the power to prevent Indigenous peoples from leaving their communities. In 1887, Sir John A. MacDonald stated, "The great aim of our legislation has been to do away with the tribal system and assimilate the Indian people in all respects with other inhabitants of the Dominion as speedily as they are fit to change"

- in terms of health, the *Indian Act* gives the Governor in Council control over the decisions made surrounding regulations of public health and treatment. However, this act does not present any obligation of the Canadian government to provide health services for Indigenous peoples

- Section 141 of the *Indian Act* prevented Indigenous peoples from gathering and discussing their rights or hiring legal representation to fight against this oppression

- Judge Alfred Scow describes the impact that this has had on his peoples: "This provision of the Indian Act was in place for close to 75 years and what that did was it prevented the passing down of our oral history. It prevented the passing down of our values. It meant an interruption of the respected forms of government that we used to have, and we did have forms of government be they oral and not in writing before any of the Europeans came to this country. We had a system that worked for us. We respected each other. We had ways of dealing with disputes"

- in 1951, some amendments were made to the *Indian Act*. The more oppressive sections were amended or erased, such as the outlawing of sacred practices, the inability to leave reserve without permission of an Indian agent, the inability to hire legal counsel, and the inability of Indigenous women to vote in Band Council elections
- the *Indian Act* continued to oppress Indigenous women uniquely by taking away their status if they married a non-Indigenous man. This means that a woman would have to leave her family and community, and consequently lose her treaty and health benefits, including her right to be buried on reserve with her ancestors. The opposite held true for Indigenous men, as it allowed for non-Indigenous women to gain Indian status through marriage

- in the 1970s-80s, Indigenous women began lobbying for equal rights and *Bill C-31* was passed that nullified this law, allowing many women to regain status. However, this law continues to pose significant controversy as this status is only allowed to be passed down to one generation

- Indian status is defined under section 6 of the *Indian Act* and denotes who qualifies and therefore becomes a ward of the government. This is a paternalistic legal relationship that creates two categories of First Nations status
  - 6(1): this person can pass on their status to their children regardless of their partner's heritage
  - 6(2): this person can only pass on their status if their partner is also Indigenous

- this idea of status complicates the identities of many Indigenous peoples (including non-status First Nations, Métis, and Inuit peoples who do not fall under the *Indian Act*) who are prevented from registering and therefore lose government support, their treaty, and health benefits. They also lose their ability to:
  - participate in community politics
  - partake in land claims
  - connect to their ancestral lands

- this displacement and the misconception that non-status peoples are "less Indian" is extremely harmful and often serves as a platform for lateral violence. In this context, lateral violence refers to when a member of an oppressed group behaves in a malicious or violent manner towards another member of that same oppressed group or in a lower position of power. Lateral violence can be traced back to the impact of colonialism

- Indigenous individuals are generally subject to full taxation, though individuals with status are eligible for select tax exemptions through section 87 of the *Indian Act*. It is a pervasive and harmful myth that Indigenous individuals do not pay taxes. For the most part, exemptions only apply to financial matters located on-reserve, with complex and specific criteria to be met. Matters located off-reserve are generally taxed in full. A summary of this is available in Bob Joseph's "Dispelling Common Myths about Indigenous Peoples" https://www.ictinc.ca/hubfs/ebooks/ebooks%202019/Common%20Myths%20eBook%20July%202019.pdf

- the *Indian Act* is a controversial piece of legislature because it undermines the nationhood and sovereignty of Indigenous peoples. However, it is important to understand the Indian Act because it also provides the basis for the historical and constitutional relationship between Indigenous peoples and the Canadian government. Therefore, it cannot be easily removed without having significant ramifications

Movement Towards Reconciliation

- in 1991, the Royal Commission on Aboriginal Peoples (RCAP) was formed to address the inequities that exist, and to work to repair the relationship between Indigenous peoples and Canada. This commission was brought about after the Oka Crisis. The Oka crisis (The Mohawk Resistance) arose from a long-standing history of rejection and ignoring of Indigenous land rights by the Canadian government, and resulted in a 78-day protest of a proposed golf course expansion onto sacred Mohawk territory. The RCAP report (1996) detailed extensive research and recommendations needed to heal and restructure the relationship between Indigenous and non-Indigenous peoples. The majority of these recommendations have not been implemented and there continues to be little government interest in the constitutional issues that affect Indigenous peoples and communities

- in 2008, the Prime Minister of Canada apologized to all those who were affected by the residential school system, where Indigenous children were forced into abusive schools (see Public Health and Preventive Medicine, *Colonization and Healthcare*, PH7). The Truth and Reconciliation Commission was born out of a settlement agreement between the government and residential school survivors. The mission of this commission is to learn and tell the stories of those who attended these schools. This commission hopes to bring about renewed relationships and healing based on mutual understanding and respect. To achieve this goal, the commission put out 94 Calls to Action aiming to bring us closer to reconciliation. These calls urge all levels of the Government of Canada to work together to address systemic inequities by changing policies and programs that continue to oppress Indigenous peoples. Under the category of health, the following recommendations are quoted below:
  - we call upon the federal, provincial, territorial, and Aboriginal governments to acknowledge that the current state of Aboriginal health in Canada is a direct result of previous Canadian government policies, including residential schools, and to recognize and implement the healthcare rights of Aboriginal people as identified in international law, constitutional law, and under the Treaties
  - we call upon the federal government, in consultation with Aboriginal peoples, to establish measurable goals to identify and close the gaps in health outcomes between Aboriginal and non-Aboriginal communities, and to publish annual progress reports and assess long-term trends. Such efforts would focus on indicators such as: infant mortality, maternal health, suicide, mental health, addictions, life expectancy, birth rates, infant and child health issues, chronic diseases, illness and injury incidence, and the availability of appropriate health services
  - in order to address the jurisdictional disputes concerning Aboriginal people who do not reside on reserves, we call upon the federal government to recognize, respect, and address the distinct health needs of the Métis, Inuit, and off-reserve Aboriginal peoples
  - we call upon the federal government to provide sustainable funding for existing and new Aboriginal healing centres to address the physical, mental, emotional, and spiritual harms caused by residential schools, and to ensure that the funding of healing centres in Nunavut and the Northwest Territories is a priority
  - we call upon those who can effect change within the Canadian healthcare system to recognize the value of Aboriginal healing practices and use them in the treatment of Aboriginal patients in collaboration with Aboriginal healers and Elders requested by Aboriginal patients
  - we call upon all levels of government to:
    i. increase the number of Aboriginal professionals working in the healthcare field
    ii. ensure the retention of Aboriginal healthcare providers in Aboriginal communities
    iii. provide cultural competency training for all healthcare professionals
  - we call upon medical and nursing schools in Canada to require all students to take a course dealing with Aboriginal health issues, including the history and legacy of residential schools, the United Nations Declaration on the Rights of Indigenous Peoples, Treaties and Aboriginal rights, and Indigenous teachings and practices. This will require skills-based training in intercultural competency, conflict resolution, human rights, and anti-racism

- going forward as healthcare professionals, we are uniquely responsible for knowing and understanding the impact these historical and legal truths have on our patients. When addressing health inequities that are disproportionately experienced by Indigenous peoples, we need to take into account the impact of 500 years of colonialism. We need to understand how our patients and their ancestors have experienced structural violence and trauma in order to address their physical, mental, emotional, and spiritual health needs. Physicians need to understand that we are all treaty people, and that the above legislation not only applies to Indigenous peoples, but to physicians as well, and all those who benefit from these laws

Indigenous Disproportionate Over-Representation of Biological, Psychological, and Social Co-Morbidities

- physicians may work in various settings in which Indigenous peoples make up a large proportion of the population. Treatment approaches in these settings must consider issues unique to Indigenous peoples, particularly considering that past colonial practices and historical traumas have led to their over-representation in vulnerable groups. Indigenous peoples in Canada have shown great resilience against a long history of colonialism, structural oppression, dispossession, and harmful policies. These historical realities perpetuate current structural barriers that impact the health of Indigenous peoples (see Public Health and Preventive Medicine, *Colonization and Healthcare,* PH7)

- importantly, physicians will encounter Indigenous peoples from a wide variety of personal and historical experiences. Individuals should be invited to share their backgrounds and perspectives if they would like to do so, in an effort to understand the individual's unique context and to endeavour to provide culturally safe care (see *Resources in Indigenous Health, ELOM30*)

Those Receiving Child Welfare Services (The Cycle of Apprehension and the Millennial Scoop)

- similar continuation of the legacies of the residential school systems and the Sixties Scoop, Indigenous families face higher rates of child apprehension currently. In Canada, 52.2% of children (ages 0-14) in foster care are Indigenous, while Indigenous children account for only 7.7% of all Canadian children in this age range (2016)
- 38% of Indigenous children live in poverty compared to 13% of non-Indigenous non-racialized children in Canada (2011)
- in 2016, the Canadian Human Rights Tribunal ruled that the federal government discriminates against First Nations children on reserves by failing to provide the same level of funding for child welfare services that exists for non-Indigenous children, resulting in inequitable services. Despite the ruling recommending compensation, the Tribunal has issued 10 subsequent orders to ensure Canada's compliance. In 2019, the federal government argued the Tribunal was the wrong forum to discuss compensation and suggested there was no evidence of harm to individual children before the Tribunal. The Tribunal rejected both arguments. In September 2019, the Tribunal found that Canada's ongoing discrimination against First Nations children and families was "wilful and reckless" and that it had caused serious pain and suffering for victims of the discrimination. Canada was ordered to pay the maximum amount allowable under the Canadian Human Rights Act to compensate First Nations children, youth, and families who have been harmed by the child welfare system. In October 2019, the federal government launched a court challenge at the Federal Court in an attempt to quash the compensation order, which was subsequently denied
- only once the Tribunal reinforced the initial ruling in December 2019 did the federal government pass an Act respecting First Nations, Inuit, and Métis children, youth, and families, which came into effect in January 2020. This act allows Indigenous communities to exercise jurisdiction in the welfare of their own children over Indigenous Services Canada and provincial or territorial governments. However, the federal government continues to delay compensation and oppose the order for the maximum allowable amount of compensation, despite other federal parties calling on the government to pay

Those in State Custody and the Colonial Legacy Within the Canadian Judicial System

- there is a direct link between family breakdown due to the residential school system, intergenerational trauma and abuse from colonialism, and subsequent higher rates of child apprehension. Interacting with the foster care system and the instability of multiple (sometimes abusive) homes is a predictor of future interaction with the criminal justice system along with poverty and higher unemployment
- 27-30% of adults and 50% of youth taken into custody in 2016-17 were Indigenous, yet Indigenous peoples make up only 4.1% and 8% of Canada's adult and youth populations, respectively
- Indigenous youth are also overrepresented in community supervision
- from 2000 to 2010, the number of incarcerated Indigenous women increased by 86.4%, representing the fastest growing incarcerated population
- Indigenous-based restorative (rather than punitive) justice programs have been proposed to lower recidivism rates for Indigenous offenders

Those with no Fixed Address and the Colonial Legacy of Homelessness

- Toronto's Indigenous population is approximately 2-4x larger than estimates reported by Statistics Canada, as the National Household Survey relies on mailing addresses, and some Indigenous People may be skeptical about providing information to the government given historical and ongoing breaches of trust
- as the statistics significantly underestimate the Indigenous population, resource allocation is severely compromised. More information is available here: http://www.welllivinghouse.com/wp-content/uploads/2022/03/OHC-Toronto-2021-Population-Estimates.pdf
- in Toronto, Indigenous peoples make up roughly 15% of the homeless population, yet only 0.5% of the total population (2010)
- enfranchisement (giving up Indigenous status in order to become a Canadian citizen), on-reserve housing limitations and shortages, dislocation from community and lands in concert with poor government funding and support are important links to Indigenous homelessness today

- attempts to serve the needs of Indigenous people in urban areas include the employment of traditional healers or cultural coordinators in urban health centres as well as the use of traditional medicines (e.g. sage, cedar, sweetgrass, tobacco)

Missing and Murdered Indigenous Women, Girls and Gender Diverse People

- in Canada, Indigenous women and girls are significantly more likely to be murdered or go missing than any other demographic of women
- between 2001 and 2015, homicide rates for Indigenous women were nearly 6 times higher than for non-Indigenous women
- interpersonal violence within Indigenous communities is closely tied to the lasting trauma suffered in the residential school era and has far-reaching health impacts including acute injuries, chronic pain, sexually transmitted infections, unplanned pregnancies, addiction, self-harm, and suicide
- loss of a mother, sister, or daughter also incurs multi-generational trauma on family and family structure in Indigenous communities

Indigenous Health Coverage and Jurisdictions

- policy pertaining to the health of Indigenous peoples is considered to be shared amongst various levels of government, the private sector, and First Nations communities themselves
- this current model relies heavily on state-imposed definitions of Indigenous identity and limits the right to self-determination and self-governance for Indigenous peoples in Canada
- significant historical legislative vagueness, in combination with the multiplicity of authorities involved, creates much variation across provinces and territories, contributing to inequitable distribution of care for Indigenous peoples
- bureaucratic delays in approving and providing care, and jurisdictional debates between authorities over the responsibilities of care, further contribute to a healthcare system which frequently fails to adequately respond to the needs of Indigenous peoples and communities
- the federal government is responsible for the Non-Insured Health Benefits (NIHB) program, which is managed by the First Nations and Inuit Health Branch of Indigenous Services Canada and is based on the Indian Health Policy (1979) and the Health Transfer Policy (1989)
  - the role of the NIHB is to provide eligible First Nations and Inuit individuals with coverage for specific health benefits and services (most predominantly: eye and dental care, pharmacare, transport to and from medical appointments, and mental health counselling). There are very strict criteria to have certain medications and procedures covered
  - the NIHB relies on state-imposed definitions of Indigenous identity; access to the NIHB extends only to individuals who are (1) registered under the Indian Act (and consequently referred to using the paternalistic term "Status Indian"); (2) Inuk, as recognized by the Inuit Land Claim Organization; or (3) a child under 18 months of age whose parent is registered First Nations or recognized Inuk
  - access to care for non-status First Nations and Métis patients is consequently denied under NIHB criteria, despite encountering similar social determinants of health and barriers to healthcare experienced by eligible individuals
  - clients deemed ineligible for NIHB must then rely on provincial or territorial health insurance, social programs, or private insurance plans for healthcare
  - note that NIHB eligibility does not guarantee access to care, as the criteria for approved services is subject to frequent changes and impacted by factors including whether the applicant lives on- or off-reserve
- the Canadian healthcare system must recognize that Indigenous communities are best positioned to identify their own unique health priorities and manage and deliver health care in their communities
  - although there is some development and implementation of Indigenous-led and Indigenous-directed healthcare services in Canada, the effects of colonialist policies and practices continue to perpetuate inequities among Indigenous peoples
  - healthcare providers can work towards dismantling the effects of colonialism in a number of manners, including allyship and advocacy, engaging in cultural safety training, and better educating oneself on Indigenous history, the impact of colonialism, and resources available to meet the unique needs of their patients (see *Resources in Indigenous Health*)
  - British Columbia (BC) has established a First Nations Health Authority as a step in addressing Indigenous self-determination in healthcare

Resources in Indigenous Health

- please consider watching "The Unforgotten," a 36-minute film, which consists of five segments: https://theunforgotten.cma.ca/full-film/
- please consider reviewing this Indigenous Health Guide for Medical Students
  - https://temertymedicine.utoronto.ca/sites/default/files/IndigenousHealthinOntario-compressed.pdf
- the following is a list of fact sheets, reports, and toolkits as well as organizational websites providing resources relating to Indigenous health. All were created by or with Indigenous peoples and organizations unless otherwise stated. These resources share the aim of highlighting Indigenous resilience and promoting strength in Indigenous communities. Though not exhaustive, this list serves as a foundation for the kinds of resources that are available to healthcare providers and/or Indigenous Peoples seeking care. Of note, physicians have a responsibility to become familiar with local or regional services that may be able to provide culturally safe trauma-informed care for Indigenous People

Table 7. Resources in Indigenous Health

	Resource	Ref #
Health Care		
National Collaborating Centre for Indigenous Health (NCCIH)	Extensive database of Indigenous Health research and resources across Canada. Please note that some of these materials may have been collated without Indigenous consultation	1
Canadian Institutes for Health Research (CIHR)	Recommendations in culturally appropriate care for healthcare providers in Canada working with Indigenous peoples, reviewed by the Aboriginal Health Issues Committee	2
Wellesley Institute		
First Peoples, Second Class Treatment: The Role of Racism in the Health and Well-being of Indigenous Peoples in Canada	Report looking in-depth at the relationship between racism, health, and the well-being of Indigenous peoples in Canada	3
First Nations Health Authority (FNAH) (BC)	BC has its own health authority responsible for the planning, delivery, and funding of First Nations Health Programs across the province	4
Indigenous Health Primer produced by the Royal College of Physicians and Surgeons of Canada	An extensive document that discusses anti-racism interventions, trauma-informed care, Indigenous health principles, impact of policies on Indigenous peoples, and the diversity of present Indigenous communities	5
Thunderbird Partnership Foundation	Offers special skills, knowledge, and resources to healthcare workers providing care to First Nations communities. Has particular expertise in providing addiction care	6
Child and Family		
First Nations Child and Family Services (FNCFS)	Interactive map of Canada with all FNCFS service provider locations	7
National Aboriginal Council of Midwives (NACM)	Subset of the larger organization, Canadian Association of Midwives, that provides Indigenous midwives for natal care	8
Indigenous Services Canada	Social programs, such as women's shelters and income assistance in Indigenous communities, funded federally by Indigenous Services Canada	9
Population-Specific		
Inuit Tapiriit Kanatami (ITK)	The national representational body for Inuit people in Canada, with publications on TB elimination strategies and Inuit-specific health literacy resources	10
Patients Facing Additional Layers of Systemic Barriers		
People with no fixed address	Description of Indigenous homelessness from an Indigenous perspective, emphasizing criteria that are not captured in colonial definitions of "homelessness"	11
Indigenous women, girls, and gender diverse people	Multitude of fact sheets published by the Native Women's Association of Canada covering issues such as housing, violence, and health with an intersectional lens	12
	The Final Report of the National Inquiry into Missing and Murdered Indigenous Women and Girls containing testimonies from survivors and Knowledge Keepers, discussion of influencing factors such as intergenerational trauma and insecure housing, as well as 231 calls for justice directed at Canadians and institutions alike	13
Mental health and suicide	The Centre for Suicide Prevention (branch of the Canadian Mental Health Association) offers many Indigenous-specific resources on suicide prevention, life planning, trauma, and cultural sensitivity	14
	Online course called "River of Life," created for people working with Indigenous youth ages 15-24, discusses strategies to strengthen the protective factors of youth at risk of suicide	15
	Trauma-informed Indigenous programs, e.g. Biidaaban Healing Lodge in Ontario and Tsow-Tun Le Lum Society in BC	16, 17
Building Cultural Competency		
University of Alberta's Indigenous Canada online course	Indigenous Canada is a Massive Open Online Course (MOOC) from the Faculty of Native Studies that explores Indigenous histories and contemporary issues in Canada.	18
Cancer Care Ontario, Indigenous Relationship and Cultural Safety Courses	13 courses available to provide knowledge about the history and culture of First Nations, Inuit and Métis people and communities	19

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A Anesthesia

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Acronyms

2,3-BPG	2,3-Bisphosphoglycerate	CVS	cardiovascular system	ITP	immune thrombocytopenic purpura	PCV	pressure-controlled ventilation
ABG	arterial blood gas	CVP	central venous pressure	IV	intravenous	PEEP	positive end-expiratory pressure
ACC	American College of Cardiology	CVD	cardiovascular disease	LA	local anesthetic	PNS	parasympathetic nervous system
ACh	acetylcholine	CXR	chest X-ray	LABA	long-acting β-agonist	PACU	post-anesthetic care unit
AChE	acetylcholinesterase	DIC	disseminated intravascular coagulation	LES	lower esophageal sphincter	PONV	postoperative nausea and vomiting
ACV	assist-control ventilation	DKA	diabetic ketoacidosis	LMA	laryngeal mask airway	PPV	positive pressure ventilation
AFib	atrial fibrillation	DM	diabetes mellitus	LOC	level of consciousness	PVD	peripheral vascular disease
AHA	American Heart Association	$ETCO_2$	end-tidal CO_2	MAC	minimum alveolar concentration	RA	regional anesthesia
ALS	amyotrophic lateral sclerosis	ETT	endotracheal tube	MAP	mean arterial pressure	RSI	rapid sequence induction
aPTT	activated partial thromboplastin time	FiO2	fraction of oxygen in inspired air	MH	malignant hyperthermia	SABA	short-acting β-agonist
ARDS	acute respiratory distress syndrome	FFP	fresh frozen plasma	MS	multiple sclerosis	SCh	succinylcholine
ASA	American Society of Anesthesiologists	FRC	functional residual capacity	MSK	musculoskeletal	SIADH	syndrome of inappropriate antidiuretic hormone
atm	atmosphere	GA	general anesthesia	NDMR	non-depolarizing muscle relaxant	SNS	sympathetic nervous system
BBB	blood brain barrier	GE	gastroesophageal	NMJ	neuromuscular junction	SV	stroke volume
BMV	bag-mask ventilation	GERD	gastroesophageal reflux disease	NPO	nil per os	SVR	systemic vascular resistance
BP	blood pressure	GI	gastrointestinal	NYHA	New York Heart Association	TIA	transient ischemic attack
CCS	Canadian Cardiovascular Society	GU	genitourinary	OCS	oral corticosteroids	TBW	total body water
CHF	congestive heart failure	Hb(i)	initial hemoglobin	OG	orogastric	TIVA	total intravenous anesthetic
CK	creatine kinase	Hb(f)	final hemoglobin	OR	operating room	TURP	transurethral resection of prostate
CNS	central nervous system	Hct	hematocrit	OSA	obstructive sleep apnea	URTI	upper respiratory tract infection
CO	cardiac output	HES	hydroxyethyl starch	PA	pulmonary artery	V/Q	ventilation/perfusion
CPAP	continuous positive airway pressure	HHS	hyperosmolar hyperglycemic state	$PaCO_2$	arterial partial pressure of carbon dioxide	VT	ventricular tachycardia
CSF	cerebrospinal fluid	HR	heart rate	PaO_2	arterial partial pressure of oxygen	VTE	venous thromboembolism
CV	cardiovascular	ICP	intracranial pressure	PC	patient-controlled		
		ICS	inhaled corticosteroids	PCA	patient-controlled analgesia		
		INR	international normalized ratio				
		IOP	intraocular pressure				

Overview of Anesthesia

- anesthesia: lack of sensation/perception

Preoperative	Preoperative/Intraoperative	Postoperative
Preoperative assessment Patient optimization	Plan anesthetic Pre-medication Airway management Monitors Induction Maintenance Emergence Tracheal extubation	Postoperative care

Difficult Mask Ventilation
Anesth Analg 2009;109(6):1870-1880
Purpose: Define and predict difficult mask ventilation.
Conclusions: Age >55, obesity with BMI >26, history of snoring, beard, lack of teeth, Mallampati III/IV (see *Figure 1, A3*), abnormal mandibular protrusion test, and male gender are all independent risk factors that should be used as predictors for difficult mask ventilation.

Preoperative Assessment

Purpose
- identify concerns for medical and surgical management of patient
- allow for questions to help allay any fears or concerns patient and/or family may have
- arrange further investigations, consultations, and treatments for patients not yet optimized
- plan and consent for anesthetic techniques

History and Physical

History
- age and gender
- indication for surgery
- surgical/anesthetic Hx: previous anesthetics, any complications, previous intubations, and PONV
- FMHx: abnormal anesthetic reactions, MH, and pseudocholinesterase deficiency (see *Uncommon Complications, A29*)
- medications and allergies (see *Preoperative Optimization: Medications, A4*)
- PMHx
  - neurologic: seizures, TIA/strokes, raised ICP, spinal disease, aneurysm, and conditions affecting NMJ (e.g. myasthenia gravis)
  - CVS: angina/CAD, MI, CHF, HTN, valvular disease, dysrhythmias, PVD, conditions requiring endocarditis prophylaxis, exercise tolerance, and CCS/NYHA class (see Cardiology and Cardiac Surgery *sidebar for CCS Classification,* C23and *sidebar for New York Heart Association Classification,* C54)
  - respiratory: smoking, asthma, COPD, recent URTI, and OSA
  - GI: GERD, liver disease, and NPO status
  - renal: acute vs. chronic renal insufficiency, dialysis, and chronic kidney disease
  - hematologic: anemia, coagulopathies, and blood dyscrasias

- MSK: arthritis (e.g. rheumatoid arthritis, scleroderma), cervical spine pathology (e.g. cervical tumours, cervical infections/abscesses, trauma to cervical spine, and previous cervical spine surgery), and cervical spine instability (e.g. trisomy 21)
- endocrine: DM, thyroid disorders, and adrenal disorders
- other: morbid obesity, pregnancy, and ethanol/recreational drug use

Physical Exam

- weight, height, BP, HR, respiratory rate, and O_2 saturation
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
- airway assessment is done to determine intubation difficulty (no single test is specific or sensitive) and ventilation difficulty
  - cervical spine stability and neck movement – upper cervical spine extension, lower cervical spine flexion ("sniffing" position – see *Figure 6C, A8*)
  - Mallampati classification (see *Figure 1*)
  - "3-3-2 rule" (see *Figure 2*)
    - 3 of patient's own fingers can be placed between the incisors (incisor distance)
    - 3 fingers along the floor of the mandible between the mentum and hyoid bone (hyoid-mental distance)
    - 2 fingers in the superior laryngeal notch (thyroid-hyoid distance)
  - thyromental distance (distance from the mentum to the thyroid notch in midline with neck extended); <3 finger breadths (<6 cm) is associated with difficult intubation
  - anterior jaw subluxation; <1 finger breadth is associated with difficult intubation
- tongue size
- dentition, dental appliances/prosthetic caps, existing chipped/loose teeth – pose aspiration risk if dislodged and patients should be informed of rare possibility of damage
- nasal passage patency (if planning nasotracheal intubation)
- assess potential for difficult ventilation
- examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, CVP, and PA catheters

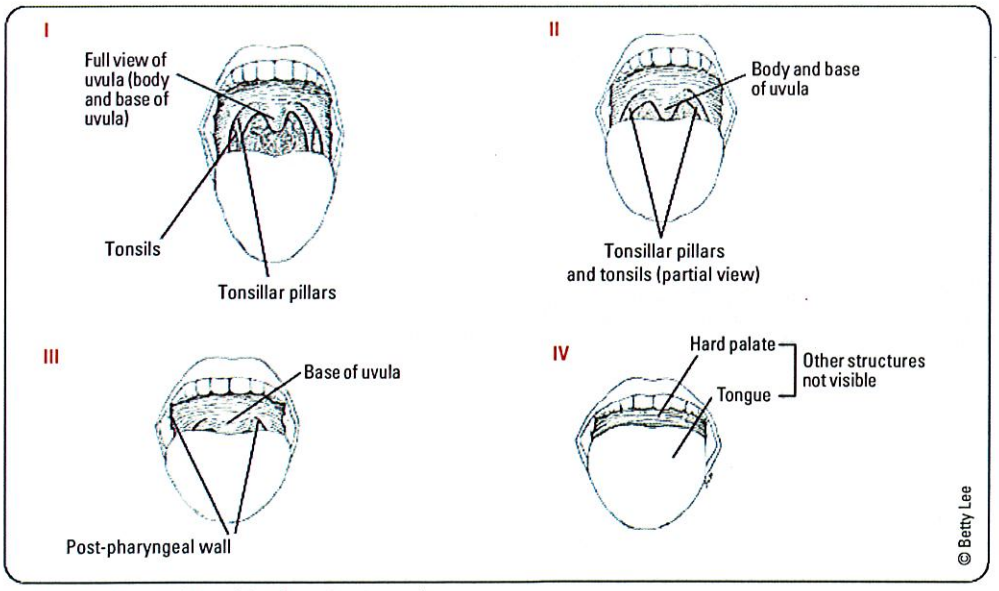


Figure 1. Mallampati classification of oral opening

Evaluation of Difficult Airway

LEMON
Look – obesity, beard, dental/facial abnormalities, neck, facial/neck trauma
Evaluate – 3-3-2 rule
Mallampati score (≥3)
Obstruction – stridor, foreign bodies, masses
Neck mobility

Assessment of Difficult Ventilation
Anesthesiology 2000:92:1229-1236

BONES
Beard
Obesity (BMI >26)
No teeth
Elderly (age >55)
Snoring Hx (OSA)

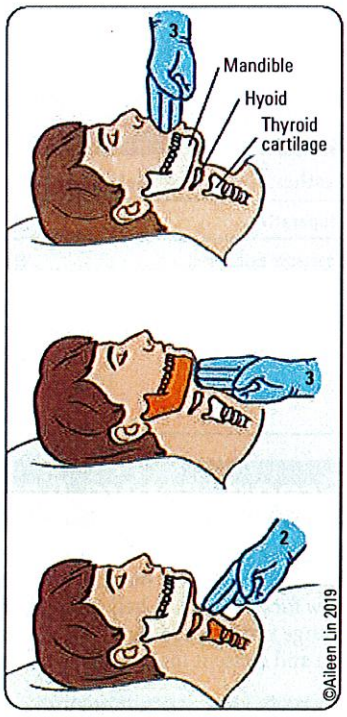


Figure 2. 3-3-2 Rule

Cormack-Lehane Classification of Laryngeal View (*Figure 3, A4*)
Grade 1: all laryngeal structures revealed
Grade 2: posterior laryngeal showing posterior vocal folds and arytenoids
Grade 3: larynx concealed, only epiglottis
Grade 4: neither glottis nor epiglottis

Preoperative Investigations

- routine preoperative investigations are only necessary if there are comorbidities or certain indications

Table 1. Suggested Indications for Specific Investigations in the Preoperative Period

Test	Indications
CBC	Major surgery requiring group and screen or cross and match; chronic CV disease, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient <1 y/o
Sickle Cell Screen	Genetically predisposed patient (hemoglobin electrophoresis if screen is positive)
INR, aPTT	Anticoagulant therapy, bleeding diathesis, liver disease
Electrolytes and Creatinine	HTN, renal disease, DM, pituitary or adrenal disease; vascular disease, digoxin, diuretic, or other drug therapies affecting electrolytes
Fasting Glucose Level	DM (repeat on day of surgery)
Pregnancy (β-hCG)	Women of reproductive age
ECG	Heart disease, DM, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma
CXR	Patients with new or worsening respiratory symptoms/signs

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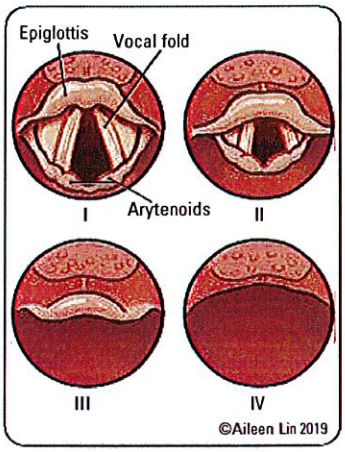


Figure 3. Laryngeal views

American Society of Anesthesiology Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- **ASA 1**: a healthy, fit patient
- **ASA 2**: a patient with mild systemic disease
  - e.g. controlled T2DM, controlled essential HTN, obesity, smoker
- **ASA 3**: a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- **ASA 4**: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure
- **ASA 5**: a moribund patient not expected to survive 24 h without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- **ASA 6**: declared brain dead, a patient whose organs are being removed for donation purposes
- for emergency operations, add the letter E after classification (e.g. ASA 3E)

Preoperative Optimization

- in general, prior to elective surgery:
  - any fluid and/or electrolyte imbalance should be corrected
  - extent of existing comorbidities should be understood and these conditions should be optimized prior to surgery
  - medications may need adjustment

Medications

- pay particular attention to cardiac and respiratory medications, opioids, and drugs with many side effects and interactions
- **preoperative medications to consider as prophylaxis**
  - risk of GE reflux: antacids (e.g. sodium citrate), H_2 antagonists and/or prokinetic agents (e.g. metoclopramide) 0.5-1 h prior to surgery
  - risk of infective endocarditis, GI/GU interventions: antibiotics
  - risk of adrenal suppression: steroid coverage
  - anxiety: consider benzodiazepines
  - COPD, asthma: bronchodilators
  - CAD risk factors: nitroglycerin and β-blockers
- **preoperative medications to stop prior to surgery**
  - oral antihyperglycemics: do not take on the day of surgery
  - angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB): do not take on the day of surgery (controversial – they increase the risk of hypotension post-induction but have not been shown to increase mortality or adverse outcomes; therefore, some people hold and some do not)
  - warfarin (consider bridging with heparin), antiplatelet agents (e.g. clopidogrel), Xa inhibitor, direct thrombin inhibitors
    - discuss perioperative use of ASA and NSAIDs with surgeon (± patient's cardiologist/internist)

Continuation vs. Discontinuation of Antiplatelet Therapy for Bleeding and Ischaemic Events in Adults Undergoing Non-Cardiac Surgery
Cochrane DB Syst Rev 2018; CD012584
Purpose: To compare the effect of continuation vs. discontinuation of antiplatelet therapy on the occurrence of bleeding and ischaemic events in adults undergoing non-cardiac surgery.
Methods: RCTs in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase that compared adults taking single or dual antiplatelet therapy for at least two weeks, including patients with at least one cardiac risk factor. Included general, spinal, and regional anesthesia and excluded minor procedures involving only local anesthetic/sedation.
Results: 5 trials, 666 adult patients. Continuation or discontinuation had no difference on mortality at 30 d postoperative (RR 1.21, 95% CI 0.34-4.27), blood loss (RR 1.37, 95% CI 0.83-2.26), or ischaemic events within 30 d of surgery (RR 0.67, 95% CI 0.25-1.77).
Conclusions: Moderate evidence supporting continuation or discontinuation of antiplatelet therapy makes no difference on bleeding requiring transfusion. Low evidence supporting no difference in mortality or ischaemic events.

See Landmark Anesthesiology Trials table for more information on the POISE-2 trial, which evaluates low-dose aspirin vs. placebo on the rate of death and major cardiovascular events in patients having noncardiac surgery.

- for patients undergoing non-cardiac surgery, starting or continuing low-dose ASA in the perioperative period does not appear to protect against postoperative MI or death, but increases the risk of major bleeding
  note: this does not apply to patients with bare metal stents or drug-eluting coronary stents
- herbal supplements (e.g. ephedra, garlic, ginkgo, ginseng, kava, St. John's Wort, valerian, echinacea – stop one week prior to elective surgery)

- **preoperative medications to adjust**
  - insulin (consider insulin/dextrose infusion or holding dose), prednisone, bronchodilators

Fasting Guidelines

Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists' Society)

- fasting guidelines should change depending on patients' pre-existing medical conditions. In the case of emergent procedures, consider the risk of delaying surgery against the risk of aspiration
- before elective procedures, the minimum duration of fasting should be:
  - 8 h after a large meal of solids particularly containing protein (e.g. meat) or fatty foods
  - 6 h after a light meal (e.g. non-fatty meal such as toast)
  - 6 h after ingestion of infant formula, non-human milk, or expressed breast milk fortified with additions
  - 4 h after ingestion of breast milk
  - 2 h after clear fluid intake (including water, pulp-free juice, complex carbohydrate beverages, and tea or coffee without milk) for adults
  - 2 h after clear fluid intake for infants and children

Hypertension

- sBP >180 mmHg or dBP >110 mmHg is an independent risk factor for perioperative cardiac events, target below these values
- continue antihypertensive medications up to morning of surgery and resume as soon as possible postoperatively
- assess for end-organ damage and treat accordingly

Coronary Artery Disease

- ACC/AHA Guidelines (2014) recommend that at least 60 d should elapse after a MI before non-cardiac surgery in the absence of a coronary intervention
  - this period carries an increased risk of re-infarction/death
  - if operative procedure is essential and cannot be delayed, then invasive intra- and postoperative ICU monitoring is required to reduce the above risk
- mortality with perioperative MI is 20-50%
- perioperative β-blockers
  - may decrease cardiac events and mortality (but increases risk of perioperative strokes)
  - continue β-blocker if patient is routinely taking it prior to surgery
  - consider initiation of β-blocker in:
    - patients with CAD or indication for β-blocker
    - intermediate or high-risk surgery, especially vascular surgery

Respiratory Diseases

- smoking
  - adverse effects: altered mucus secretion and clearance, decreased small airway calibre, altered O_2 carrying capacity, increased airway reactivity, and altered immune response
  - abstain at least 4-8 wk preoperatively if possible
  - if unable, abstaining even 24 h preoperatively has been shown to increase O_2 availability to tissues
- asthma
  - preoperative management depends on degree of baseline asthma control
  - increased risk of bronchospasm from intubation
  - administration of short course (up to 1 wk) preoperative corticosteroids and inhaled β2-agonists decreases the risk of bronchospasm and does not increase the risk of infection or delay wound healing
  - avoid non-selective β-blockers due to risk of bronchospasm (cardioselective β-blockers (metoprolol, atenolol) do not increase risk in the short-term)
  - delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
  - ideally, delay elective surgery by a minimum of 6 wk if patient develops URTI
- COPD
  - anesthesia, surgery (especially abdominal surgery and upper abdominal surgery, in particular) and pain predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation, and respiratory failure

Perioperative β-blockers for Preventing Surgery-Related Mortality and Morbidity in Adults undergoing Cardiac Surgery
Cochrane DB Syst Rev 2019;9:CD013435
Purpose: To assess the effectiveness of preoperatively-administered β-blockers for the prevention of surgery-related mortality and morbidity in adults undergoing cardiac surgery.
Conclusions: No evidence of a difference in early all-cause mortality, MI, cerebrovascular events, hypotension, and bradycardia. However, there may be a reduction in AFib and ventricular arrhythmias when β-blockers are used. A larger sample size is likely to increase the certainty of this evidence.

Perioperative β-blockers for Preventing Surgery-Related Mortality and Morbidity in Adults undergoing Non-Cardiac Surgery
Cochrane DB Syst Rev 2019;9:CD013438
Purpose: Assess effectiveness of preoperatively-administered β-blockers in prevention of surgery-related morbidity and mortality after non-cardiac surgery.
Conclusions: No difference in cerebrovascular events or ventricular arrhythmias. β-blockers may reduce AFib and MI. However, β-blockers may increase bradycardia and probably increase hypotension. Overall low quality and certainty evidence for these findings.

β-blockers

β1-receptors are located primarily in the heart and kidneys

β2-receptors are located in the smooth muscle (i.e. bronchi, uterus)

Non-selective β-blockers block β1 and β2-receptors (labetalol*, carvedilol**, nadolol). Caution is required with non-selective β-blockers, particularly in patients with respiratory conditions where β2 blockade can result in airway reactivity

*labetalol is both an α- and β-blocker
**carvedilol is also both an α- and β-blocker

- preoperative ABG is needed for all COPD stage II and III patients to assess baseline respiratory acidosis and plan postoperative management of hypercapnia
- cancel/delay elective surgery for acute exacerbation

Aspiration

- increased risk of aspiration with:
  - decreased LOC (drugs/alcohol, head injury, CNS pathology, trauma/shock)
  - delayed gastric emptying (non-fasted within 8 h, diabetes, narcotics)
  - decreased sphincter competence (GERD, hiatus hernia, nasogastric tube, pregnancy, obesity)
  - increased intra-abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
  - unprotected airway (LMA and any other supraglottic airway)
- management
  - manage risk factors if possible
  - utilize protected airway (i.e. ETT)
  - reduce gastric volume and acidity
  - delay inhibiting airway reflexes with muscular relaxants
  - employ RSI (see *Rapid Sequence Induction, A16*)

Hematological Disorders

- history of congenital or acquired conditions (sickle cell anemia, factor VIII deficiency, ITP, liver disease)
- evaluate hemoglobin, hematocrit, and coagulation profiles when indicated (see *Table 1, A4*)
- anemia
  - preoperative treatments to increase hemoglobin (PO or IV iron supplementation, erythropoietin, or pre-admission blood collection in certain populations)
- coagulopathies
  - discontinue or modify anticoagulation therapies (warfarin, clopidogrel, ASA, apixaban, dabigatran) in advance of elective surgeries
  - administration of reversal agents if necessary: vitamin K, FFP, prothrombin complex concentrate, recombinant activated factor VII

Endocrine Disorders

- DM
  - clarify type 1 vs. type 2
  - clarify treatment – oral anti-hyperglycemics and/or insulin
  - assess glucose control with history and HbA1c; patients with well-controlled diabetes have more stable glucose levels intraoperatively
  - end organ damage: be aware of damage to cardiovascular and renal, and central, peripheral, and autonomic nervous systems
  - preoperative guidelines for DM:
    - verify target blood glucose concentration with frequent glucose monitoring: <10 mmol/L in critical patients, <7.8 mmol/L in stable patients
    - use insulin therapy to maintain glycemic goals
    - hold biguanides, α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, and GLP-1 agonists on the morning of surgery
    - consider cancelling non-emergency procedures if patient presents with metabolic abnormalities (e.g. DKA, HHS, etc.) or glucose reading above 22.2-27.7 mmol/L
      - formulate intraoperative glucose management plan based on type (1 vs. 2), glucose control, and extent of end organ damage
- hyperthyroidism
  - can experience sudden release of thyroid hormone (i.e. thyroid storm) if not treated or well-controlled preoperatively
  - treatment: β-blockers and preoperative prophylaxis
- adrenocortical insufficiency (e.g. Addison's, exogenous steroid use)
  - consider intraoperative steroid supplementation

Obesity and Obstructive Sleep Apnea

- assess for comorbid conditions and administer testing to characterize the severity, if needed
- severity of OSA may be determined from sleep studies and prescribed pressure settings of home CPAP device



Implementation of a Comprehensive Patient Blood Management Program for Hospitalized Patients at a Large United States Medical Center
Mayo Clin Proc. 2021;96(12):2980
Purpose: To assess changes to utilization of inpatient transfusion and the associated outcomes with implementation of a Patient Blood Management Program.
Methods: An observational study was conducted between 2010 and 2017 at a major US academic centre. Transfusion usage and clinical outcomes were assessed.
Results: 400998 admissions were assessed. Overall usage of inpatient transfusion decreased from 607 to 405 per 1000 admissions. Also, length of stay in hospital and in-hospital adverse events decreased.
Conclusion: This study exhibits that hospital-wide patient blood management protocols result in an overall decrease in transfusion usage and improved clinical outcomes.



Interventions for Preoperative Smoking Cessation
Cochrane DB Syst Rev 2014;3:CD002294
Purpose: Assess the effect of preoperative smoking intervention on smoking cessation at the time of surgery and 12 mo postoperatively, and on the incidence of postoperative complications.
Methods: Systematic review including RCTs that recruited people who smoked prior to surgery, offered a smoking cessation intervention, and measured preoperative and long-term abstinence from smoking or the incidence of postoperative complications or both.
Results: Thirteen trials enrolling 2010 participants included. Overall quality of evidence was moderate. Compared studies involving intensive intervention, which included multi-session face to face counselling or computer-based scheduled interventions, vs. brief interventions. These were pooled separately. An effect on cessation at the time of surgery was apparent in both subgroups, but the effect was larger for intensive intervention. For long term cessation, only the intensive intervention showed effect. In those that had intensive intervention there was significant effect in preventing any postoperative complications.
Conclusion: There is evidence that preoperative smoking interventions providing behavioural support and offering NRT increase short-term smoking cessation and may reduce postoperative morbidity. Interventions that begin 4 to 8 wk before surgery, include weekly counselling, and use NRT are more likely to have an impact on complications and long-term smoking cessation.



Preoperative Anemia and Postoperative Outcomes in Non-Cardiac Surgery: A Retrospective Cohort Study
Lancet 2011;378:1396-1407
Purpose: Assess effect of preoperative anemia on 30 d postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.
Methods: Patients undergoing major non-cardiac surgery in 2008 from the American College of Surgeons' National Surgical Quality Improvement Program database.
Results: 227425 adult patients. Postoperative mortality at 30 d was higher in patients with anemia than those without (OR 1.42, 95% CI 1.31-1.54).
Conclusion: Preoperative anemia, even to a mild degree, is independently associated with an increased risk of 30 d morbidity and mortality.

Monitoring

Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: "the only indispensable monitor"
- a completed preanesthetic checklist: including ASA class, NPO policy, and Hx and investigations
- a perioperative anesthetic record: HR and BP every 5 min, O_2 saturation, $ETCO_2$, dose and route of drugs and fluids
- continuous monitoring: see *Routine Monitors for All Cases*

Routine Monitors for All Cases

- pulse oximeter, BP monitor, ECG, capnography (required for GA and deep procedural sedation, Ramsay Sedation Scale 4-6), and an agent-specific anesthetic gas monitor when inhalational anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometry, and manometer to measure ETT cuff pressure

Elements to Monitor

- anesthetic depth
  - end-tidal inhaled anesthetic monitoring and EEG monitoring, such as a Bispectral Index monitor, can be used as assessments of anesthetic depth
  - inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing, or sweating. However, these findings are non-specific
  - excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, FiO_2
- ventilation: verify correct position of ETT, chest excursions, breath sounds, $ETCO_2$ analysis, end-tidal inhaled anesthesia analysis
- circulation: HR, rhythm, BP, telemetry, oximetry, pulmonary capillary wedge pressure
- temperature
- hourly urine output

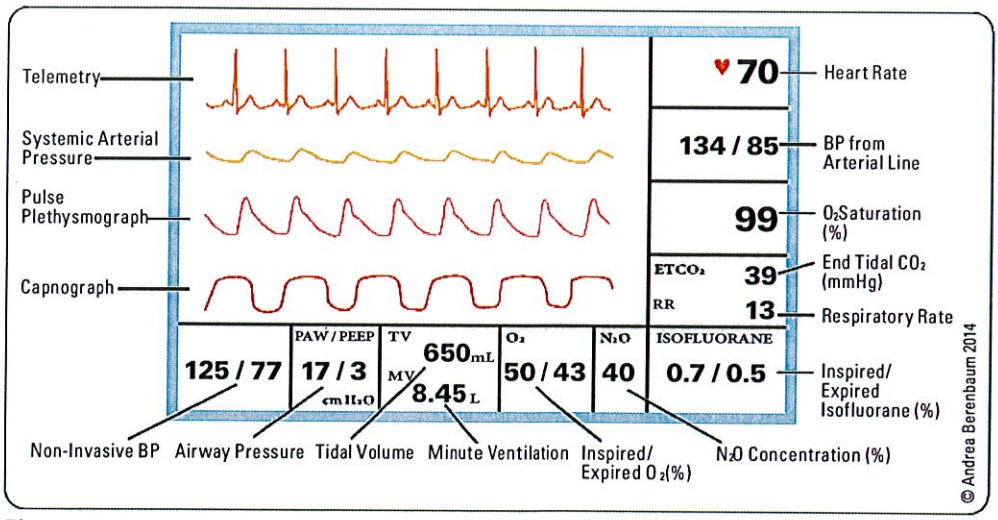


Figure 4. Typical anesthesia monitor

Airway Management

Airway Anatomy

- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- glottic opening: triangular space formed between the true vocal cords; narrowest segment of the laryngeal opening in adults
  - space through which one visualizes proper placement of the ETT
- trachea begins at the level of the thyroid cartilage, C6, and bifurcates into the right and left main bronchi at T4-T5 (approximately the sternal angle)

Pre-Anesthetic Checklist

MS MAIDS
Machine: connected, pressures okay, all metres functioning, vaporizers full
Suction: connected and working
Monitor: all monitors appropriate for the case
Airway: laryngoscope and blades, ETT, syringe, stylet, oral and nasal airways, tape, bag, and mask
IV: second IV set-up and ready if needed
Drugs: case-specific drugs ready and emergency medications in correct location and accessible
Special equipment: OG tube, CVP monitor, shoulder roll, etc.

Screening for OSA
Br J Anaesth 2012;108:768–775

STOP-BANG
Snoring – loud
Tiredness – day-time
Observed apnea – during sleep
Pressure – HTN
Body mass index – >35
Age – >50 y/o
Neck – large neck circumference (>40 cm)
Gender – male

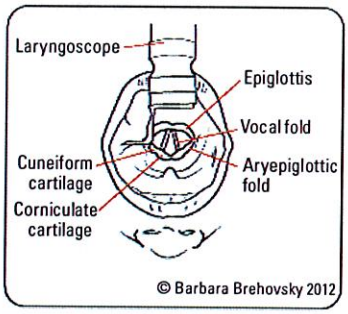


Figure 5. Landmarks for intubation

See Landmark Anesthesiology Trials table for more information on the BAG-RECALL trial, which compares the EEG-derived BIS and end-tidal anesthetic-agent concentration (ETAC) for the prevention of unintended intraoperative awareness in patients at high risk for awareness during surgery.

Will This Patient Be Difficult to Intubate?
JAMA 2019;321:493-503
Purpose: To identify risk factors and physical findings that predict difficult intubation.
Methods: Systematic review of high quality studies (n=62) that evaluate the accuracy of clinical findings for identifying difficult intubation.
Results: Difficult intubation was best predicted by an upper lip bite test (LR 14, 95% CI 9.9 to 22), hyomental distance range <3-5.5 cm (LR 9.4, 95% CI 4.1-10), and a Mallampati score ≥3 (LR 4.1, 95% CI 3.0-5.6). The strongest risk factor for difficult intubation is prior history of difficult intubation.
Conclusion: Although clinical findings are useful for predicting difficult intubation, no clinical finding reliably exclude a difficult intubation.

Methods of Supporting Airways

1. non-definitive airway (patent airway)
   - jaw thrust/chin lift
   - oropharyngeal and nasopharyngeal airway
   - bag mask ventilation
   - LMA
2. definitive airway (patent and protected airway)
   - ETT (oral or nasal)
   - surgical airway (cricothyrotomy or tracheostomy)

Table 2. Methods of Supporting the Airway

	Bag and Mask	LMA	ETT
Advantages/ Indications	Basic Non-invasive Readily available	Easy to insert Less airway trauma/irritation than ETT Frees up hands (vs. face mask) Primarily used in spontaneously ventilating patient	Indications for intubation (5 Ps) Patent airway Protects against aspiration Positive pressure ventilation Pulmonary toilet (suction) Pharmacologic administration during hemodynamic instability
Disadvantages/ Contraindications	Risk of aspiration if decreased LOC Cannot ensure airway patency Inability to deliver precise tidal volume Operator fatigue	Risk of gastric aspiration PPV<20 cm H_2O needed Oropharyngeal/retropharyngeal pathology or foreign body Does not protect against laryngospasm or gastric aspiration	Insertion can be difficult Muscle relaxant usually needed Most invasive – see *Complications During Laryngoscopy and Intubation, A9* Supraglottic/glottic pathology that would preclude successful intubation
Other	Facilitate airway patency with jaw thrust and chin lift Can use oropharyngeal/ nasopharyngeal airway	Sizing by body weight (approx.): 40-50 kg: 3 50-70 kg: 4 70-100 kg: 5	Auscultate to avoid endobronchial intubation Sizing (approx.): Male: 8.0-9.0 mm Female: 7.0-8.0 mm Pediatric Uncuffed (age >2 y/o): (age/4) + 4 mm

Tracheal Intubation

Preparing for Intubation

- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare, and assess for potential difficulties (see *Preoperative Assessment, A2*)
- ensure equipment is available and working (test ETT cuff, check laryngoscope light and suction, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O_2 for 3-5 min or for 4-8 vital capacity breaths
- may need to suction mouth and pharynx first

Proper Positioning for Intubation

- align the three axes (mouth, pharynx, and larynx) to allow visualization from oral cavity to glottis
- "sniffing position": flexion of lower C-spine (C5-C6), bow head forward, and extension of upper C-spine at atlanto-occipital joint (C1), nose in the air (see *Figure 6C*)
  - contraindicated in known/suspected C-spine fracture/instability
  - poor/no view of glottic opening can be remediated by anterior laryngeal pressure
- laryngoscope tip placed in the epiglottic vallecula in order to visualize vocal cords

Equipment for Intubation

MDSOLES
Monitors
Drugs
Suction
Oxygen source and self-inflating bag with oropharyngeal and nasopharyngeal airways
Laryngoscope
ETT (appropriate size and one size smaller)
Stylet, Syringe for tube cuff inflation

Medications that can be given through the ETT

NAVEL
Naloxone
Atropine
Ventolin
Epinephrine
Lidocaine

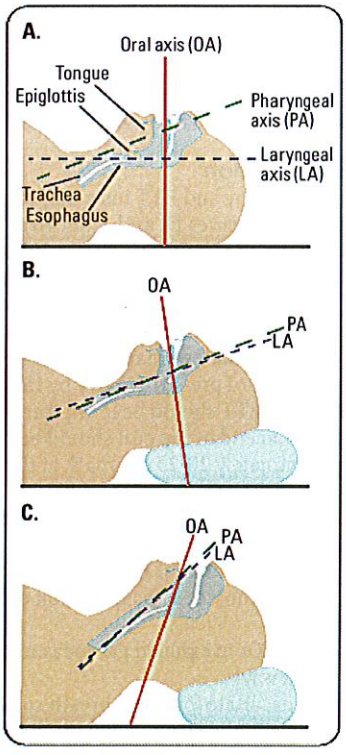


Figure 6. Anatomic considerations in laryngoscopy
A. Neutral position
B. C-spine flexion
C. C-spine flexion with atlanto-occipital extension

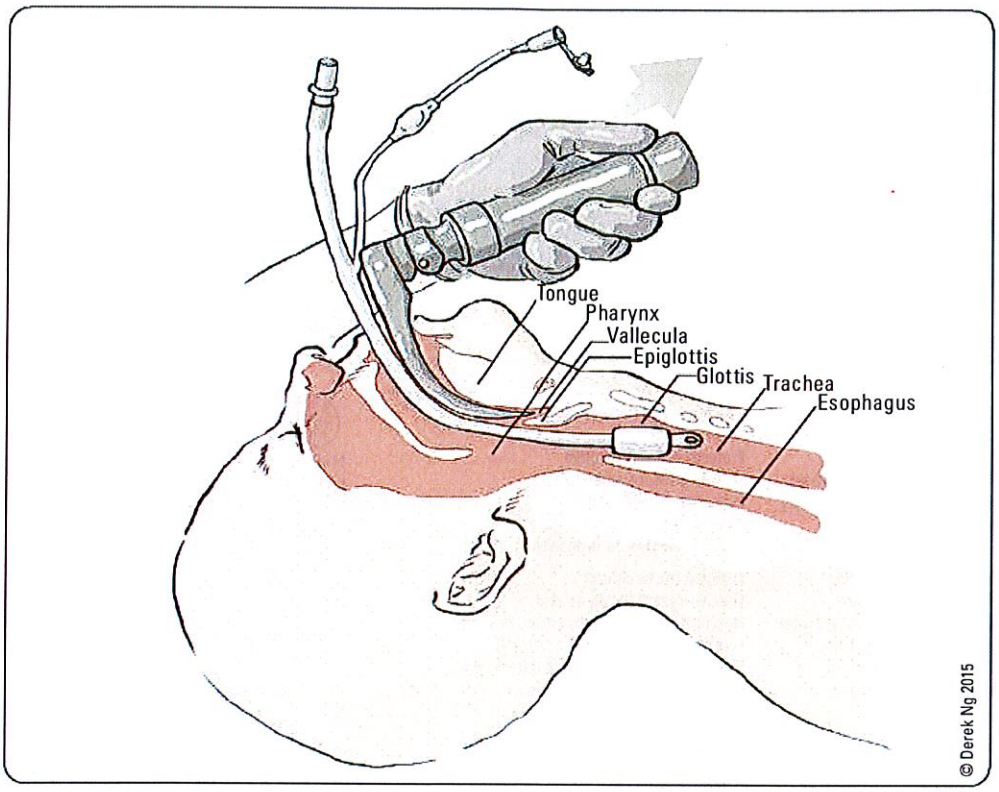


Figure 7. Sagittal view of airway with laryngoscope in vallecula

Tube Insertion

- laryngoscopy and ETT insertion can incite a significant sympathetic response via stimulation of cranial nerves IX and X due to a "foreign body reflex" in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP, and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
  - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  - if too shallow, may lead to accidental extubation, vocal cord trauma, or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina, and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
- approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

Confirmation of Tracheal Placement of Endotracheal Tube

- direct
  - visualization of ETT passing through cords
  - bronchoscopic visualization of ETT in trachea
- indirect
  - $ETCO_2$ in exhaled gas measured by capnography (gold standard for confirming the ETT is in the airway)
  - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  - bilateral chest movement, condensation of water vapour in ETT visible during exhalation, and no abdominal distention
  - refilling of reservoir bag during exhalation
  - CXR (rarely done): only confirms the position of the tip of ETT, not its location in the trachea vs. esophagus, but can confirm endobronchial intubation
- esophageal intubation suspected when:
  - $ETCO_2$ zero or near zero on capnograph
  - abnormal sounds during assisted ventilation
  - impairment of chest excursion
  - hypoxia/cyanosis
  - presence of gastric contents in ETT
  - breath sounds heard when auscultating over epigastrium/left upper quadrant
  - distention of stomach/epigastrium with ventilation

Complications During Laryngoscopy and Intubation

- dental damage
- laceration (lips, gums, tongue, pharynx, vallecula, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation

Differential Diagnosis of Poor Bilateral Breath Sounds after Intubation

DOPE
Displaced ETT
Obstruction
Pneumothorax
Esophageal intubation

ALGrawany

- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see *Extubation, A20, for definition*)
- bronchospasm
- accidental extubation

Difficult Airway

- difficulties with bag-mask ventilation, supraglottic airway, laryngoscopy, passage of ETT through the cords, infraglottic airway, or surgical airway
- algorithms exist for difficult airways (Can J Anesth 2013;60:1119-1138), see *Appendices, A30*
- preoperative assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider:
  - awake intubation
  - intubating with bronchoscope, fiberoptic laryngoscope, video laryngoscope, etc.
- if intubation unsuccessful after induction:
  1. CALL FOR HELP
  2. ventilate with 100% O_2 via bag and mask
  3. consider returning to spontaneous ventilation and/or waking patient
- if bag and mask ventilation inadequate:
  1. CALL FOR HELP
  2. attempt ventilation with oral airway
  3. consider/attempt LMA
  4. emergency invasive airway access (e.g. surgical or percutaneous airway, jet ventilation, and retrograde intubation)

If you encounter difficulty with tracheal intubation, oxygenation is more important than intubation

Oxygen Therapy

- in general, the goal of O_2 therapy is to maintain arterial O_2 saturation (SaO_2) >90%
- small decrease in saturation below SaO_2 of 90% corresponds to a large drop in PaO_2
- in intubated patients, O_2 is delivered via the ETT
- in patients not intubated, there are many O_2 delivery systems available; the choice depends on O_2 requirements (FiO_2) and the degree to which precise control of delivery is needed

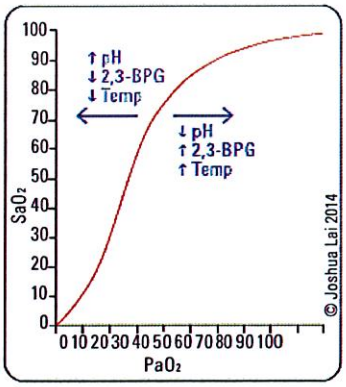


Figure 8. HbO_2 saturation curve

Low Flow Systems

- provide O_2 at flows between 0-10 L/min
- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25 breaths/min, consistent ventilation pattern
- dilution of O_2 with room air results in a decrease in FiO_2
- an increase in minute ventilation (tidal volume x RR) results in a decrease in FiO_2
- e.g. nasal cannula (prongs)
  - well tolerated if flow rates <5-6 L/min; drying of nasal mucosa at higher flows
  - nasopharynx acts as an anatomic reservoir that collects O_2
  - delivered O_2 concentration (FiO_2) can be estimated by adding 4% for every additional litre of O_2 delivered
  - provides FiO_2 of 24-44% at O_2 flow rates of 1-6 L/min

Composition of Air
78.1% nitrogen
20.9% oxygen
0.9% argon
0.04% carbon dioxide

Reservoir Systems

- use a volume reservoir to accumulate O_2 during exhalation, thus increasing the amount of O_2 available for the next breath
- simple face mask
  - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O_2 tubing at a rate of at least 6 L/min to ensure that exhaled CO_2 is flushed through the exhalation ports and not rebreathed
  - provides FiO_2 of 55% at O_2 flow rates of 10 L/min
- non-rebreather mask
  - a reservoir bag and a series of one-way valves prevent expired gases from re-entering the bag
  - during the exhalation phase, the bag accumulates with O_2
  - provides FiO_2 of 80% at O_2 flow rates of 10-15 L/min

High Flow Systems

- generate flows of up to 50-60 L/min
- meet/exceed patient's inspiratory flow requirement
- deliver consistent and predictable concentration of O_2
- Venturi mask
  - delivers specific FiO_2 by varying the size of air entrapment
  - O_2 concentration determined by mask's port and NOT the wall flow rate
  - enables control of gas humidity
  - FiO_2 ranges from 24-50%

Ventilation

- ventilation is maintained with PPV in patients given muscle relaxants
- assisted or controlled ventilation can also be used to assist spontaneous respirations in patients not given muscle relaxants as an artificial means of supporting ventilation and oxygenation

Mechanical Ventilation

- indications for mechanical ventilation
  - apnea
  - hypoventilation/acute respiratory acidosis
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)
  - deliver PEEP
  - increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation
  - airway complications
    - tracheal stenosis, laryngeal edema
  - alveolar complications
    - ventilator-induced lung injury (barotrauma, volutrauma, atelectatrauma), ventilator-associated pneumonia (nosocomial pneumonia), inflammation, auto-PEEP, patient-ventilator asynchrony
  - cardiovascular complications
    - reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension
  - neuromuscular complications
    - muscle atrophy
    - increased ICP
  - metabolic complications
    - decreased CO_2 due to hyperventilation
    - alkalemia with overcorrection of chronic hypercarbia

Ventilator Strategies

- mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental O_2, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

Modes of Ventilation

- assist-control ventilation (ACV) or volume control (VC)
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a pre-set constant inspiratory pressure
  - in traditional PCV, tidal volume is not guaranteed, thus changes in compliance and resistance affect tidal volume
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure depending on whether in VC or PCV, respectively)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - occasionally used in adults when conventional mechanical ventilation is failing
- non-invasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask
  - Bi-level positive airway pressure (BiPAP): increased pressure (like PSV) on inspiration and lower constant pressure on expiration (i.e. PEEP)
  - CPAP: delivers constant pressure on both inspiration and expiration



Tracheostomy
Tracheostomy should be considered in patients who require ventilator support for extended periods of time. Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities



Changes in peak pressures in ACV and tidal volumes in PCV may reflect changes in lung compliance and/or airway resistance – patient may be getting better or worse



Positive End Expiratory Pressure (PEEP)
Positive pressure applied at the end of ventilation that helps to keep alveoli open, decreasing V/Q mismatch

Used with all invasive modes of ventilation



Monitoring Ventilatory Therapy
Pulse oximetry, $ETCO_2$ concentration
Regular arterial blood gases
Assess tolerance regularly



Patients who develop a pneumothorax while on mechanical ventilation require a chest tube



Causes of Intraoperative Hypoxemia

Inadequate Oxygen Supply
e.g. breathing system disconnection, obstructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply
Hypoventilation
Ventilation-Perfusion Inequalities
e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax
Reduction in Oxygen Carrying Capacity
e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy
Leftward Shift of the Hemoglobin-Oxygen Saturation Curve
e.g. hypothermia, decreased 2,3-BPG, alkalosis, hypocarbia, carbon monoxide poisoning
Right-to-Left Cardiac Shunt

Table 3. Causes of Abnormal End Tidal CO_2 Levels

Hypocapnea (Decreased CO_2)	Hypercapnea (Increased CO_2)
Hyperventilation	Hypoventilation
Hypothermia (decreased metabolic rate)	Malignant hyperthermia, other hypermetabolic states
Decreased pulmonary blood flow (decreased cardiac output)	Improved pulmonary blood flow after resuscitation or hypotension
Technical issues Incorrect placement of sampling catheter Inadequate sampling volume	Technical issues Water in capnography device Anesthetic breathing circuit error Inadequate fresh gas flow Rebreathing Exhausted soda lime Faulty circuit absorber valves
V/Q mismatch Pulmonary thromboembolism Incipient pulmonary edema Air embolism	Low bicarbonate

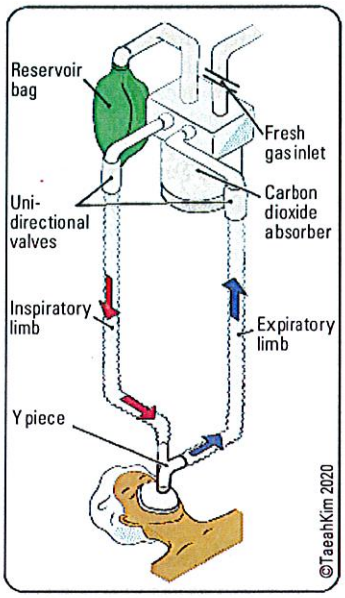


Figure 9. The anesthesia circuit

Intraoperative Management

Temperature

Causes of Hypothermia (<36.0°C)

- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
  - OR environment (e.g. cold room, IV fluids, instruments)
  - open wound
- prevent with forced air warming blankets/warm-water blankets, heated humidification of inspired gases, warmed IV fluid, and increased OR temperature

Impact of Hypothermia (<36°C)

Increased risk of wound infections due to impaired immune function

Increases the period of hospitalization by delaying healing

Reduces platelet function and impairs activation of coagulation cascade, increasing blood loss and transfusion requirements

Triples the incidence of VT and morbid cardiac events

Decreases the metabolism of anesthetic agents, prolonging postoperative recovery

See Landmark Anesthesiology Trials table for more information on results from study of Wound Infection and Temperature, which details the impact of normothermia on wound healing and length of stay as seen in 200 patients aged 18-80 yr who underwent elective colorectal surgery.

See Landmark Anesthesiology Trials table for more information on the PROTECT trial, which describes the effect of aggressive vs. routine warming on major cardiovascular outcomes in patients having noncardiac surgery.

Causes of Hyperthermia (>37.5-38.3°C)

- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- hypermetabolic states (e.g. malignant hyperthermia, neuroleptic malignant syndrome, pheochromocytoma)
- over-zealous warming efforts

Heart Rate

Cardiac Arrest

- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (pVT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/pVT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclusion of all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts)
  - 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hypo/hyperkalemia
  - 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
  - when a patient sustains a cardiac arrest during anesthesia, it is important to remember that there are other causes on top of the Hs and Ts to consider (e.g. local anesthetic systemic toxicity (LAST), excessive anesthetic dosing, etc.)
- for management of cardiac arrest, see *Appendices, A30*

Intraoperative Tachycardia

- tachycardia – HR >100 bpm; divided into sinus tachycardia (HR = 100-150 bpm) or supraventricular tachycardia (SVT)
- SVT: can be further divided into narrow complex or wide complex tachycardia
  - narrow complex: atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
  - wide complex: VT, SVT with aberrant conduction
- causes of sinus tachycardia
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis

- drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium) and withdrawal
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, pheochromocytoma, thyrotoxicosis, serotonin syndrome

• for management of tachycardia, see *Appendices, A30*

Intraoperative Bradycardia

• bradycardia – HR <50 bpm; most concerning are 2nd degree (Mobitz type II) and 3rd degree heart block, which can both degenerate into asystole
• causes of sinus bradycardia
- increased parasympathetic tone vs. decreased sympathetic tone
- must rule out hypoxemia
- arrhythmias (see Cardiology and Cardiac Surgery, C19)
- baroreceptor reflex due to increased ICP or increased BP
- vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
- drugs (e.g. opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
- high spinal/epidural anesthesia
- hypothermia and hypothyroidism

• for management of bradycardia, see *Appendices, A30*

Blood Pressure

Causes of Intraoperative Hypotension/Shock

• shock: inability of cardiovascular system to maintain adequate end-organ perfusion and delivery of O_2 to tissues
a) septic shock
- see Infectious Diseases, ID20

b) spinal/neurogenic shock
- decreased sympathetic tone
- hypotension without tachycardia or peripheral vasoconstriction (warm skin)

c) hypovolemic/hemorrhagic shock
- most common form of shock, due to decrease in intravascular volume

d) obstructive shock
- obstruction of blood into or out of the heart
- increased JVP, distended neck veins, increased SVR, insufficient CO
- e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism (and other emboli – i.e. fat, air)

e) cardiogenic shock
- inability of the heart to pump an adequate volume of blood
- increased JVP, distended neck veins, increased SVR, decreased CO
- e.g. myocardial dysfunction, dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction

f) anaphylactic(K) shock
- see Emergency Medicine, ER3

g) endocrine/other
- transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
- see Hematology and Endocrinology

h) drugs
- vasodilators, high spinal anesthetic interfering with sympathetic outflow

Causes of Intraoperative Hypertension

• inadequate anesthesia causing pain and anxiety
• pre-existing HTN, coarctation, or preeclampsia
• hypoxemia/hypercarbia
• hypervolemia
• increased intracranial pressure
• full bladder
• drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine) and withdrawal
• allergic/anaphylactic reaction
• hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, pheochromocytoma (see Endocrinology, E29, E40)

Fluid Balance and Resuscitation

• total requirement = maintenance + deficit + ongoing loss
• in surgical settings, this formula must take into account multiple factors including preoperative fasting/decreased fluid intake, increased losses during or before surgery, and fluids given with blood products and medications
• increasingly, Enhanced Recovery After Surgery protocols recommend consumption of clear fluids up to 2 h prior to surgery
• both inadequate fluid resuscitation AND excessive fluid administration increase morbidity postoperatively



Intraoperative Shock Box

SHOCKED
Sepsis or Spinal shock
Hypovolemic/Hemorrhagic
Obstructive
Cardiogenic
anaphylactiK
Endocrine/other (e.g. Addison's disease, hyperthyroidism, transfusion reaction)
Drugs



BP = CO x SVR, where CO = SV x HR
SV is a function of preload, afterload, and contractility



Intraoperative Hypotension and the Risk of Postoperative Adverse Outcomes: A Systematic Review
Br J Anaesth 2018;4:706-721
Purpose: To determine to what extent hypotension during noncardiac surgery is associated with unfavorable outcomes.
Methods: Systematic review of RCTs, cohort studies, and case-control studies (n=42) on reported associations between intraoperative hypotension and associations with postoperative adverse outcomes after noncardiac surgery.
Results: Prolonged exposure (≥10 min) to MAPs <80 mmHg and for shorter durations <70 mmHg was associated with mildly elevated risks of end-organ injury. Increased durations for MAP <65-60 mmHg or for any exposures <55-50 mmHg were associated with moderately or highly elevated risks.
Conclusions: Organ injury may occur when MAP decreases <80 mmHg for ≥10 min. This risk increases with blood pressures becoming progressively lower.



See Landmark Anesthesiology Trials table for more information on the POISE-3 trial, which assesses the effects of a hypotension-avoidance and a hypertension-avoidance strategy on major vascular complications after noncardiac surgery.



See Landmark Anesthesiology Trials table for more information on the POISE-2 trial, which compares low-dose clonidine vs. placebo on the rate of death and major cardiovascular events in patients having noncardiac surgery.



See Landmark Anesthesiology Trials table for more information on the POISE trial, which assesses the effects of perioperative β blockers in patients having non-cardiac surgery.

Maintenance Fluid

- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (beware of renal failure)
- maintenance should not exceed 3 mL/kg/h
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- maintenance electrolytes
  - Na^+: 3 mEq/kg/d
  - K^+: 1 mEq/kg/d
- 4-2-1 rule: 4 mL/h first 10 kg, 2 mL/h next 10 kg, 1 mL/h for every kg after to calculate maintenance fluid requirement
  - alternatively, may add 40 to adults who weigh ≥20kg to calculate maintenance fluid requirement in mL/h
- e.g. a 50 kg patient's maintenance requirements
  - fluid = (4 mL/h x 10 kg) + (2 mL/h x 10 kg) + (1 mL/h x 30 kg) = 40 mL/h + 20 mL/h + 30 mL/h = 90 mL/h = 2160 mL/d
  - Na^+ = 150 mEq/d (therefore 150 mEq/2.16 L/d ≈ 69 mEq/L)
  - K^+ = 50 mEq/d (therefore 50 mEq/2.16 L/d ≈ 23 mEq/L)
- above patient's requirements roughly met with 2/3 dextrose 5% in water (D5W), 1/3 normal saline (NS) 0.9%
  - 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre

Fluid Deficit

- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na^+ content determines ECF volume; [Na^+] determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal Na^+ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/respiratory: insensible losses (fever), sweating, burns
    - vascular: hemorrhage
    - renal Na^+ and H_2O loss
    - diuretics
    - osmotic diuresis
    - hypoaldosteronism
    - salt-wasting nephropathies
    - renal H_2O loss
    - diabetes insipidus (central or nephrogenic)
    - hypovolemia with normal or expanded ECF volume
    - decreased CO
    - redistribution
- hypoalbuminemia: cirrhosis, nephrotic syndrome
- capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
- replace water and electrolytes as determined by patient's needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

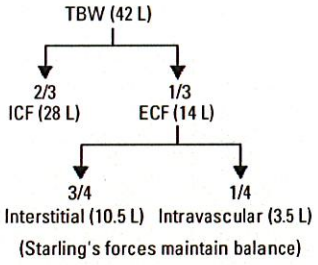


Figure 10. Total body water division in a 70 kg adult

Table 4. Signs and Symptoms of Dehydration

Percentage of Body Water Loss	Severity	Signs and Symptoms
3%	Mild	Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating
6%	Moderate	Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy
9%	Severe	Profound oliguria or anuria and compromised CNS function with or without altered sensorium

What are the Ongoing Losses?

- traditionally thought that fluid loss during surgery resulted from blood loss, losses from Foley catheter, NG, surgical drains, and minor losses due to sequestration of fluid into other body compartments
- fluid therapy accounting for these losses often resulted in excess crystalloid administration
- goal-directed fluid regimens associated with lower rate of postoperative complications compared to predetermined calculations. These can be done using point of care ultrasound (POCUS), esophageal doppler, or pulse or pressure variation available either using arterial line monitoring or certain pulse oximetry

IV Fluids

- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT O_2 carrying capacity of blood

Initial Distribution of IV Fluids

- H_2O follows ions/molecules to their respective compartments

Crystalloid Infusion

- salt-containing solutions that distribute only within ECF
- consensus guidelines recommend use of balanced crystalloid (i.e. Ringer's lactate) over NS for routine replacement and resuscitation
- maintain euvolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement)
- best practice is to use goal-directed therapy
- if large volumes are to be given, use balanced fluids such as Ringer's lactate or Plasmalyte®, as too much NS may lead to hyperchloremic metabolic acidosis

Colloid Infusion

- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (dextrans and starches, (e.g. hydroxyethyl starch) (HES))
- distributes within intravascular volume
- 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
- the use of HES solutions is controversial because of recent RCTs and meta-analyses highlighting their renal (especially in septic patients) and coagulopathic side effects, as well as a lack of specific indications for their use
  - colloids are being used based on mechanistic and experimental evidence but there is a paucity of definitive studies investigating their safety and efficacy; routine use of colloids should be avoided

Table 5. IV Fluid Solutions

		ECF	Ringer's Lactate	0.9% NS	0.45% NS in D5W	D5W	2/3 D5W + 1/3 NS	Plasmalyte
mEq/L	Na^+	142	130	154	77	-	51	140
	K^+	4	4	-	-	-	-	5
	Ca^{2+}	4	3	-	-	-	-	-
	Mg^{2+}	3	-	-	-	-	-	3
	Cl^-	103	109	154	77	-	51	98
	HCO_3^-	27	28*	-	-	-	-	27
mOsm/L		280-310	273	308	154	252	269	294
pH		7.4	6.5	5.0	4.5	4.0	4.3	7.4

*Converted from lactate

Table 6. Colloid HES Solutions

	Concentration	Plasma Volume Expansion	Duration (h)	Maximum Daily Dose (mL/kg)
Voluven®	6%	1:1	4-6	33-50
Pentaspan®	10%	1:1.2-1.5	18-24	28

Blood Products

- see Hematology, H54

Colloids vs. Crystalloids for Fluid Resuscitation in Critically Ill People

Cochrane DB Syst Rev 2018:CD000567

Purpose: To assess effect of colloids vs. crystalloids in critically ill patients on mortality, need for transfusions or renal replacement therapy, and adverse events.

Methods: Systematic review of RCTs and quasi-RCTs involving trauma, burns, or medical conditions (i.e. sepsis). Searched CENTRAL, MEDLINE, and Embase.

Outcomes: 69 studies, 30020 participants. Starches, dextrans, albumin or FFP (moderate-certainty evidence), or gelatins (low-certainty evidence) vs. crystalloids has no difference on mortality. Starches slightly increase the need for blood transfusion (moderate-certainty evidence), and albumin or FFP may make little or no difference to the need for renal replacement therapy (low-certainty evidence). Evidence for blood transfusions for dextrans, and albumin or FFP, is uncertain.

Calculating Acceptable Blood Losses (ABL)

- Blood volume
  term infant 80 mL/kg
  adult male 70 mL/kg
  adult female 60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
  EBV = 70 kg x 70 mL/kg = 4900 mL
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion (e.g. 70 g/L for a person with Hb(initial) = 150 g/L)
  Hb(final) = 70 g/L
- Calculate

$$ABL = Hb(i) - \frac{Hb(f) \times EBV}{Hb(i)}$$
$$= 150 - \frac{70 \times 4900}{150}$$
$$= 2613 \text{ mL}$$

Therefore, in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost

Transfusion Infection Risks

Virus	Risk per 1 unit pRBCs
HIV	1 in 21 million
Hepatitis C virus	1 in 13 million
Hepatitis B virus	1 in 7.5 million
HTLV	1 in 1-1.3 million
Symptomatic Bacterial Sepsis	1 in 40,000 from platelets and 1 in 250,000 from RBC
West Nile virus	No cases since 2003

Source: Callum JL, Pinkerton PH. Bloody Easy. Fourth Edition ed. Toronto: Sunnybrook and Women's College Health Science Centre; 2016

See Landmark Anesthesiology Trials table for more information on the RELIEF trial, which compares the risk of complications for restrictive vs. liberal IV fluid regimen in patients having major abdominal surgery.

Induction

Routine Induction vs. Rapid Sequence Induction

- routine induction is the standard in general anesthesia; however, an RSI is indicated in patients at risk of regurgitation/aspiration (see *Aspiration, A6*)
- RSI uses
  1. pre-determined doses of induction drugs given in rapid succession to minimize the time patient is at risk for aspiration (e.g. from the time when they are unconscious without an ETT until the time when the ETT is inserted and the cuff inflated)
  2. no bag mask ventilation
  3. cricoid pressure may be applied (although there are some exceptions, e.g. trauma to upper airway)
  4. use of rapid onset muscle relaxant (i.e. SCh)

Table 7. Comparison of Routine Induction vs. RSI

Steps	Routine Induction	RSI
Equipment Preparation	Check equipment, drugs, suction, and monitors; prepare an alternative laryngoscope blade and a second ETT one size smaller, suction on	
Pre-Oxygenation/ Denitrogenation	100% O_2 for 3 min or 4-8 vital capacity breaths; reduce risk of hypoxemia during apneic period following induction	
Pre-Treatment Agents	Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy	Use agent of choice to blunt physiologic responses to airway manipulation; if possible, give 3 min prior to laryngoscopy, but can skip this step in an emergent situation
Induction Agents	Use IV or inhalation induction agent of choice	Use pre-determined dose of fast acting induction agent of choice
Muscle Relaxants	Muscle relaxant of choice given after the onset of the induction agent	Pre-determined dose of fast acting muscle relaxant (SCh or high dose rocuronium) given IMMEDIATELY after induction agent
Ventilation	Bag-mask ventilation	DO NOT bag ventilate – can increase risk of aspiration
Additional Helpful Maneuvers	External Laryngeal Manipulation using Backwards, Upwards, Rightward Pressure (BURP)	Cricoid pressure (Sellick Maneuver) to prevent regurgitation
Intubation	Intubate, inflate cuff, confirm ETT position	Intubate once paralyzed (~45 s after SCh given), inflate cuff, confirm ETT position; cricoid pressure maintained until ETT cuff inflated and placement confirmed
Secure	Secure ETT, and begin manual/machine ventilation	

Rocuronium vs. Succinylcholine for Rapid Sequence Induction Intubation
Cochrane DB Syst Rev 2015:CD002788
Purpose: Whether rocuronium creates intubating conditions comparable to those of succinylcholine during RSI intubations.
Methods: Systematic review of RCTs or CCTs with a dose of at least 0.6 mg/kg for rocuronium and 1 mg/kg for succinylcholine.
Results: 50 trials, 4151 participants. Succinylcholine was superior to rocuronium for achieving excellent intubating conditions (RR 0.86, 95% CI 0.81-0.92) and clinically acceptable intubation conditions (RR 0.97, 95% CI 0.95-0.99).
Conclusion: Succinylcholine created superior intubation conditions to rocuronium in achieving excellent and clinically acceptable intubating conditions.

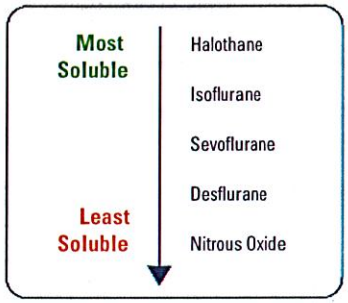


Figure 11. Solubility of volatile anesthetics in blood

Effects of Cricoid Pressure Compared with a Sham Procedure in the Rapid Sequence Induction of Anesthesia: The Iris Randomized Clinical Trial
JAMA Surg 2019;154(1):9–17
Purpose: To determine if cricoid pressure impacts pulmonary aspiration in people undergoing rapid sequence induction (RSI) of anesthesia.
Methods: Randomized and double-blind trial to assess 3472 patients undergoing rapid sequence induction of anesthesia at 10 academic centers.
Results: Results demonstrated that patients undergoing anesthesia using RSI experience increased prevention of pulmonary aspiration using cricoid pressure when compared to the sham condition.
Conclusion: This study provides evidence to show the benefit of cricoid pressure in RSI and found that it is superior to the sham procedure in preventing aspiration.

Induction Agents

- induction of general anesthesia may be achieved with intravenous agents and/or volatile inhalational agents

Intravenous Agents

- IV induction agents are non-opioid drugs used to provide hypnosis, amnesia, and blunt reflexes to laryngoscopy
- these are initially used to establish the plane of anesthesia rapidly and smoothly
  - most commonly used is propofol or ketamine
  - a continuous propofol infusion may be used as an alternative to inhalational volatile agents during the maintenance phase of general anesthesia. An indication would be malignant hyperthermia

Table 8. Intravenous Induction Agents

	Propofol (Diprivan®)	Thiopental (sodium thiopental, sodium thiopentone)*	Ketamine (Ketalar®, Ketaject®)	Etomidate	Methohexital (Brevital®)
Class	Alkylphenol – hypnotic	Short acting thiobarbiturate – hypnotic	Phencyclidine (PCP) derivative – dissociative	Imidazole derivative - hypnotic	Ultra short-acting barbiturate
Action	Inhibitory at GABA synapse Decreased cerebral metabolic rate and blood flow, decreased ICP, decreased SVR, decreased BP, and decreased SV	Inhibitory at GABA synapse Decreased cerebral metabolic rate and blood flow, decreased CPP, decreased CO, decreased BP, decreased reflex tachycardia, decreased respiration	May act on NMDA (antagonistically), opiate, and other receptors Increased HR, increased BP, increased SVR, increased coronary flow, increased myocardial O_2 uptake CNS and respiratory depression, bronchial smooth muscle relaxation	Decreases concentration of GABA required to activate receptor CNS depression Minimal cardiac or respiratory depression	Binds to the chloride ionophore site of GABA-A receptor
Indications	Induction Maintenance Total intravenous anesthesia (TIVA)	Induction Control of convulsive states, obstetric patients	Induction when sympathetic stimulation required (e.g. major trauma, hypovolemia), IM induction in children/uncooperative adults (i.e. when there is lack of IV access), severe asthma because sympathomimetic	Induction Poor cardiac function, severe valve lesions, uncontrolled hypertension	Procedural induction Electroconvulsive therapy (ECT)

*As of 2011, Thiopental has been discontinued from production for North America

Table 8. Intravenous Induction Agents

	Propofol (Diprivan®)	Thiopental (sodium thiopental, sodium thiopentone)*	Ketamine (Ketalar®, Ketaject®)	Etomidate	Methohexital (Brevital®)
Caution	Patients who cannot tolerate sudden decreased BP (e.g. fixed cardiac output or shock)	Allergy to barbiturates Uncontrolled hypotension, shock, cardiac failure Porphyria, liver disease, status asthmaticus, myxedema	Ketamine allergy TCA medication (interaction causes HTN and dysrhythmias) History of psychosis Patients who cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm)	Postoperative nausea and vomiting Venous irritation	Contraindicated in acute intermittent porphyria
Dosing	IV induction: 1.5-2.5 mg/kg (less with opioids) Unconscious <1 min Lasts 4-6 min $t_{1/2}$ = 55 min Decreased postoperative sedation, recovery time, N/V	IV induction: 3-5 mg/kg Unconscious about 30 s Lasts 5 min Accumulation with repeat dosing – not for maintenance $t_{1/2}$ = 5-10 h Postoperative sedation lasts hours	IV induction 1-2 mg/kg Dissociation in 15 s, analgesia, amnesia, and unconsciousness in 45-60 s Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h $t_{1/2}$ = ~3 h	IV induction 0.3 mg/kg Onset 30-60 s Lasts 4-8 min	IV induction 1 to 1.5 mg/kg of a 1% solution; doses must be titrated to effect
Special Considerations	-30% decreased BP due to vasodilation Reduce burning at IV site by mixing with lidocaine	Combining with rocuronium causes precipitates to form	High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions) Pretreat with glycopyrrolate to decrease salivation	Adrenal suppression after first dose, cannot repeat dose or use as infusion Myoclonic movements during induction	

*As of 2011, Thiopental has been discontinued from production for North America

Volatile Inhalational Agents

- e.g. sevoflurane, desflurane, isoflurane, enflurane, halothane, and nitrous oxide

Table 9. Volatile Inhalational Agents

	Sevoflurane	Desflurane*	Isoflurane**	Enflurane	Halothane	Nitrous oxide (N_2O)***
MAC (% gas in O_2)	2.0	6.0	1.2	1.7	0.8	104
CNS	Increased ICP	Increased ICP	Decreased cerebral metabolic rate Increased ICP	ECG seizure-like activity Increased ICP	Increased ICP and cerebral blood flow	–
Resp	Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO_2 reflexes, bronchodilation					–
CVS	Less decrease of contractility, stable HR	Tachycardia with rapid increase in concentration	Decreased BP and CO, increased HR, theoretical chance of coronary steal**	Stable HR, decreased contractility	Decreased BP, CO, HR, and conduction Sensitizes myocardium to epinephrine-induced arrhythmias	Can cause decreased HR in pediatric patients with existing heart disease
MSK	Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation					

*Airway irritant: desflurane can provoke breath holding, laryngospasm, and salivation, so it is not used for inhalational induction
**Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis)
***Properties and Adverse Effects of N_2O
Due to its high MAC, N_2O is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only
Second Gas Effect
Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen, and ETT cuff will markedly enlarge if N_2O is administered
Diffusion hypoxia: during anesthesia, the washout of N_2O from body stores into alveoli can dilute the alveolar [O_2], creating a hypoxic mixture if the original [O_2] is low



See Landmark Anesthesiology Trials table for more information on MYRIAD trial, which details the impact of volatile anesthetics vs. total intravenous anesthesia in patients undergoing CABG.

Minimum Alveolar Concentration

- minimum alveolar concentration (MAC) is the minimal alveolar concentration of a volatile anesthetic required (at one atmosphere of pressure in 100% oxygen) that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- potency of inhalational agents is compared using MAC
- MAC of halogenated volatile anesthetics decreases by approximately 6% per additional decade of age in adults
- 1.2-1.3 times MAC will often ablate response to stimuli in the general population
- MAC values are roughly additive when mixing N_2O with another volatile agent; however, this only applies to movement, not other effects such as BP changes (e.g. 0.5 MAC of a potent agent + 0.5 MAC of N_2O = 1 MAC of potent agent)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation; generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli; generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command; generally 0.3-0.4 of the usual MAC



Factors increasing MAC: chronic alcohol use, hyperthyroidism, hyperthermia, acute amphetamine use, cannabinoids, young age
Factors decreasing MAC: acute alcohol intoxication, hypothermia, sedating drugs, advanced age, chronic amphetamine use, drugs (opioids, benzodiazepines), α2 adrenergic agonists, nitrous oxide, IV anesthetics, shock



See Landmark Anesthesiology Trials table for more information on the ENIGMA-II trial, which evaluates the rate of cardiovascular complications in patients receiving nitrous oxide (NO) or NO-free anesthesia.

Muscle Relaxants and Reversing Agents

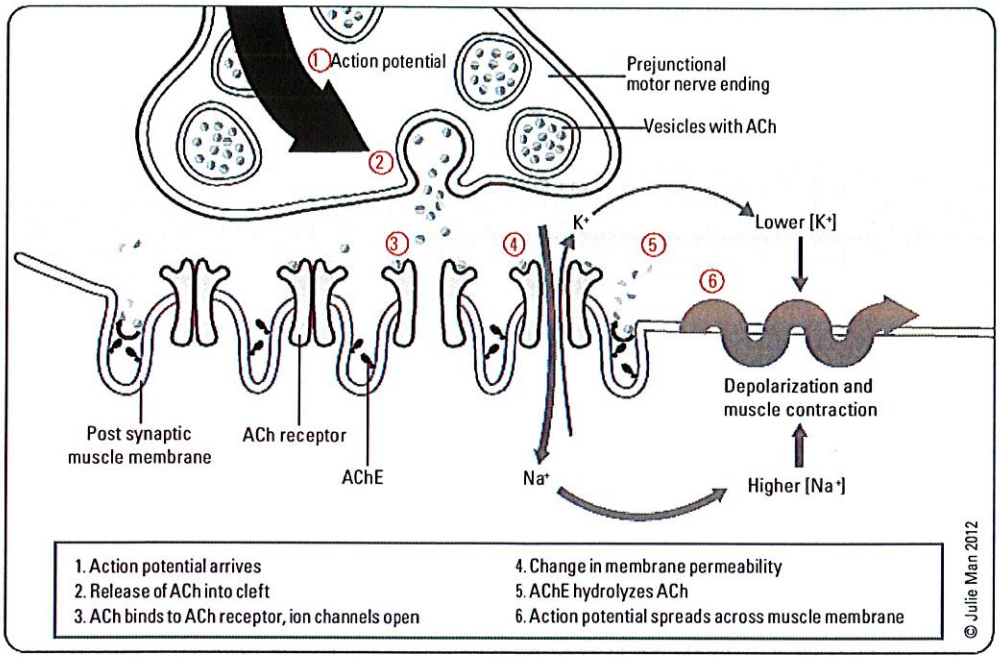


Figure 12. Review of anatomy and physiology of the neuromuscular junction (NMJ)

Muscle Relaxants

- two types of muscle relaxants
  1. depolarizing muscle relaxants: SCh
  2. non-depolarizing muscle relaxants (NDMRs): rocuronium, mivacurium, vecuronium, cisatracurium, pancuronium
- block nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- never use muscle relaxants without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects:
  1. facilitates intubation
  2. assists with mechanical ventilation
  3. prevents muscle stretch reflex and decreases muscle tone
  4. allows access to the surgical field (intracavity surgery)
- nerve stimulator (i.e. train of four) is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade



Pseudocholinesterase
Pseudocholinesterase is produced by the liver and metabolizes SCh and mivacurium. A prolonged duration of blockade by SCh occurs with:
(a) decreased quantity of plasma cholinesterase (e.g. congenital (hereditary), liver disease, pregnancy, malignancy, malnutrition, collagen vascular disease, hypothyroidism)
(b) abnormal quality of plasma cholinesterase (e.g. normal levels but impaired activity of enzymes, genetically inherited)

Table 10. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

Mechanism of Action	Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh
Intubating Dose (mg/kg)	1-1.5
Onset	30-60 s – rapid (fastest of all muscle relaxants)
Duration	3-5 min – short (no reversing agent for SCh)
Metabolism	SCh is hydrolyzed by plasma cholinesterase (i.e. pseudocholinesterase), found only in plasma and not at the NMJ
Indications	Assist intubation Increased risk of aspiration (e.g. full stomach, hiatus hernia, obesity, pregnancy, trauma); need rapid paralysis and airway control Short procedures Electroconvulsive Therapy (ECT) Laryngospasm
Side Effects	1. Simulation of muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors) may cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children) 2. Hyperkalemia Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells Patients at risk: 3rd degree burns 24 h-6 mo after injury Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy) Severe intra-abdominal infections Severe closed head injury Upper motor neuron lesions 3. Can trigger MH (see *Malignant Hyperthermia, A29*) 4. Increased ICP/intraocular pressure/intragastric pressure (no increased risk of aspiration if competent LES) 5. Fasciculations, postoperative myalgia – may be minimized if small dose of NMBA given before SCh administration
Contraindications	
Absolute	Known hypersensitivity or allergy, positive history of MH, myotonia (m. congenita, m. dystrophica, paramyotonia congenital), high-risk for hyperkalemic response
Relative	Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury

Table 11. Non-Depolarizing Muscle Relaxants (Competitive)

Mechanism of Action	Competitive blockade of postsynaptic ACh receptors preventing depolarization				
Classification	**Short**		**Intermediate**		**Long**
	Mivacurium	Rocuronium	Vecuronium	Cisatracurium	Pancuronium
Intubating Dose (mg/kg)	0.2	0.6-1.0	0.1	0.2	0.1
Onset (min)	2-3	1.5	2-3	3	3-5
Duration (min)	15-25	30-45	45-60	40-60	90-120
Metabolism	Plasma cholinesterase	Liver (major) Renal (minor)	Liver	Hofmann Elimination	Renal (major) Liver (minor)
Intubating Dose (mg/kg)	0.2	0.6-1.0	0.1	0.2	0.1
Indications	Assist intubation, assist mechanical ventilation in some ICU patients, and reduce fasciculations and postoperative myalgias secondary to SCh				
Side Effects					
Histamine Release	Yes	No	No	No	No
Other	–	–	–	–	Tachycardia
Considerations	Increased duration of action in renal or liver failure	Quick onset of rocuronium allows its use in rapid sequence induction	–	Good for patients with renal or hepatic insufficiency	Use when increased HR and BP desired

Reversal Agents

- sugammadex is a selective relaxant binding agent and can be administered immediately after dose of NDMR
- neostigmine, pyridostigmine, and edrophonium are acetylcholinesterase inhibitors - these are competitive inhibitors and therefore can only be administered when there has been some recovery of blockade (i.e. train of four muscle response to stimulation)
- can only reverse the effects of NDMRs
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation, increased peristalsis, and bronchoconstriction)

ALGrawany

Table 12. Reversal Agents for Non-Depolarizing Relaxants

Agent	Pyridostigmine	Neostigmine	Edrophonium	Sugammadex
Onset	Slow	Intermediate	Intermediate	Fast
Mechanism of Action	AChE; inhibit enzymatic degradation of ACh, increase ACh at nicotinic and muscarinic receptors, displace NDMRs Muscarinic effects of reversing agents include unwanted bradycardia, salivation, and increased bowel peristalsis*			Encapsulates and inactivates rocuronium and vecuronium → ↓ amount of agent available to bind to receptors in NMJ
Dose (mg/kg)	0.1-0.4	0.04-0.08	0.5-1	2-16
Recommended Anticholinergic	Glycopyrrolate	Glycopyrrolate	Atropine	N/A
Dose of Anticholinergic (per mg)	0.05 mg	0.2 mg	0.014 mg	N/A

*Atropine and glycopyrrolate are anticholinergic agents administered to minimize muscarinic effects of reversal agents

Analgesia

- opioids are used during induction to provide analgesia, sedation, and blunt autonomic responses
- their sedative properties supplement the IV induction agent and they blunt autonomic response during laryngoscopy and intubation

Maintenance

- general anesthesia is maintained using volatile inhalation agents and/or IV agents (i.e. propofol infusion)
- analgesia (usually IV opioids)
  - ± muscle relaxants given as needed



See Landmark Anesthesiology Trials table for more information on results from the ENGAGES trial, which details the efficacy of using EEG guided anesthetic administration in patients with postoperative delirium.

Extubation

- criteria: patient must no longer have intubation requirements
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- general guidelines
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% O_2 for 3-5 min
  - suction secretions from pharynx, deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for O_2 delivery available
  - proper positioning of patient during transfer to recovery room (supine, head elevated)

Complications of Extubation

- early extubation: aspiration, laryngospasm
- late extubation: transient vocal cord incompetence, edema (glottic, subglottic), pharyngitis, tracheitis

Laryngospasm

- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (by oropharyngeal secretions, blood, early extubation)
- causes partial or total airway obstruction
- more likely to occur in semi-conscious patients
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: suction, remove oral airway/LMA, apply CPAP with anesthetic reservoir bag and partial closure of adjustable pressure-limiting (APL) valve, BMV with 100% O_2, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose SCh (approximately 0.25 mg/kg), and re-intubate if hypoxia develops

Regional Anesthesia

- local anesthetic applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) to reduce or prevent impulse transmission
- no CNS depression (unless overdose of LA); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

Patient Preparation

- sedation and/or anxiolysis may be indicated before block
- monitoring should be as extensive as for GA

Epidural and Spinal Anesthesia

- most common for surgeries performed below the level of umbilicus but can be extended to any level (useful in thoracic, abdominal, and lower extremity surgeries)
- typically placed in thoracic or lumbar spine

Anatomy of Spinal/Epidural Area

- spinal cord extends to L1; dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated (superficial to deep)
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

Table 13. Epidural vs. Spinal Anesthesia

	Epidural	Spinal
Deposition Site	LA injected in epidural space (space between ligamentum flavum and dura) Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura	LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots
Onset	Significant blockade requires 10-15 min Slower onset of side effects	Rapid blockade (onset in 2-5 min)
Effectiveness	Effectiveness of blockade can be variable	Very effective blockade
Difficulty	Technically more difficult; greater failure rate	Easier to perform due to visual confirmation of CSF flow
Patient Positioning Post-injection	Position of patient not as important; specific gravity not an issue	Hyperbaric LA solution – position of patient important
Specific Gravity/ Spread	Epidural injections spread throughout the potential space; specific gravity of solution does not affect spread	LA solution may be made hyperbaric (of greater specific gravity than the CSF by mixing with dextrose 10%, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)
Dosage	Larger volume/dose of LA (usually > toxic IV dose)	Smaller dose of LA required (usually < toxic IV dose)
Continuous Infusion	Use of catheter allows for continuous infusion or repeat injections	None
Complications	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T4 block), e.g. "high block" Epidural or subarachnoid hematoma Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications) Systemic toxicity of LA (accidental intravenous) Catheter complications (shearing, kinking, vascular, or subarachnoid placement) Infection Post-dural puncture	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T4 block), e.g. "high spinal" Epidural or subarachnoid hematoma Post-spinal headache (CSF leak) Transient paresthesias Spinal cord trauma Infection
Combined Spinal-Epidural	Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter	

Benefits of Regional Anesthesia

- Reduced perioperative pulmonary complications
- Reduced perioperative analgesia requirements
- Decreased PONV
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE
- Shorter recovery and improved rehabilitation
- Pain blockade with preserved motor function

Landmarking Epidural/Spinal Anesthesia

- Spinous processes should be maximally flexed
- L4 spinous processes found between iliac crests
- T7 landmark at the tip of the scapula

Classic Presentation of Dural Puncture Headache

- Onset 6 h-3 d after dural puncture
- Postural component (worse when sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia

Effect of Anaesthesia Type on Postoperative Mortality and Morbidities: A Matched Analysis of the NSQIP Database

Br J Anaesth 2017;118:105-111

Purpose: Determine the effects of RA vs. GA on postoperative survival and morbidities.

Methods: Matched surgical procedures and type of anesthesia using the US National Surgical Quality Improvement database. Primary outcome was 30 d postoperative mortality and secondary outcomes were hospital length of stay and postoperative organ system dysfunction.

Results: There was no difference in 30 d mortality. RA was significantly associated with increased likelihood of early discharge (HR 1.09; P<0.001). There were lower odds of intraoperative complications (47%), respiratory complications (24%), DVT (16%), and any one postoperative complication (15%) (OR 0.85; P<0.001).

Conclusion: RA was associated with significantly lower odds of several postoperative complications, decreased hospital length of stay, but not mortality when compared with GA.

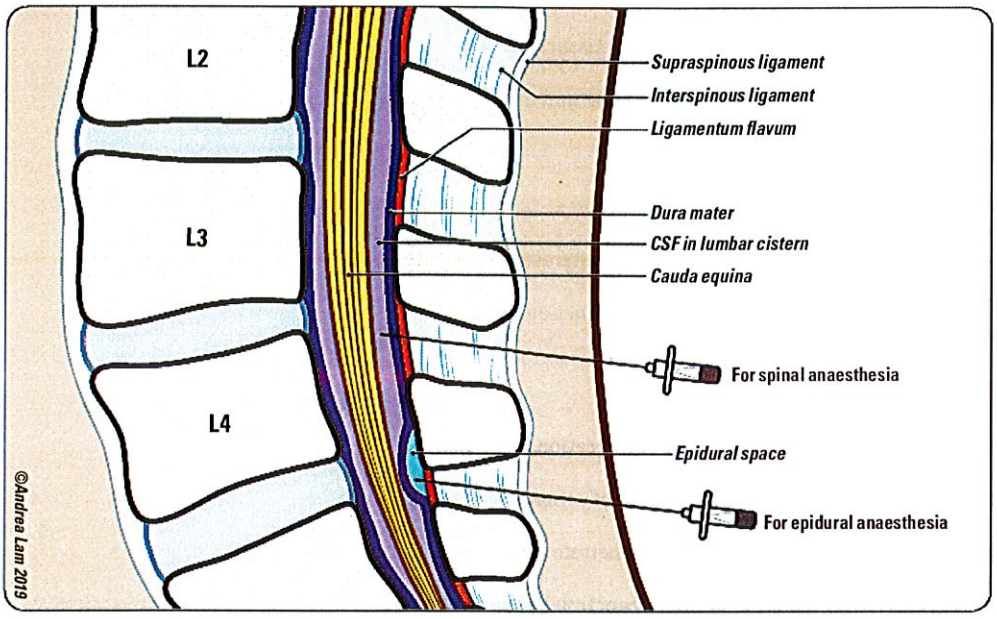


Figure 14. Sagittal cross-section of the anatomy of neuraxial anesthesia

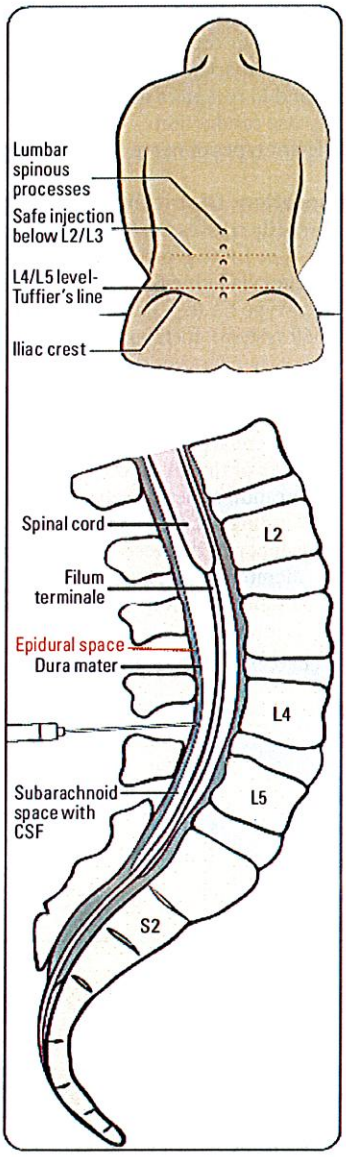


Figure 13. Landmarks for placement of epidural/spinal anesthesia

Contraindications to Spinal/Epidural Anesthesia

- absolute contraindications
  - lack of resuscitative drugs/equipment
  - patient refusal
  - allergy to local anesthetic
  - infection at puncture site or underlying tissues
  - coagulopathies/bleeding diathesis
  - raised ICP
  - sepsis/bacteremia
  - severe hypovolemia
  - cardiac lesion with fixed output states (e.g. severe mitral/aortic stenosis)
  - lack of IV access
- relative contraindications
  - pre-existing neurological disease (e.g. demyelinating lesions)
  - previous spinal surgery; severe spinal deformity
  - prolonged surgery
  - major blood loss or maneuvers that can compromise reaction

Peripheral Nerve Blocks

- deposition of LA around the target nerve or plexus
- ultrasound guidance and peripheral nerve stimulation may be used to guide needle to target/stimulate nerve while avoiding neural trauma or intraneural injection
- most major nerves or nerve plexuses can be targeted (e.g. brachial plexus block, femoral nerve block, sciatic nerve block)
- performed with standard monitors
- risk of late neurologic injury is approximately 2-4/10000 peripheral nerve blocks
- resuscitation equipment must be available

Contraindications to Peripheral Nerve Blockade

- absolute contraindications
  - allergy to LA
  - patient refusal
- relative contraindications
  - certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
  - local infection at block site
  - bleeding disorder

Local Anesthesia

Local Anesthetic Agents

- see *Table 14, A23, for list of LA agents*

Definition and Mode of Action
- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptors on the cytosolic side of the Na^+ channels, inhibiting Na^+ flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

Absorption, Distribution, and Metabolism
- LA readily crosses the BBB once absorbed into the bloodstream
- ester-type LA (e.g. procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (e.g. lidocaine, bupivacaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

Selection of LA
- choice of LA depends on:
  - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA, and the faster the onset of action)
  - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivacaine at low doses)
  - potential for toxicity

Table 14. Local Anesthetic Agents

	Maximum Dose (mg/kg)	Maximum Dose with Epinephrine (mg/kg)	Potency	Duration	Onset
Chloroprocaine	11	14	Low	15-30 min	Fast
Lidocaine	5	7	Medium	1-2 h	Fast
Mepivacaine	5	7	Medium	3-6 h	Fast
Bupivacaine	2.5	3	High	3-8 h	Slow
Ropivacaine	2.5	3	High	2-8 h	Medium

Systemic Toxicity
- see *Table 14* for maximum doses, potency, and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption

CNS Effects
- first appear to be excitatory due to initial block of inhibitory fibres, followed by subsequent blockade of excitatory fibres
- effects in order of appearance
  - numbness of tongue, perioral tingling, metallic taste
  - disorientation, drowsiness
  - tinnitus
  - visual disturbances
  - muscle twitching, tremors
  - unconsciousness
  - convulsions, seizures
  - generalized CNS depression, coma, respiratory arrest

CVS Effects
- vasodilation, hypotension
- decreased myocardial contractility
- dose-dependent delay in cardiac impulse transmission
  - prolonged PR, QRS intervals
  - sinus bradycardia
- CVS collapse

Treatment of Systemic Toxicity
- early recognition of signs; get help
- 100% O_2, manage ABCs
- diazepam or other anticonvulsant to prevent potential onset of seizures
- manage arrhythmias
- Intralipid® 20% to bind local anesthetic in circulation

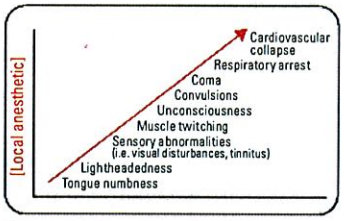


Figure 15. Local anesthetic systemic toxicity

Local Infiltration and Hematoma Blocks

Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerves
- suitable for small incisions, suturing, and excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100000-1:200000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

Topical Anesthetics

- various preparations of LAs available for topical use, which may be a mixture of agents (e.g. EMLA® cream is a combination of lidocaine 2.5% and prilocaine)
- must be able to penetrate the skin or mucous membrane

Postoperative Care

- pain management should be continuous from OR to PACU to hospital ward and home

Common Postoperative Anesthetic Complications

Uncontrolled/Poorly Controlled Pain
- See below

Nausea and Vomiting
- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), ondansetron (Zofran®), granisetron (Kytril®), dexamethasone (Decadron®), metoclopramide (Maxeran®; not with bowel obstruction), prochlorperazine (Stemetil®)

Confusion and Agitation
- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnia, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (e.g. hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (e.g. stroke, raised ICP)
- drug effect (e.g. ketamine, anticholinergics, serotonin, benzodiazepines, opioids)
- elderly patients are more susceptible to postoperative delirium

Respiratory Complications
- susceptible to aspiration of gastric contents due to PONV and unreliable airway reflexes
- airway obstruction (secondary to reduced muscle tone from residual anesthetic, soft tissue trauma and edema, or pooled secretions) may lead to inadequate ventilation, hypoxemia, and hypercapnia
- airway obstruction can often be relieved with head tilt, jaw elevation, and anterior displacement of the mandible. If the obstruction is not reversible, a nasal or oral airway may be used

Hypotension
- must be identified and treated quickly to prevent inadequate perfusion and ischemic damage
- reduced cardiac output (the most common cause is hypovolemia) and/or peripheral vasodilation (e.g. residual anesthetic agent)
- first step in treatment is usually the administration of fluids ± inotropic agents

Hypertension
- pain, hypercapnia, hypoxemia, increased intravascular fluid volume, and sympathomimetic drugs can cause hypertension
- IV nitroglycerin, hydralazine, calcium channel blockers, or β-blocking drugs (e.g. esmolol and metoprolol) can be used to treat hypertension

Local Anesthetics and Regional Anaesthesia vs. Conventional Analgesia for Preventing Persistent Postoperative Pain in Adults and Children
Cochrane DB Syst Rev 2018;6:CD007105
Purpose: Compare LA and RA vs. conventional anesthesia for the prevention of persistent postoperative pain (PPP) beyond 3 mo.
Methods: Searched CENTRAL, MEDLINE, and Embase to December 2016. RCTs comparing RA vs. conventional anesthesia were included.
Results: Total 63 RCTs included. Data on RA for the prevention of PPP beyond 3 mo after surgery from 39 studies, enrolling a total of 3027 participants in inclusive analysis. Moderate quality evidence favoring RA over conventional for thoracotomy, C-section (OR 0.52 and OR 0.46 respectively). Moderate quality evidence showing the infusion of IV LA for the prevention of PPP 3-6 mo after breast cancer surgery with an OR of 0.24. Low quality evidence in RA for the prevention of PPP 3-12 mo after breast cancer surgery with an OR of 0.43.
Conclusions: There is moderate-quality evidence that RA may reduce the risk of developing PPP after 3-18 mo after thoracotomy and 3-12 mo after cesarean section. Further studies including larger populations are needed.

Risk Factors for PONV
- Young age*
- Female*
- History of PONV*
- Non-smoker*
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N_2O, opioids, volatile agents

*These factors refer to the Apfel tool for PONV risk stratification and management

See Landmark Anesthesiology Trials table for more information on results from the IMPACT trial which compares the efficacy of six well-established prophylactic antiemetic interventions in patients scheduled to undergo elective surgery during general anesthesia at high risk for postoperative nausea and vomiting.

See Landmark Anesthesiology Trials table for more information on results from the DREAMS trial, which details the effect of preoperative dexamethasone administration in patients with postoperative vomiting.

See Landmark Anesthesiology Trials table for more information on the BALANCEDLT trial, which compares all-cause-1 yr mortality in light vs. deep GA in patients having major surgery.

Pain Management

Definitions

- pain: an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (International Association for the Study of Pain (IASP); definition updated in 2020)
- nociception: detection, transduction, and transmission of noxious stimuli

Pain Classifications

- temporal: acute vs. chronic
- mechanism: nociceptive vs. neuropathic

Acute Pain

- pain of short duration (<6 wk) usually associated with surgery, trauma, or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

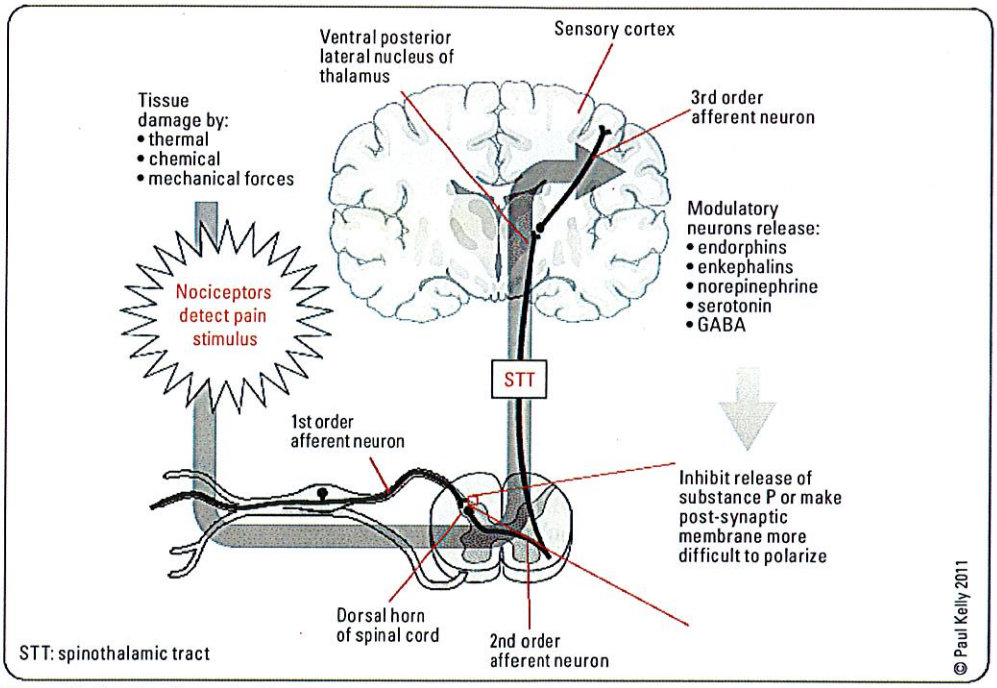


Figure 16. Acute pain mechanism

Pharmacological Management of Acute Pain

- ask the patient to rate the pain out of 10 or use visual analog scale to determine severity
- pharmacological treatment guided by WHO analgesia ladder (*Figure 17*)

Table 15. Commonly Used Analgesics

	Acetaminophen	NSAIDs	Opioids
Examples	Tylenol®	Aspirin®, ibuprofen, naproxen, ketorolac (IV)	Oral: codeine, oxycodone, morphine, hydromorphone Parenteral: morphine, hydromorphone, fentanyl
Indications	First-line for mild acute pain	Mild-moderate pain	Oral: moderate acute pain Parenteral: moderate-severe acute pain
Mechanism of Action	Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition Unclear, hypothesized modulation of endogenous cannabinoid system	Non-selective COX-1 and -2 inhibition reducing proinflammatory prostaglandin synthesis	Dampens nociceptive transmission between 1st and 2nd order neurons in the dorsal horn Activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters Inhibits peripheral inflammatory response and hyperalgesia Affects mood and anxiety – alleviates the affective component of perceived pain
Dosing/ Administration	Limited by analgesic ceiling beyond which there is no additional analgesia Opioid-sparing Max dose of 4 g/24 h	Limited by analgesic ceiling beyond which there is no additional analgesia Opioid-sparing Significant inter-individual variation in efficacy	No analgesic ceiling (except for codeine) Can be administered intrathecally (e.g. spinal block) or by continuous infusion Consider breakthrough dose and/or co-administration with anti-emetics, laxatives

Comparison of Intraoperative Sedation with Dexmedetomidine vs. Propofol on Acute Postoperative Pain in Total Knee Arthroplasty under Spinal Anesthesia: A Randomized Trial
Anesth Analg 2019;129:1512-1518
Purpose: Compare the postoperative analgesic effect of intraoperative sedation with dexmedetomidine (DEX) vs. propofol.
Methods: Patients (n=48) were randomly assigned to DEX or propofol. After the initial pre-determined loading dose, drug infusion rate was determined according to sedation level. Cumulative amounts of PCA fentanyl were recorded at 24-48 h postoperatively (primary outcome). The postoperative numerical rating scale for pain was assessed at 6, 12, 24, and 48 h (secondary outcome).
Results: DEX significantly reduced postoperative fentanyl consumption at all of the studies' time points. The numerical rating scale for pain was significantly lower at all time points.
Conclusion: Intraoperative DEX sedation was associated with a small but clinically important reduction in postoperative opioid use after total knee arthroplasty.

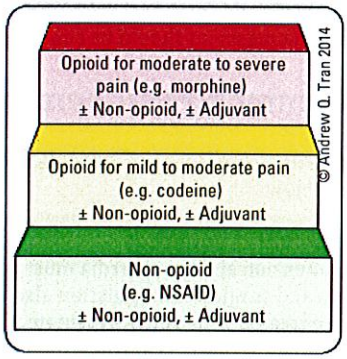


Figure 17. WHO analgesia ladder

Cautionary Use of NSAIDs in Patients with:
Asthma
Coagulopathy
GI ulcers
Renal insufficiency
Pregnancy, 3rd trimester

Table 15. Commonly Used Analgesics

	Acetaminophen	NSAIDs	Opioids
Side Effects/ Toxicity	Considered relatively safe Liver toxicity in elevated doses	Gastric ulceration/bleeding Decreased renal perfusion Photosensitivity Premature closure of the ductus arteriosus in pregnancy	Respiratory depression Constipation and abdominal pain Urinary retention Sedation N/V Pruritus Confusion (particularly in the elderly) Dependence

Table 16. Opioids

Agent	Relative Dose to Morphine 10 mg IV	Moderate Dose	Onset	Duration	Special Considerations
Codeine	100 mg IV 200 mg PO	15-30 mg PO	Late (30-60 min)	Moderate (4-6 h)	Primarily postoperative use, not for IV use Not ideal, as analgesic effect depends on highly variable CYP2D6 metabolism
Meperidine (Demerol®)	75 mg IV	2-3 mg/kg IV	Moderate (10 min)	Moderate (2-4 h)	Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures Decreased use for pain management due to potential toxicity compared to other opioids. Typically reserved to treat postoperative shivering. Absolute contraindication in patients taking MAO-inhibitors
Morphine	10 mg IV 30 mg PO	0.2-0.3 mg/kg IV 0.4-0.6 mg/kg PO	Moderate (5-10 min)	Moderate (4-5 h)	Histamine release leading to decrease in BP
Morphine Extended Release (e.g M-Eslon®, MS Contin®)	20 mg PO	5-20 mg PO	Late	Long	Do not split, crush, or chew tablet
Oxycodone Controlled Release (Oxyneo®)	20 mg PO	10-20 mg PO (no IV)	Late (30-45 min)	Long (8-12 h)	Do not split, crush, or chew tablet (but can be difficult to swallow)
Oxycodone Regular Tablet (Oxy IR®)	20 mg PO (no IV)	5-15 mg PO	Moderate (15 min)	Moderate (3-6 h)	Percocet® = oxycodone 5 mg + acetaminophen 325 mg
Hydromorphone (Dilaudid®)	1.5-2.0 mg IV 6-8 mg PO	40-60 µg/kg IV 2-4 mg PO	Moderate (15 min)	Moderate (4-5 h)	Less pruritus, N/V, and sedation compared to morphine
Hydromorphone Extended Release (e.g. Hydromorph Contin)	4.0-6.0 mg PO	3-12 mg PO	Late (30-45 min)	Long	Do not split, crush or chew tablet
Fentanyl	100 µg IV	2-3 µg/kg IV	Rapid (<5 min)	Short (0.5-1 h)	Transient muscle rigidity in very high doses
Remifentanil	100 µg IV	0.5-1.5 µg/kg IV	Rapid (1-3 min)	Ultra short (<10 min)	Only use during induction and maintenance of anesthesia
Methadone (opioid agonist)	Morphine to methadone conversion is variable based on patient's morphine dose. Ranges from 1/4 to 1/20	15-40 mg/d in divided doses	Rapid (8 min)	15-90 h (24 h average)	Can only be prescribed by federally/ provincially licensed physicians and nurse practitioners Acts through both NMDA and µ-opioid receptors Challenging due to variable equianalgesic dose and half-life After titration, accumulates in tissue for once/twice daily dosing Metabolized by CYP3A4 Caution with high doses, may cause QT prolongation, baseline ECG required
Buprenorphine (opioid agonist antagonist)	Varies depending on route of administration (pill/film, transdermal)	Film: 2 mg up to max of 24 mg	Moderate-to-severe (30 min)	6-8 h	For moderate to severe chronic pain and opioid addiction Ceiling effect for respiratory depression but not analgesia High affinity to µ-opioid receptors, very resistant to reversal with opioid antagonists

In general, parenteral route is 2-3x more potent than oral

Opioid Conversion

	Parenteral (IV)	Equivalent Oral Dose
Morphine	10 mg	30 mg
Hydromorphone	2 mg	4 mg
Codeine	120 mg	200 mg
Oxycodone	N/A	20 mg
Fentanyl	100 µg	N/A

Patient Controlled Analgesia

- use of computerized pumps to deliver a constant infusion and bolus breakthrough doses of parenterally-administered opioid analgesics
- limited by lockout intervals
- most commonly used agents: morphine and hydromorphone
- see *Table 17, A27* for suggested infusion rate, PCA dose, and lockout intervals

PCA Parameters

Loading dose
Bolus dose
Lockout interval
Continuous infusion (optional)
Maximum 4h dose (limit)

Advantages of PCA

Improved patient satisfaction
Fewer side effects
Accommodates patient variability
Accommodates changes in opioid requirements

Table 17. Opioid PCA Doses

Agent	PCA Dose	PCA Lockout Interval	PCA 4 h Maximum
Morphine	1-2 mg	5 min	30 mg
Hydromorphone	0.2-0.4 mg	5 min	10 mg
Fentanyl	25-50 µg	5 min	400 µg

Opioid Antagonists (naloxone, naltrexone)

- indication: opioid overdose (manifests primarily at CNS, e.g. respiratory depression)
- mechanism of action: competitively inhibit opioid receptors, predominantly µ-opioid receptors
  - naloxone is short-acting ($t_{1/2}$ = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
  - naltrexone is longer acting ($t_{1/2}$ = 10 h); less likely to see return of opioid effects
- side effects: relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, HTN, re-emergence of pain, pulmonary edema, and seizures (essentially opioid withdrawal)

Neuropathic Pain

- see Neurology, N43

Chronic Pain

- chronic pain: pain greater than 3 mo, or recurrent pain that occurs at least 3 times throughout 3 mo period
- pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
- in the perioperative period, consider continuing regular long-acting analgesics and augmenting with regional techniques, adjuvants, additional opioid analgesia, and non-pharmacological techniques (e.g. mindfulness, physiotherapy, acupuncture)

Central Sensitization

- central sensitization: hyperalgesia (i.e. increased sensitivity to pain) as a result of CNS mechanisms
- may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
- plays a role in fibromyalgia

Chronic Post-Surgical Pain

- pain that develops after surgery and persists for at least 2 mo
- primary predictor is history of chronic pain; other risk factors include female gender, surgical procedure/approach, poor social supports, catastrophizing behaviour

Obstetrical Anesthesia

Anesthesia Considerations in Pregnancy

- **airway**
  - possible difficult airway as tissues becomes edematous and friable, especially in labour
- **respiratory system**
  - decreased FRC and increased O_2 consumption cause more rapid desaturation during apnea
- **cardiovascular system**
  - increased blood volume > increased RBC mass results in mild anemia
  - decreased SVR proportionately greater than increased CO results in decreased BP
  - prone to decreased BP due to aortocaval compression (supine hypotensive syndrome) – a pregnant patient is positioned in left uterine displacement (approximately 15° - angle) using a wedge under right flank when supine
- **central nervous system**
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- **gastrointestinal system**
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration; therefore, for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity

Options for Analgesia during Labour

- psychoprophylaxis – Lamaze method
  - patterns of breathing and focused attention on fixed object



Patient Controlled Opioid Analgesia vs. Non-Patient Controlled Opioid Analgesia for Postoperative Pain
Cochrane DB Syst Rev 2015:CD003348
Purpose: To evaluate the efficacy of patient controlled analgesia (PCA) vs. non-patient controlled opioid analgesia of as-needed opioid analgesia for postoperative pain relief.
Methods: Meta-analyses of RCTs comparing PCA vs. conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay, and adverse side effects.
Results: 49 studies with a total of 1725 patients receiving PCA and 1687 patients assigned to a control group. PCA had a lower VAS pain intensity score vs. non-patient controlled analgesia over most time intervals in the first 48 h. PCA was associated with higher patient satisfaction and consumed higher amounts of opioids than controls. PCA was also associated with higher incidence of pruritus but not other adverse events.
Conclusions: Moderate to low quality evidence that PCA is an efficacious alternative to non-patient controlled systemic analgesia for postoperative pain control.



Nociceptive Pathways in Labour and Delivery
Labour
Cervical dilation and effacement stimulates visceral nerve fibres entering the spinal cord at T10-L1
Delivery
Distention of lower vagina and perineum causes somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4



Epidural vs. Non-Epidural or No Analgesia for Pain Management in Labour
Cochrane DB Syst Rev 2018:CD000331
Purpose: To assess effectiveness and safety of all types of epidural analgesia when compared with non-epidural or no pain relief during labour.
Methods: Systematic review of RCTs comparing epidural with any form of pain relief not involving regional blockade, or no pain relief in labour.
Results: 52 studies involving over 11000 women were included; 34 studies compared epidural analgesia with opioids. Epidural analgesia was associated with lower pain intensity, higher satisfaction, and decreased need for additional pain relief vs. opioids. While it was also associated with increased risk of assisted vaginal birth (RR 1.44, 95% CI 1.29-1.60), post-hoc analysis of studies conducted after 2005 eliminates this risk (RR 1.19, 95% CI 0.97-1.46). Women with epidural analgesia experienced more hypotension, motor blockage, fever, and urinary retention with less risk of respiratory depression and nausea/vomiting. There was no difference in neonatal outcomes, admission to NICU, caesarean section rates, or maternal long-term backache.
Conclusions: Epidural analgesia may be more effective in reducing pain during labour and increasing maternal satisfaction than non-epidural methods and, when considering modern approaches, is not associated with increased instrumentation. Epidural analgesia had no impact on the risk of caesarean section or long-term backache, and did not appear to have an immediate effect on neonatal status as determined by Apgar scores or in admissions to NICU.

- systemic medication
  - easy to administer, but risk of maternal or neonatal respiratory depression
  - opioids most commonly used if delivery is not expected within 4 h; fentanyl can be considered
- inhalational analgesia
  - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  - nitrous oxide 50% is insufficient alone but good safety profile for mother and child
- neuraxial anesthesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

Options for Cesarean Section

- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade (see *Regional Anesthesia, Epidural and Spinal Anesthesia, A21*)

Pediatric Anesthesia

Respiratory System

- in comparison to adults, anatomical differences in infants include:
  - large head, short trachea/neck, large tongue, larynx positioned more superior and anterior, adenoids, and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U-shaped and angled at 45°; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include:
  - faster respiratory rate, immature respiratory centres that are depressed by hypoxia/hypercapnia (airway closure occurs in the neonate at the end of expiration)
  - less O_2 reserve during apnea – decreased total lung volume, vital capacity, and FRC together with higher metabolic needs
  - to increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume
  - neonate: 30-40 breaths/min
  - age 1-13: (24 – [age/2]) breaths/min
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm, and higher resistance to airflow

Cardiovascular System

- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume is lost
- children have a high HR and low BP
- CO is dependent on HR, not SV because of low heart wall compliance; therefore, bradycardia severely compromises CO

Temperature Regulation

- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases, and warming of infused solutions

Central Nervous System

- MAC of halothane is increased compared to the adult (0.75% adult, 1.2% infant, 0.87% neonate)
- NMJ is immature for the first 4 wk of life, and thus, there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathetics mature at 4-6 mo; thus, there is an autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

Glucose Maintenance

- infants <1 yr can become seriously hypoglycemic during preoperative fasting and postoperatively if feeding is not recommenced as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

Pharmacology

- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB

Techniques for Preventing Hypotension During Spinal Anaesthesia for Cesarean Section
Cochrane DB Syst Rev 2017;8:CD002251
Purpose: To assess the effects of prophylactic interventions for maternal hypotension following spinal anesthesia for caesarean section.
Methods: Searched Cochrane Pregnancy and Childbirth's Trials Register and reference lists. Included RCTs comparing interventions to prevent hypotension with placebo or alternative treatment.
Results: 126 studies were included involving 9565 participants. Identified 3 intervention groups which were IV fluids (colloid vs. crystalloid vs. no fluid), pharmacological interventions (ephedrine vs. phenylephrine, or ondansetron vs. control), and physical interventions (lower limb compression, or lying vs. walking). All groups showed better control of hypotension with no differences between colloid vs. crystalloid, ephedrine vs. phenylephrine, or lying vs. walking. All evidence was very-low quality to low-quality.
Conclusions: While interventions such as crystalloids, colloids, ephedrine, phenylephrine, ondansetron, or lower leg compression can reduce the incidence of hypotension, none have been shown to be superior to the other.

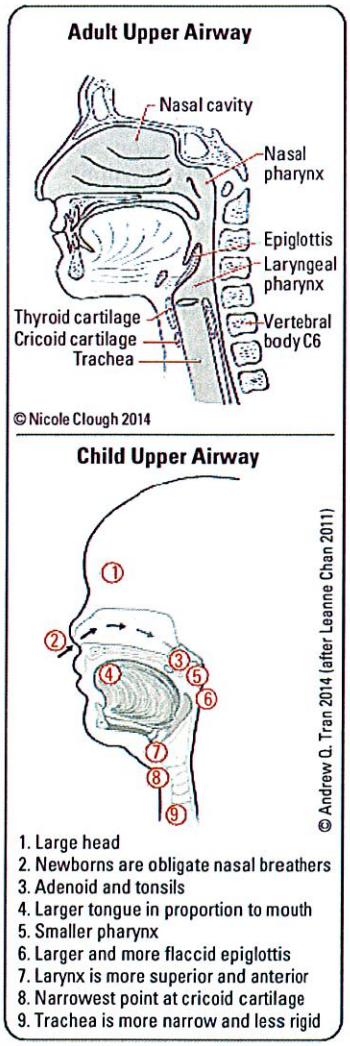


Figure 18. Comparison of pediatric vs. adult airway

See Landmark Anesthesiology Trials table for more information on the WOMAN trial, which determines the effects of early tranexamic acid administration on death, hysterectomy, and other relevant outcomes in women with postpartum hemorrhage.

- muscle relaxants
  - non-depolarizing
    - immature NMJ, variable response
  - depolarizing
    - must pre-treat with atropine or may experience profound bradycardia and/or sinus node arrest due to PNS > SNS (also dries oral secretions)
    - more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm, and malignant hyperthermia

ETT Sizing in Pediatrics
Diameter (mm) of tracheal tube in children after 1 year = (age/4) + 4
Length (cm) of tracheal tube = (age/2) + 12

See Landmark Anesthesiology Trials table for more information on a study by Sun et al., 2016 , which details the association between a single general anesthesia exposure prior age 36 months and neurocognitive outcomes in later childhood.

Uncommon Complications

Malignant Hyperthermia

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular Ca^{2+} (because of an anomaly of the ryanodine receptor that regulates Ca^{2+} channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant inheritance
- incidence of 1-5 in 100000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include:
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxants: SCh

Signs of Malignant Hyperthermia
unexplained rise in $ETCO_2$
increase in minute ventilation
tachycardia
rigidity
hyperthermia (late sign)

Clinical Picture
- onset: immediate or hours after contact with trigger agent
  - increased O_2 consumption
  - increased $ETCO_2$ on capnograph
  - tachycardia/dysrhythmia
  - tachypnea/cyanosis
  - diaphoresis
  - HTN
  - hyperthermia (late sign)
- muscular symptoms
  - trismus (i.e. masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

Basic Principles of MH Management

"Some Hot Dude Better Get Iced Fluids Fast"
Stop all triggering agents, give 100% O_2
Hyperventilate
Dantrolene 2.5 mg/kg q5 min
Bicarbonate
Glucose and insulin
IV fluids; cool patient to 38°C
Fluid output; consider furosemide
Fast Heart [tachycardia]; be prepared to treat VT

Complications
- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

Prevention
- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications, use vapour-free equipment, use regional anesthesia if possible
- central body temp and ETCO 2 monitoring

Malignant Hyperthermia Management
Based on Malignant Hyperthermia Association of the U.S. [MHAUS] Guidelines, 2008
1. notify surgeon, discontinue volatile agents and SCh, hyperventilate with 100% O_2 at flows of 10 L/min or more, halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
   - repeat until there is control of signs of MH; up to 30 mg/kg as necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature >39°C
   - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
   - stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
   - use standard drug therapy except Ca^{2+}channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene

ALGrawany

6. hyperkalemia
   - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg, or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia and check glucose levels hourly
7. follow $ETCO_2$, electrolytes, blood gases, CK, core temperature, urine output/colour with Foley catheter, coagulation studies
   - if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce diuresis to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids, and propofol
9. transfer to ICU bed

Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- individuals with abnormal pseudocholinesterase will have prolonged muscular blockade
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors as it will cause rebound neuromuscular blockade once cholinesterase inhibitor effect is terminated)

Appendices

Difficult Tracheal Intubation in Unconscious Patient

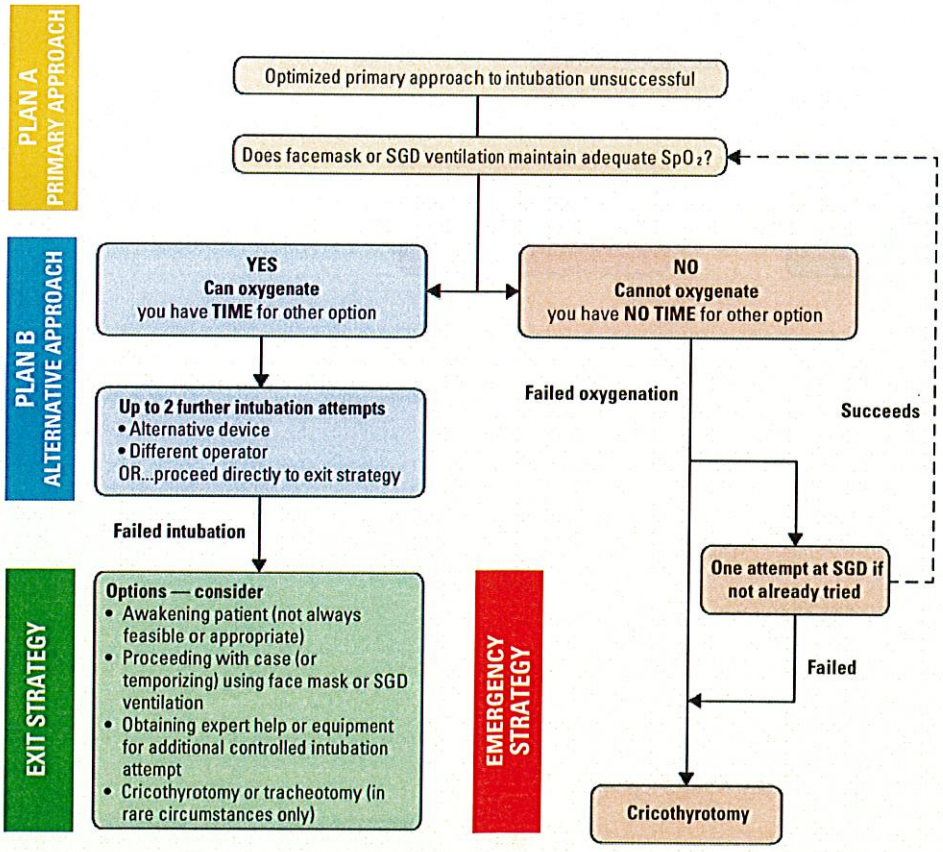


Figure 19. Difficult tracheal intubation encountered in the unconscious patient
SGD = supraglottic device

Reprinted with permission. Law JA, Broemling N, Copper RM, et al. The difficult airway with recommendations for management – Part 1 – Difficult tracheal intubation encountered in an unconscious/induced patient. Can J Anesth 2013;60:1089–1118.

Difficult Tracheal Intubation

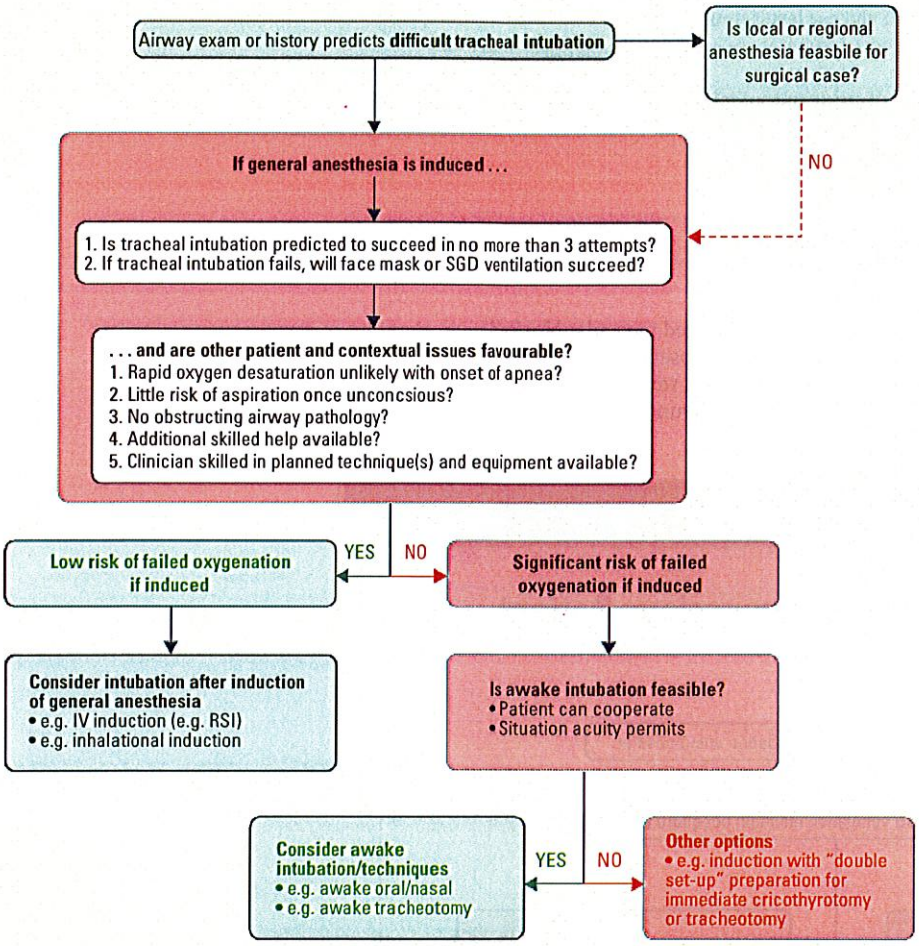


Figure 20. Anticipated difficult tracheal intubation
SGD = supraglottic device

Reprinted with permission: Law JA, Broemling N, Copper RM, et al. The difficult airway with recommendations for management – Part 2 – The anticipated difficult airway. Can J Anesth 2013;60:1119-1138.

Advanced Cardiac Life Support Guidelines

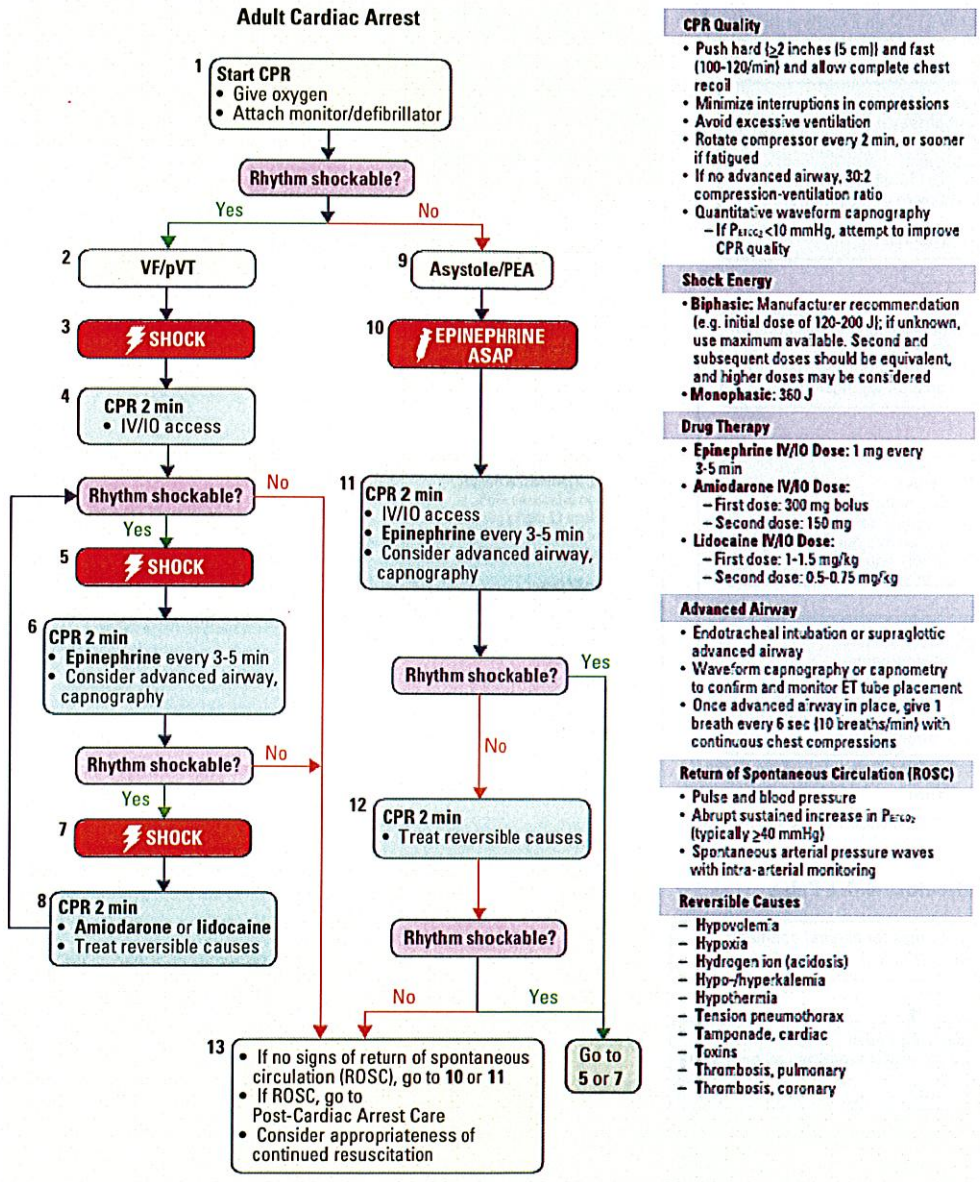


Figure 21. Adult cardiac arrest algorithm

Reprinted with permission: Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020;142:S366-S468.

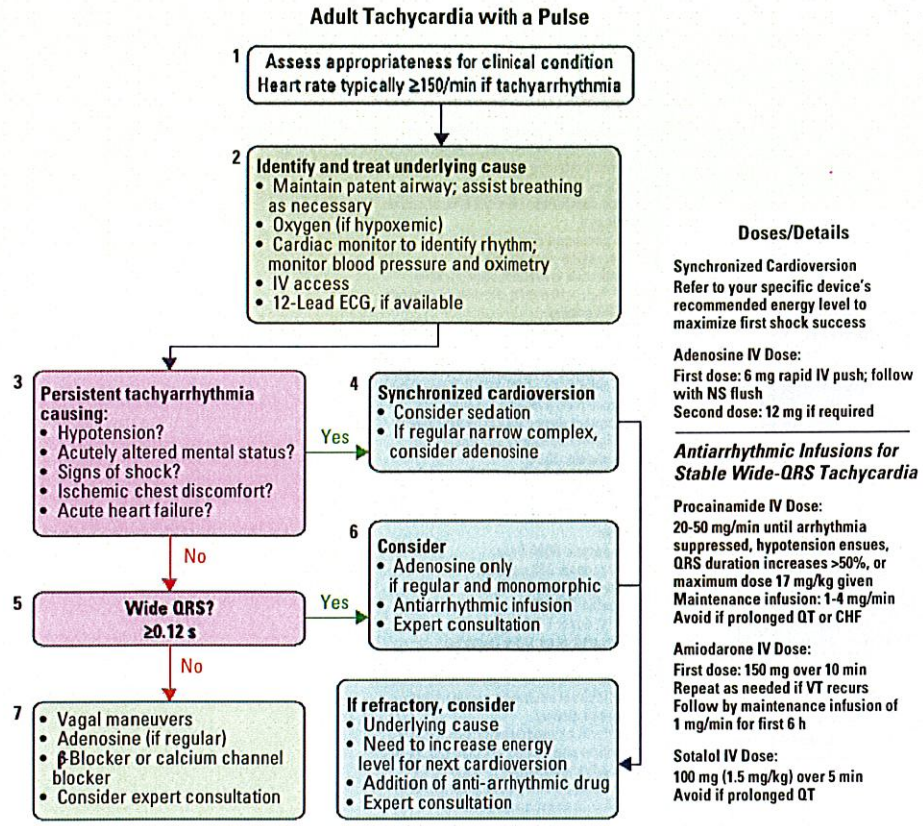


Figure 22. Adult tachycardia with a pulse algorithm

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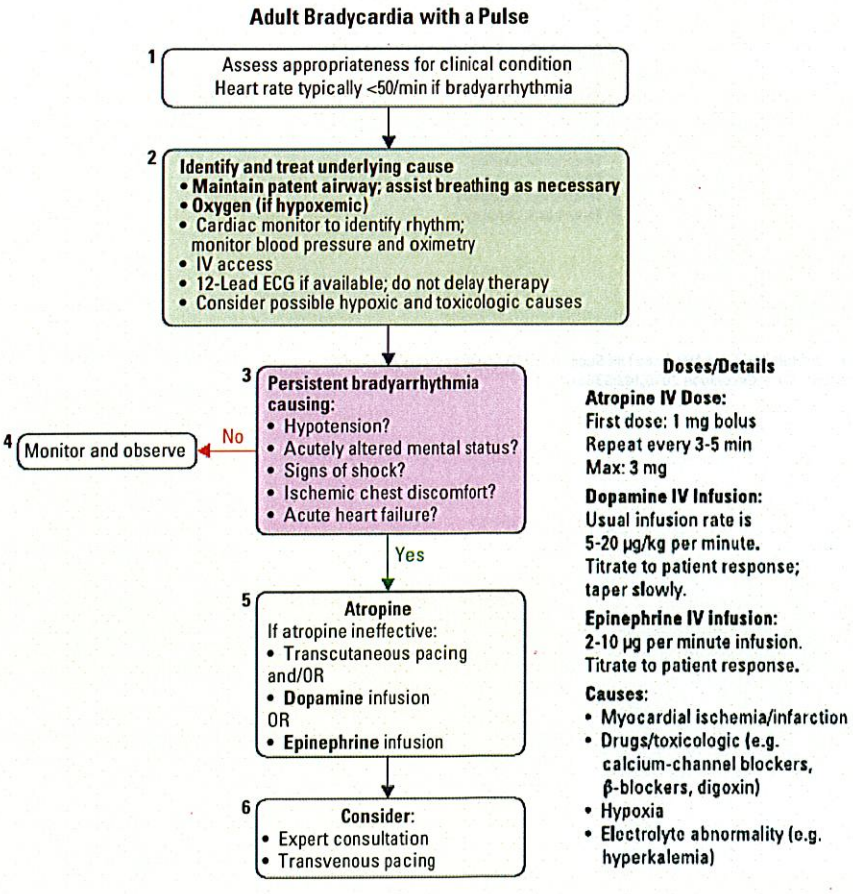


Figure 23. Adult bradycardia algorithm

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Landmark Anesthesiology Trials

Trial Name	Reference	Clinical Trial Details
INTRAOPERATIVE MANAGEMENT		
MYRIAD	NEJM 2019;380:1214-1225	**Title:** Volatile Anesthetics vs. Total Intravenous Anesthesia (TIVA) for Cardiac Surgery **Purpose:** Volatile agents have cardioprotective effects which could improve clinical outcomes in cardiac surgery patients. **Methods:** Multicenter, single-blind, controlled trial. Patients scheduled to undergo elective CABG were randomly assigned to an intraoperative anesthetic regimen that included a volatile anesthetic (desflurane, isoflurane, or sevoflurane) or to TIVA. The primary outcome was all-cause mortality at 1 yr. **Results:** A total of 5400 patients were randomized. No significant difference between the groups with respect to all-cause mortality was seen at 1 yr (2.8% in the volatile anesthetics group and 3.0% in the TIVA group; RR, 0.94; 95% CI, 0.69 to 1.29; P=0.71), or at 30 d (1.4% and 1.3%, respectively; RR, 1.11; 95% CI, 0.70 to 1.76). There were no significant differences between the groups in any of the secondary outcomes or in the incidence of prespecified adverse events, including MI. **Conclusion:** Among patients undergoing elective CABG, anesthesia with a volatile agent did not result in significantly fewer deaths at 1 yr than TIVA.
BAG-RECALL	NEJM 2011;365:591-600	
Study of Wound Infection and Temperature	NEJM 1996; 334:1209-1216	**Title:** Prevention of Intraoperative Awareness in High-Risk Surgical Population **Purpose:** To determine if EEG derived bispectral index (BIS) is superior to a protocol incorporating standard monitoring of end-tidal anesthetic-agent concentration (ETAC) for the prevention of unintended intraoperative awareness. **Methods:** Patients (n=6041) at high risk for awareness were randomly assigned to BIS-guided anesthesia or ETAC-guided anesthesia. **Results:** 0.24% of patients in the BIS group vs. 0.07% of patients in the ETAC group had definite intraoperative awareness (95% CI -0.3 to 0.38, p=0.98). There was no difference between the groups with respect to the amount of anesthesia administered or rate of major postoperative adverse outcomes. **Conclusions:** The superiority of the BIS protocol over the ETAC protocol was not established. Fewer patients in the ETAC group than the BIS group experienced awareness.
POSTOPERATIVE MANAGEMENT		
IMPACT	NEJM 2004; 350:2441-2451	**Title:** A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting **Purpose:** To compare the efficacy of six well-established antiemetic strategies and to determine the extent to which efficacy could be improved by combining two or three interventions. **Methods:** Patients (n=5199) were randomly assigned to receive prophylactic antiemetics independently, in combination or placebo. Primary outcome was nausea and vomiting within 24 h after surgery. **Results:** Ondansetron, dexamethasone, and droperidol each reduced risk of postoperative nausea and vomiting by 26%. Propofol reduced risk by 19%, and nitrogen by 12%. Relative risks associated with combined interventions could be estimated by multiplying the relative risks associated with each intervention. Absolute risk reduction was a critical function of patients' baseline risk. **Conclusion:** All interventions were similarly effective and acted independently. The safest or least expensive should be used first. Moderate-risk patients may benefit from a single intervention and high-risk patients from multiple interventions.
DREAMS	BMJ 2017;357:j1455	**Title:** Dexamethasone vs. Standard Treatment for Postoperative Nausea and Vomiting in Gastrointestinal Surgery: Randomised Controlled Trial (DREAMS Trial) **Purpose:** Whether preoperative dexamethasone reduces postoperative nausea and vomiting (PONV) in patients undergoing elective bowel surgery and whether it is associated with other measurable benefits during recovery from surgery. **Method:** Pragmatic two-arm parallel-group randomized trial with blinded postoperative care and outcome assessment. **Results:** Administration of dexamethasone 8 mg IV at induction was associated with lower rates of vomiting within 24 h of surgery (NNT=13) and reduced need for antiemetics up to 72 h (NNT=8) vs. standard of care. **Conclusions:** A single dose of dexamethasone at induction of anesthesia significantly reduces incidence of PONV and need for rescue antiemetics postoperatively with no increase in adverse events.
ENGAGES	JAMA 2019;321:473-483	**Title:** Effect of EEG-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES RCT **Purpose:** To assess whether EEG-guided anesthetic administration decreases the incidence of postoperative delirium. **Methods:** RCT of 1232 adults >60 yr old undergoing major surgery and receiving guided anesthetic. Patients randomized 1:1 to receive EEG-guided anesthetic administration or usual care. Primary outcome was incident delirium during postoperative days 1-5. **Results:** Delirium during postoperative days 1-5 occurred in 26.0% of the guided group and in 23.0% of the usual care group (P = .22). Median end-tidal volatile anesthetic concentration was significantly lower in the guided group than the usual care group, and median cumulative time with EEG suppression was significantly less (7 vs. 13 min; difference, -6.0 [95% CI, -9.9 to -2.1]). **Conclusion:** There is no difference in postoperative delirium between EEG-guided anesthetic or usual care of older adults.
COMPLICATIONS		
POISE-3	NEJM 2022;386(21):1986	**Title:** Tranexamic Acid in Patients Undergoing Noncardiac Surgery **Purpose:** To assess the efficacy of tranexamic acid in reducing bleeding in non-cardiac surgery. **Methods:** 9535 patients were randomized to receive tranexamic acid or a placebo during surgery. Life-threatening bleeding, major bleeding, and bleeding into a critical organ were assessed. **Results:** A bleeding event occurred in 433 of 4757 patients in the treatment group as opposed to 561 bleeding events in the placebo group. **Conclusion:** The use of tranexamic acid was shown to significantly reduce the number of bleeding events in non-cardiac surgery.
POISE-3	Ann Intern Med 2023;Epub ahead of print	**Title:** Hypotension-Avoidance Versus Hypertension Avoidance Strategies in Noncardiac Surgery: An International Randomized Title Trial **Purpose:** To compare the effects of a hypotension-avoidance and a hypertension-avoidance strategy on major vascular complications after noncardiac surgery. **Methods:** Patients (n=7490) having noncardiac surgery were randomly assigned to the hypotension-avoidance group (intraoperative MAP >80 mmHg, withholding of long-term antihypertensives before and after surgery) or the hypertension-avoidance group (intraoperative MAP >60 mmHg). **Results:** Within 30 days of surgery, 13.9% of the hypotension-avoidance group vs. 14.0% of the hypertension-avoidance group experienced major vascular complications (composite of vascular death and nonfatal myocardial injury, stroke, cardiac arrest) (HR 0.99, 95% CI 0.88 to 1.12, P=0.92). **Conclusion:** In patients having noncardiac surgery, there are similar incidences of major vascular complications using hypotension-avoidance and hypertension-avoidance strategies.

Trial Name	Reference	Clinical Trial Details
POISE-2	NEJM 2014;370:1504-1513	**Title:** Clonidine in Patients Undergoing Noncardiac Surgery **Purpose:** To evaluate low-dose donidine vs. placebo in patients having noncardiac surgery. **Methods:** Patients (n=10,010) with or at risk for atherosclerotic disease were randomly assigned to receive clonidine or placebo just before surgery. **Results:** Clonidine did not reduce the rate of death or nonfatal MI 30 days post-surgery. Clonidine increased clinically important hypotension (47.6% vs. 37.1%, HR 1.32, 95% CI 1.24 to 1.40, pP<0.001) and nonfatal cardiac arrest (0.3% vs. 0.1%, HR 3.20, 95% CI 1.17 to 8.73, pP=0.02). **Conclusion:** Clonidine does not reduce the rate of death and non-fatal MI, but does increase the risk of hypotension and nonfatal cardiac arrest.
POISE-2	NEJM 2014;370:1491-1503	**Title:** Aspirin in Patients Undergoing Noncardiac Surgery **Purpose:** To evaluate low-dose aspirin vs. placebo in patients having noncardiac surgery **Methods:** Patients (n=10,010) preparing to undergo noncardiac surgery and at risk for vascular complications were randomly assigned to receive aspirin or placebo. **Results:** Death and nonfatal MI occurred in 7.0% in the aspirin group and in 7.1% of patients in the placebo group (HR 0.99, 95% CI 0.86 to 1.15, pP=0.92) 30 days post-surgery. Major bleeding was more common in the aspirin group than the placebo group (4.6% vs. 3.8%, HR 1.23, 95% CI 1.01 to 1.49, P=0.04). **Conclusion:** Aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal MI but increased the risk of major bleeding.
POISE	Lancet 2008;371:1839-1847	**Title:** Effects of Extended-Release Metoprolol Succinate in Patients Undergoing Non-cardiac Surgery (POISE trial): A Randomized Controlled Trial **Purpose:** To investigate the effects of perioperative β blockers. **Methods:** Patients (n=8351) with or at risk of atherosclerotic disease having non-cardiac surgery were randomly assigned to receive extended release metoprolol succinate or placebo. **Results:** 5.8% of the metoprolol group vs. 6.9% in the placebo group had a major cardiovascular event (HR 0.84, 95% CI 0.70 to 0.99, P=0.0399). The metoprolol group had lower incidences of MI (4.2% vs. 5.7%, P=0.0017), but had higher incidences of death (3.1% vs. 2.3%, P=0.0317) and stroke (1.0% vs. 0.5%, P=0.0053). **Conclusion:** Perioperative β blockers have benefit without substantial harm. Patients are unlikely to accept the associated risks.
PROTECT	Lancet2022;399(10337):1799-1808	Ti **Title** tle: Aggressive Intraoperative Warming versus Routine Thermal Management during Non-Cardiac Surgery (PROTECT): A Multicentre, Parallel Group, Superiority Trial **Purpose:** To determine if aggressive intraoperative warming reduces major perioperative complications. **Methods:** Patients (n=5013) having non-cardiac surgery were randomly assigned to receive either aggressive warming to a target core temperature of 37°C or routine thermal management to a target of 35.5°C. **Results:** The primary outcome (MI, cardiac arrest, or mortality) occurred in 9.9% of patients in the aggressively warmed group vs. 9.6% in the routine thermal management group. The common relative risk of aggressive vs. routine thermal management was an estimated 1.04 (95% CI 0.87 to 1.27, P=0.69). **Conclusion:** The incidence of major cardiovascular complications did not differ significantly in the aggressively warmed or routine thermal management group.
GAS	Lancet 2019;393:664-677	**Title:** Neurodevelopmental Outcome at 5 Years of Age After General Anesthesia or Awake-Regional Anesthesia in Infancy (GAS): An International Multicentre, Randomized, Controlled Equivalence Trial **Purpose:** To determine if general anesthesia in early infancy affects neurodevelopmental outcomes. **Methods:** Infants (n=722) undergoing inguinal herniorrhaphy without risk factors for neurological injury were randomly assigned to receive awake-regional anesthetic or sevoflurane-based GA. **Results:** Full scale intelligence quotient score at 5 yr was 99.08 (SD 18.35) in the awake-regional anesthesia group and 98.97 (SD 19.66) in the general anesthesia group, with a difference in means (awake-regional anesthesia minus general anesthesia) of 0.23 (95% CI -2.59 to 3.06). **Conclusion:** Less than 1 hr of GA in early infancy does not alter neurodevelopmental outcome compared to awake-regional anesthesia.
BALANCEDLT	Lancet 2019;394(10212):1901-1914	**Title:** Anesthetic Depth and Complications After Major Surgery: An International, Randomized Controlled Trial **Purpose:** To compare all-cause-1 yr mortality in older patients having major surgery and randomly assigned to light (BIS target 50) or deep (BIS target 35) general anesthesia. **Methods:** Patients (n=6644) at high risk of complications after major surgery were randomly assigned to receive light general anesthesia or deep general anesthesia. **Results:** 1 yr mortality was 6.5% in the deep anesthesia group and 7.2% in the light anesthesia group (HR 0.88, 95% CI 0.73 to 1.07, absolute risk reduction 0.8%, 95% CI -0.5 to 2.0. **Conclusion:** Light anesthesia was not associated with lower 1-year mortality than deep general anesthesia.
RELIEF	NEJM 2018;378:2263-2274	**Title:** Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery **Purpose:** To assess a restrictive IV fluid strategy for patients having major abdominal surgery. **Methods:** Patients (n=3000) with an increased risk of complications were randomly assigned to receive a restrictive or liberal IV fluid regimen during and up to 24 h after surgery **Results:** The rate of disability-free survival at 1 yr was 81.9% in the restrictive fluid group and 82.3% in the liberal fluid group (HR 1.05, 95% CI 0.88 to 1.24, p=0.61). The rate of acute kidney injury was 8.6% in the restrictive fluid group and 5.0% in the liberal fluid group (P<0.001). **Conclusion:** Restrictive fluid regimen was not associated with higher.
WOMAN	Lancet 2017;389:2105-2116	**Title:** Effect of Early Tranexamic Acid Administration on Mortality, Hysterectomy, and Other Morbidities in Women with Post-Partum Hemorrhage (WOMAN): An International, Randomized, Double-blind, Placebo-controlled Trial **Purpose:** To determine the effects of early administration of tranexamic acid (TXA) on death, hysterectomy, and other relevant outcomes in women with postpartum hemorrhage. **Methods:** Patients (n=20,060) with a clinical diagnosis of postpartum hemorrhage after a vaginal birth or cesarean section were randomly assigned to receive TXA or placebo in addition to usual care. **Results:** Death due to bleeding was significantly reduced in TXA group (1.5% vs. 1.9%, RR 0.81, 95% CI 0.65 to 1.00, pP=0.045), especially if given within 3 hr of giving birth (1.2% vs. 1.7%, RR 0.69, 95% CI 0.52 to 0.91, pP=0.008). All other causes of death or thromboembolic events did not differ significant. **Conclusion:** TXA reduces death due to bleeding in women with postpartum hemorrhage and should be given as soon as possible after bleeding onset.
ENIGMA-II	Lancet 2014;384(9952):1446-1454	**Title:** The Safety of Addition of Nitrous Oxide to General Anesthesia in at-risk Patients Having a Major Non-cardiac Surgery (ENIGMA-II): A Randomized, Single-Blind Trial Purpose: To determine if nitrous oxide (NO) affects perioperative cardiovascular risk. **Methods:** Patients (n=7112) with known or suspected CAD undergoing noncardiac surgery were randomly assigned to receive NO or NO-free anesthesia. **Results:** Cardiovascular complications occurred in 8% of patients receiving NO and in 8% of patients in the NO-free group (RR 0.96, 95% CI 0.83 to 1.12, P=0.64) within 30 days of surgery. Surgical site infection (SSI) occurred in 9% of patients receiving NO and in 9% of NO-free patients (P=0.61). **Conclusions:** NO did not increase the risk of death, cardiovascular complications, or SSI in major noncardiac surgery.

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C

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Acronyms

A	atrium
AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ACEI	angiotensin converting enzyme inhibitor
ACLS	advanced cardiovascular life support
ACS	acute coronary syndrome
ACT	activated clotting time
AFib	atrial fibrillation
AKI	acute kidney injury
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARNI	angiotensin receptor-neprilysin inhibitor
AS	aortic stenosis
ASA	acetylsalicylic acid (Aspirin®)
ASCVD	atherosclerotic cardiovascular disease
ASD	atrial septal defect
AV	atrioventricular
AVNRT	atrioventricular nodal re-entrant tachycardia
AVR	aortic valve replacement
AVRT	atrioventricular reciprocating tachycardia
BIMA	bilateral internal mammary artery
BBB	bundle branch block
BNP	brain natriuretic peptide
BPM	beats per minute
BiVAD	biventricular assist device
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCB	calcium channel blocker
CHD	coronary heart disease
CM	cardiomyopathy
CMR	cardiovascular magnetic resonance imaging
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CRT	cardiac resynchronization therapy
CRT-P	cardiac resynchronization therapy pacemaker
CRT-D	cardiac resynchronization therapy defibrillator
CV	cardiovascular
CVP	central venous pressure
DCM	dilated cardiomyopathy
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECASA	enteric coated ASA
ECMO	extracorporeal membrane oxygenation
EDP	end diastolic pressure
EF	ejection fraction
EPS	electrophysiology studies
FEV1	forced expiratory volume in the first second
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFSS	heart failure survival score
HOCM	hypertrophic obstructive cardiomyopathy
HTN	hypertension
ICD	implantable cardioverter-defibrillator
IE	infective endocarditis
IMA	internal mammary artery
ITA	internal thoracic artery
JVP	jugular venous pressure
LA	left atrium
LAD	left anterior descending artery
LAE	left atrial enlargement
LBB	left bundle branch
LBBB	left bundle branch block
LCA	left coronary artery
LCC	left coronary cusp
LCx	left circumflex artery
LIMA	left internal mammary artery
LITA	left internal thoracic artery
LLSB	left lower sternal border
LMWH	low molecular weight heparin
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
MAP	mean arterial blood pressure
MAT	multifocal atrial tachycardia
MI	myocardial infarction
MPI	myocardial perfusion imaging
MR	mitral regurgitation
MS	mitral stenosis
MVD	multivessel coronary artery disease
MVP	mitral valve prolapse
MUGA	multigated acquisition scan
NSR	normal sinus rhythm
NSTEMI	non-ST elevation myocardial infarction
NYHA	New York Heart Association
OMT	optimal medical therapy
OPCAB	off-pump coronary artery bypass
OS	opening snap
PAC	premature atrial contraction
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PCWP	pulmonary capillary wedge pressure
PDA	posterior descending artery
PE	pulmonary embolism
PEA	pulseless electrical activity
PFO	patent foramen ovale
PIV	posterior interventricular artery
PMI	point of maximal impulse
PND	paroxysmal nocturnal dyspnea
PR	pulmonary regurgitation
PS	pulmonary stenosis
PT	pulmonary trunk
PTCA	percutaneous transluminal coronary angioplasty
PUD	peptic ulcer disease
PVC	premature ventricular contraction
PVD	peripheral vascular disease
PVR	pulmonary vascular resistance
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RAE	right atrial enlargement
RBB	right bundle branch
RBBB	right bundle branch block
RCA	right coronary artery
RCC	right coronary cusp
RCM	restrictive cardiomyopathy
RIMA	right internal mammary artery
RITA	right internal thoracic artery
RLSB	right lower sternal border
RF	radiofrequency
RV	right ventricle
RVAD	right ventricular assist device
RVH	right ventricular hypertrophy
RVOT	right ventricular outflow trunk
SA	sinoatrial
SAM	systolic anterior motion
SAVR	surgical aortic-valve replacement
SCD	sudden cardiac death
SEM	systolic ejection murmur
SGLT2	sodium-glucose cotransporter 2
SNS	sympathetic nervous system
SOBOE	shortness of breath on exertion
STEMI	ST elevation myocardial infarction
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
SYNTAX	synergy between percutaneous coronary intervention with taxus and cardiac surgery
TAVI	transcatheter aortic-valve implantation
TAVR	transcatheter aortic-valve replacement
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TR	tricuspid regurgitation
TS	tricuspid stenosis
TTE	transthoracic echocardiography
UA	unstable angina
V	ventricle
VAD	ventricular assist device
VFib	ventricular fibrillation
VHD	valvular heart disease
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
WPW	Wolff-Parkinson-White

Basic Anatomy Review

Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the aortic sinuses of Valsalva which penetrate the root of the aorta
  - RCA:
    - conus artery
    - acute marginal branches
    - AV nodal artery
    - PDA or PIV
  - LCA:
    - LAD
      - septal branches
      - diagonal branches
    - LCx
      - obtuse marginal branches
- dominance of circulation
  - determined by whether the RCA or the LCx supplies the PDA
    - right-dominant circulation: PDA and at least one posterolateral branch arise from RCA (80%)
    - left-dominant circulation: PDA and at least one posterolateral branch arise from LCx (15%)
    - balanced circulation/codominant: dual supply of posteroinferior LV from RCA and LCx (5%)
- the SA node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- the AV node is supplied by the AV nodal artery, which may arise from the RCA (90%) or LCx (10%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through Thebesian veins into all four chambers, contributing to the physiologic R-L shunt

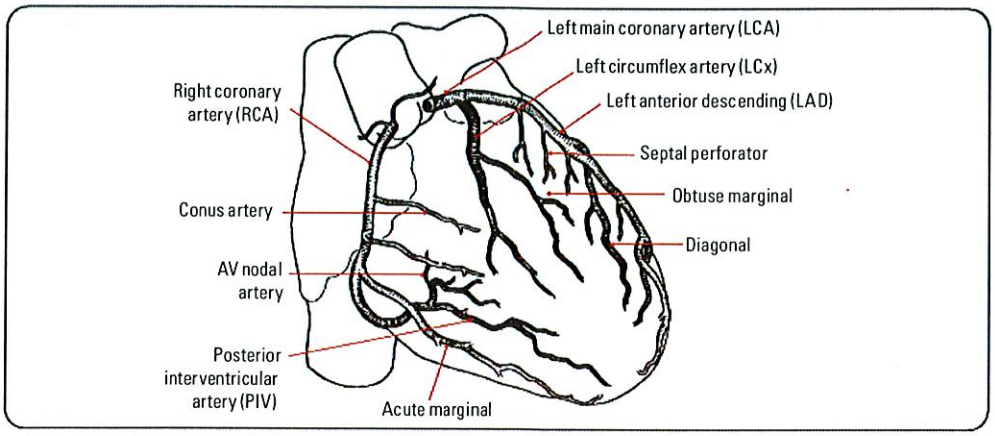


Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)

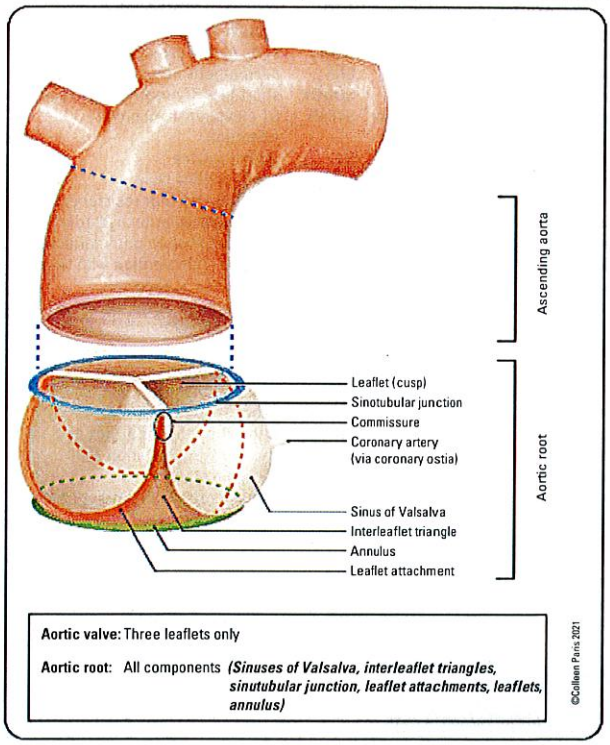


Figure 2a. Aortic root

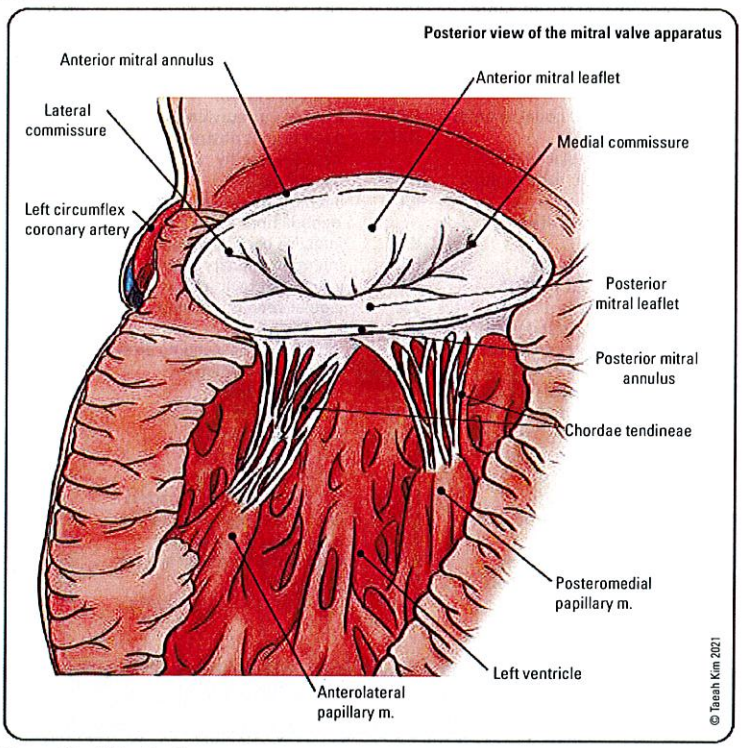


Figure 2b. Mitral valve apparatus

Modified from Sievers H-H, Hemmer W, The everyday used nomenclature of the aortic root components: the tower of Babel?, European Journal of Cardio-Thoracic Surgery, 2012, 41, 3, 478-82, by permission of Oxford University Press

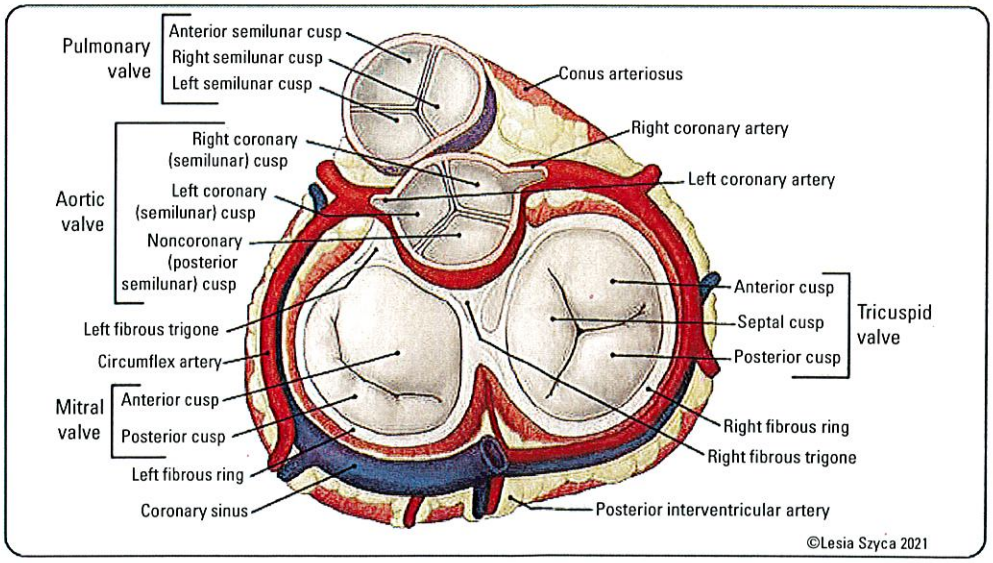


Figure 2c. Fibrous skeleton of the heart

ALGrawany

Cardiac Anatomy

- layers of the heart
  - endocardium, myocardium, epicardium, visceral pericardium, pericardial cavity, parietal pericardium
- valves
  - semilunar valves: 3 leaflets separating outflow tracts from the great arteries
    - aortic valve: noncoronary cusp, LCC, RCC; RCC and LCC have coronary ostia; separates LVOT and ascending aorta
    - pulmonary valve: anterior cusp, left cusp, right cusp; separates RVOT and PT
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendineae and papillary muscles
    - mitral valve: anterior (2/3 valve area, 1/3 valve circumference) and posterior leaflets (1/3 valve area, 2/3 valve circumference); separates LA and LV
    - tricuspid valve: anterior, posterior, and septal leaflets; separates RA and RV
- conduction system
  - SA node
    - located at the junction of the crista terminalis at the opening of the SVC at the roof of the RA
    - governs pace-making; heartbeat originates here
    - anterior-, middle-, and posterior-internal nodal tracts carry impulses in the RA with the atrial impulses converging at the AV node and along Bachmann's bundle in the LA
  - AV node
    - located within the triangle of Koch which is demarcated by: superior margin of the coronary sinus, tendon of Todaro, and hinge of the septal leaflet of the tricuspid valve
    - AV node is the conduit for electrical impulses from atria to ventricles, unless an accessory AV pathway (e.g. WPW syndrome) is present
  - bundle of His
    - AV node connects to the bundle of His, which divides into LBB and RBB
      - LBB further splits into anterior and posterior fascicles
      - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium

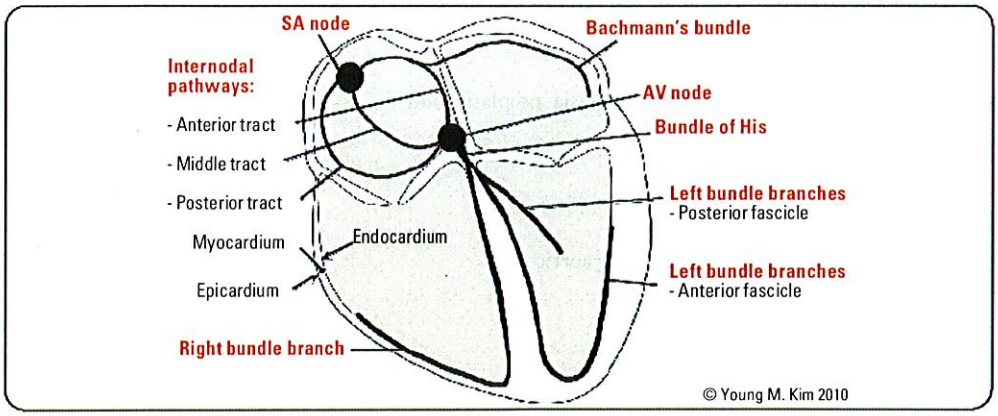


Figure 3. Conduction system of the heart

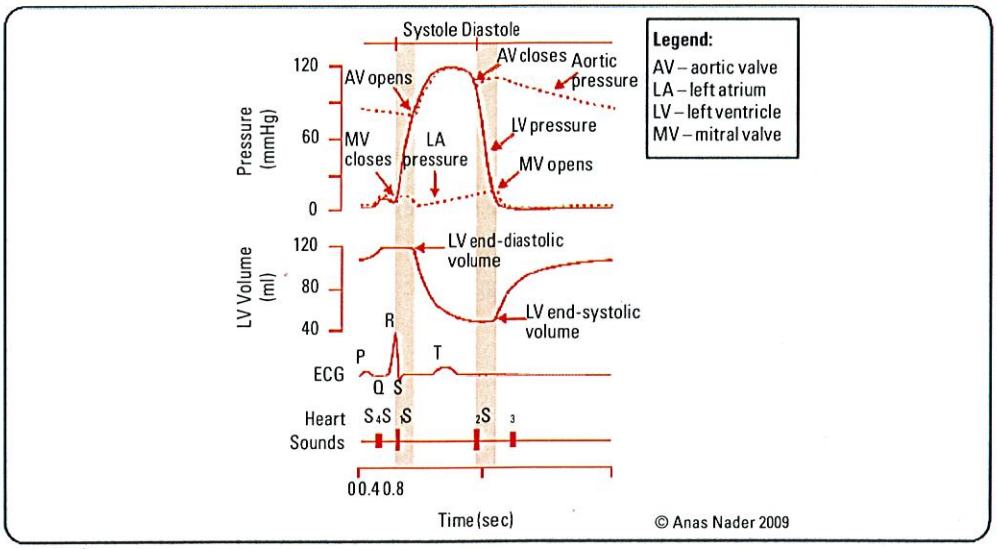


Figure 4. Cardiac cycle
Grey shaded bars indicate isovolumic contraction (left) and isovolumic relaxation (right)

- cardiovascular innervation
  - sympathetic nerves
    - innervate the SA node, AV node, ventricular myocardium, and vasculature
    - increased activity of the SA node via the β1 receptor leads to increased HR via more frequent impulses from pacemaking cells (increased chronotropy - increased HR)
    - cardiac muscle (β1) fibres increase contractility (inotropy - leads to increased SV)
    - stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
  - parasympathetic nerves
    - innervate the SA node, AV node, and atrial myocardium but few vascular beds
    - at rest, vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node, resulting in slow AV conduction, and consequently a prolonged PR interval or second or third degree AV block (i.e. reduced dromotropy (if only affecting AV node conduction))
    - parasympathetics have very little impact on total peripheral vascular resistance

Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, underlined text indicates life threatening condition

Chest Pain

- often described as pressure, heaviness, discomfort
  - note: ischemic pain is usually dull and diffuse while chest wall and pericardial pain are often sharp, localized, and worse on inspiration (i.e. pleuritic)
- cardiac
  - MI, stable myocardial ischemia (angina), myocarditis, and pericarditis/Dressler's syndrome, tamponade, and aortic valve disease
- pulmonary
  - PE, pneumothorax/hemothorax, tension pneumothorax, pneumonia, empyema, pulmonary neoplasm, bronchiectasis, pleuritis, asthma, COPD, sarcoidosis, pulmonary hypertension, and tuberculosis
- gastrointestinal
  - esophageal: **GERD**, esophageal rupture, spasm, esophagitis, ulceration, achalasia, neoplasm, and Mallory-Weiss syndrome
  - other structures: PUD, gastritis, pancreatitis, and biliary colic
- mediastinal
  - lymphoma, thymoma
- vascular
  - acute aortic syndrome: aortic dissection, intramural hematoma, penetrating aortic ulcer
- drug use: methamphetamine or cocaine intoxication
- surface structures
- costochondritis
- rib fracture
- skin (bruising, herpes zoster)
- breast
- anxiety/psychosomatic
- referred pain
- trauma

Loss of Consciousness

1. causes of true syncope (impaired cerebral perfusion)
- reflex mediated/reflex dysfunction
  - vasovagal (most common; also known as reflex mediated syncope, neurocardiogenic syncope)
  - situational (micturition, cough, carotid hypersensitivity)
  - autonomic dysfunction (often associated with neurologic diseases)
  - postural hypotension (e.g. central nervous system disorders, antihypertensive drugs)
- inadequate circulating volume (bleeding, hypovolemia with orthostasis)
- obstruction to blood flow
  - tamponade
  - pulmonary embolism
  - severe pulmonary HTN
  - severe obstructive valve disease (MS and AS)
  - left ventricular outflow obstruction (HCM)
  - cerebrovascular events (e.g. cerebrovascular accident)
- arrhythmia leading to sudden loss of CO
  - tachyarrhythmia, (e.g. AFib, SVT, VT, VFib)
  - severe bradycardia (sinus arrest, AV block)

2. loss of consciousness NOT due to impaired cerebral perfusion
- seizure
- hypoglycemia
- severe hypoxia or hypercarbia
- psychiatric
- head trauma

Local Edema

- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis, venous insufficiency, chronic lymphangitis, lymphatic tumour infiltration, filariasis
- inflammation/infection
- trauma

Generalized Edema

- increased hydrostatic pressure/fluid overload
  - HF, pregnancy, drugs (e.g. CCBs), iatrogenic (e.g. IV fluids)
- decreased oncotic pressure/hypoalbuminemia
  - **liver cirrhosis**, nephrotic syndrome, malnutrition
- increased interstitial oncotic pressure
  - myxedema
- increased capillary permeability
  - severe sepsis
- hormonal
  - hypothyroidism, exogenous steroids, pregnancy, estrogens

Palpitations

- subjective sense of abnormal/irregular heartbeats
- palpitations that may have continuous rapid heart action:
  - conditions causing sinus tachycardia: systemic (fever, inflammation, infection, neoplasm, and autoimmune conditions) endocrine (thyrotoxicosis, pheochromocytoma, and hypoglycemia), haematologic (anemia), drugs (stimulants and anticholinergics), and psychiatric (panic attacks, generalized anxiety disorder, and somatization)
  - conditions causing pathologic tachycardia: SVT (reentrant SVT, atrial tachycardia), atrial fibrillation, and atrial flutter, and VT
- palpitations that may have irregular/intermittent sensations (e.g. PACs, PVCs)

Dyspnea

- exercise
  - elevated pulmonary venous pressure
  - poor Hb-oxygen dissociation curve kinetics
- cardiovascular
  - due to elevated pulmonary venous pressure: acute MI, CHF/LV failure, aortic/mitral stenosis, AS/MS, AR/MR, arrhythmia, and left-sided obstructive lesions (e.g. left atrial myxoma)
  - due to poor cardiac output (cardiac tamponade, constrictive pericarditis, severe TR)
- respiratory
  - airway disease
    - asthma, COPD exacerbation, and upper airway obstruction (anaphylaxis, foreign body, and mucus plugging)
  - parenchymal lung disease
    - pneumonia, interstitial lung disease
  - pulmonary vascular disease
    - PE, pulmonary HTN, and pulmonary vasculitis
  - pleural disease
    - pneumothorax, pleural effusion
- neuromuscular and chest wall disorders
  - cervical spine injury
    - polymyositis, myasthenia gravis, Guillain-Barré syndrome, and kyphoscoliosis
- anxiety/psychosomatic
- hematological/metabolic
  - anemia, acidosis, and hypercapnia

Cardiac Diagnostic Tests

Electrocardiography Basics

Description

- a graphical representation (amplitude of electrical vector projection over time) of the heart's electrical activity
- on the ECG graph
  - the horizontal axis represents time (at usual paper speed of 25 mm/s)
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec
  - the vertical axis represents voltage (at usual standard gain setting of 10 mm/mV)
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV
  - standard leads of 12-lead ECG
    - limb (bipolar) leads: I, II, III, aVL, aVR, aVF
    - precordial (unipolar) leads: V1-V6 (V1-V2 (septal), V3-V4 (anterior), and V5-V6 (lateral))
  - additional leads
    - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
    - posterior leads: V7-V9 (useful in posterolateral infarction)
  - leads that indicate specific regions of the heart:
    - lateral wall = I, aVL, V5, V6
    - inferior wall = II, III, aVF
    - anterior wall= V1-V4

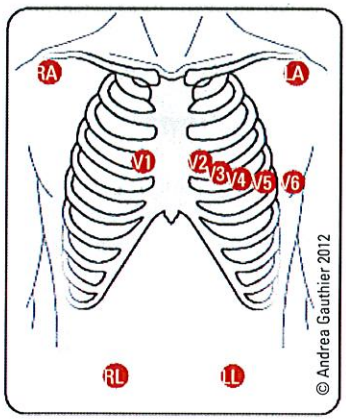


Figure 5. ECG lead placement

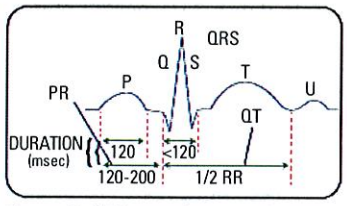


Figure 6. ECG waveforms and normal values

Indications for brief (12-lead ECG) or prolonged (24 h or more) monitoring

- myocardial injury, ischemia, or history of prior infarction
- conditions associated with palpitations or risk of serious arrhythmias (e.g. WPW, long QT, HCM, heart block, and bradycardia)
- conduction abnormalities (e.g. LBBB/RBBB)
- electrolyte abnormalities (e.g. hyperkalemia/hypokalemia)
- investigation of syncope, near syncope, or palpitations ("symptom/rhythm correlation")
- can be used for:
  - recording of cardiac rhythm during symptoms or antiarrhythmic drug monitoring
  - assessment of cardiac structure and function (e.g. RVH/LVH and cardiomyopathy)
  - detection of non-sustained arrhythmias that require prophylactic intervention

Approach to ECGs

Introduction

Below, we are presenting both the classical approach and the newer PQRSTU approach to provide students with different ways to view the ECG. Despite methodological differences, the rigor and final result is the same.

Classical Approach to ECGs

RATE

- normal = 60-100 bpm
- atrial rates above normal range:
  - 150-250 bpm = AVNRT, AVRT, AT, (sinus tachycardia)
  - 250-350 bpm = atrial flutter
  - >350 bpm = AFib (note: atrial "rate" is not discernible)
- regular rhythm (defined by equal R-R or P-P intervals between beats)
  - rate can be calculated using either of the following two methods:
    - divide 300 by the number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 s)
    - use the square counting method by counting the number of big boxes between the R waves using the following sequence of numbers: 300 (1 box)-150 (2 boxes)-100 (3 boxes)-75 (4 boxes)-60 (5 boxes)-50 (6 boxes)
- irregular rhythm
  - rate = 6 x number of R-R intervals in 10 s (a standard ECG is 10 s)
- atrial escape rhythm in case of sinus node failure = 60-80 bpm, junctional escape rhythm = 40-60 bpm, ventricular escape rhythm = 20-40 bpm



For more examples and practice visit www.ecgmadesimple.com



Classical Approach to ECG

Rate

Rhythm (defined by R-R or P-P intervals between beats)

Axis

Conduction abnormalities

Hypertrophy/chamber enlargement

Ischemia/infarction

Miscellaneous ECG changes (e.g. QT interval)



Differential Diagnosis for Left Axis Deviation

Normal variant (physiologic, often age-related change)

Left anterior hemiblock

LVH

Inferior MI

WPW

RV pacing

Elevated diaphragm

Lead misplacement

Congenital heart disease (e.g. primum ASD, endocardial cushion defect)

Hyperkalemia

Emphysema

RHYTHM

- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly irregular: repeating pattern of varying R-R intervals (e.g. Wenckebach)
- irregularly irregular: R-R intervals vary erratically (e.g. AFib, atrial flutter with variable block, VFib)
- normal sinus rhythm (NSR)
  - P wave precedes each QRS; QRS follows each P wave
  - P wave axis is normal (positive in 2 of the following 3 leads: I, II, aVF)
  - rate between 60-100 bpm

AXIS

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
  - the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane
  - normal axis: -30° to 90° (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis <-30°
  - right axis deviation (RAD): axis >90°
- QRS axis in the horizontal plane is not routinely calculated
  - transition from negative to positive is usually in lead V3

Table 1. Conduction Abnormalities

Left Bundle Branch Block (LBBB)	Right Bundle Branch Block (RBBB)
Complete LBBB QRS duration >120 msec Broad notched R waves in leads I, aVL, V5, and V6 Deep broad S waves in leads V1-2 Secondary ST-T changes (-ve in leads with broad notched R waves, +ve in V1-2) are usually present LBBB can mask ECG signs of MI LBBB: lead V1 negative, V6 positive and notched	**Complete RBBB** QRS duration >120 msec Positive QRS in lead V1 (rSR' or occasionally broad R wave) Broad S waves in leads I, V5-6 (>40 msec) Usually secondary T wave inversion in leads V1-2 Frontal axis determination using only the first 60 msec RBBB: V1 is positive (rSR'), V6 has broad S wave

Left Anterior Fascicular Block (LAFB) (Left Anterior Hemiblock)	Left Posterior Fascicular Block (LPFB) (Left Posterior Hemiblock)	Bifascicular Block
Left Axis Deviation (-30° to -90°) Small Q and prominent R in leads I and aVL Small R and prominent S in leads II, III, and aVF	**Right Axis Deviation (110° to 180°)** Small R and prominent S in leads I and aVL Small Q and prominent R in leads II, III, and aVF	**RBBB Pattern** Small Q and prominent R The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks

Nonspecific Intraventricular Block

- QRS duration >120 msec
- absence of definitive criteria for LBBB or RBBB

Table 2. Hypertrophy/Chamber Enlargement

Left Ventricular Hypertrophy	Right Ventricular Hypertrophy
S in V1 + R in V5 or V6 >35 mm above age 40, (>40 mm for age 31-40, >45 mm for age 21-30) R in aVL >11 mm R in I + S in III >25 mm Additional criteria LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, and V4-V6) Left atrial enlargement N.B. The greater the number of criteria, the more likely the diagnosis is LVH. If only one voltage criteria present, it is called minimal voltage criteria for LVH (may be a normal variant)	Right axis deviation R/S ratio >1 or qR in lead V1 RV strain pattern: ST segment depression and T wave inversion in leads V1-2
Left Atrial Enlargement	**Right Atrial Enlargement**
Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥1 mm wide and ≥1 mm deep P wave >100 msec, could be notched in lead II ("P mitrale")	P wave >2.5 mm in height in leads II, III, or aVF ("P pulmonale")

Differential Diagnosis for Right Axis Deviation

- Normal variant (vertical heart with an axis of 90°)
- RVH
- Left posterior hemiblock
- Pulmonary embolism
- COPD
- Lateral MI
- WPW
- Dextrocardia
- Septal defects

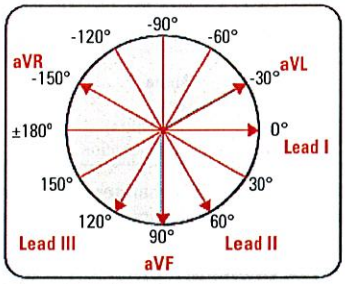


Figure 7. Axial reference system
Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead result in an upward deflection in that lead. Normal QRS axis is between -30° and +90°

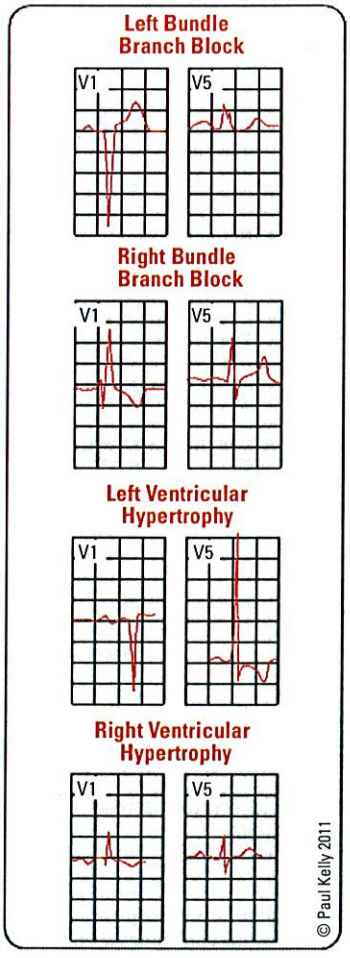


Figure 8. Complete LBBB, RBBB, LVH, and RVH (please see online examples for the full range of waveforms and the text for additional characteristics)

ISCHEMIA/INFARCTION

- look for the anatomic distribution of the following ECG abnormalities (see *Table 3*)
  - ischemia
    - ST segment depression
    - T wave inversion
  - injury/infarct
    - transmural (involving the entire wall thickness)
      - ST elevation in the leads facing the injured/infarcted area
    - subendocardial
      - marked ST depression in the leads facing the affected area
  - may be accompanied by enzyme changes (in infarction) and other signs of MI

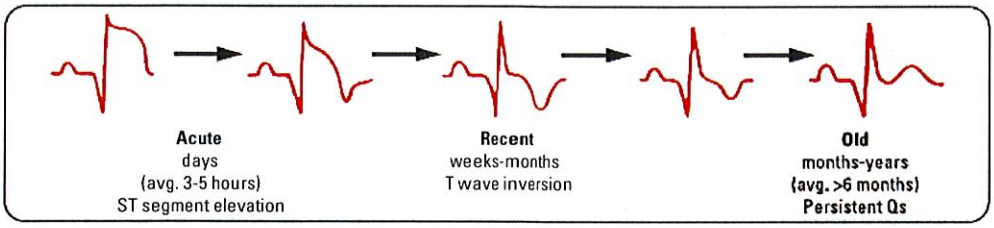


Figure 9. Typical ECG changes with infarction
Note that Q waves may gradually appear over time (not shown here)

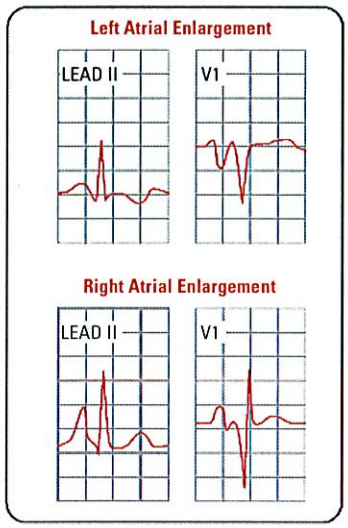


Figure 10. LAE, RAE (please see online examples and the text for characteristics)

  - ST elevation
    - new ST elevation in two contiguous leads of >0.1 mV (in all leads other than leads V2-V3)
    - for leads V2-V3: ≥0.2 mV in men ≥40 yr, ≥0.25 mV in men <40 yr, or ≥0.15 mV in women
- "typical" sequential changes of evolving MI
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
  2. ST elevation (injury pattern) in the leads facing the infarcted area
     - usually in the first hours post-infarct
     - in acute posterior MI, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads that are not recorded in the standard 12-lead ECG) hence get a 15-lead ECG
  3. significant Q waves: >40 msec or >1/3 of the total QRS amplitude and present in at least 2 consecutive leads in the same territory (hours to days post-infarct)
     - Q waves of infarction may appear in the very early stages, with or without ST changes
     - non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
  4. inverted T waves (one day to weeks after infarction)
- completed infarction
  - abnormal Q waves (Q waves may be present in lead III in normal individuals due to initial septal depolarization)
  - duration >40 msec (>30 msec in aVF for inferior infarction)
  - Q wave is >1/3 of the total QRS amplitude
  - present in at least 2 consecutive leads in the same territory
  - abnormal R waves (R/S ratio >1, duration >40 msec) in V1, and occasionally in V2, are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)

Table 3. Areas of Infarction/Ischemia (right dominant anatomy)

Vessel Usually Involved	Infarct Area (LAD and LCx)	Leads (LAD and LCx)
LAD	Anteroseptal	V1, V2
	Anterior	V3, V4
	Anterolateral	I, aVL, V3-6
	Extensive anterior	I, aVL, V1-6
RCA	Inferior	II, III, aVF
	Right ventricle	V3R, V4R (right-sided chest leads)
	Posterior MI (associated with inferior MI)	V1, V2 (prominent R waves)
LCx	Lateral	I, aVL, V5-6
	Isolated posterior MI	V1, V2 (prominent R waves)



Pacemakers

- Atrial pacemaker has discharge ("spike") prior to P wave
- Ventricular pacemaker has a pacemaker spike prior to the QRS which is usually broader with a LBBB morphology

MISCELLANEOUS ECG CHANGES

Electrolyte Disturbances

- hyperkalemia
  - mild to moderate (K +5-7 mmol/L): tall, peaked T waves
  - severe (K +>7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show abnormal morphology, axis shifts left or right, ST shift with tall T waves, eventually becomes a "sine wave" pattern
- hypokalemia
  - ST segment depression, prolonged QT interval (with risk for Torsades de Pointes VT if extreme), low T waves, prominent U waves (U>T)
  - enhances the toxic effects of digitalis

- hypercalcemia
  - shortened QT interval (more extracellular Ca^{2+} means shorter plateau in cardiac action potential)
- hypocalcemia
  - prolonged QT interval (less extracellular Ca^{2+} means longer plateau in cardiac action potential)

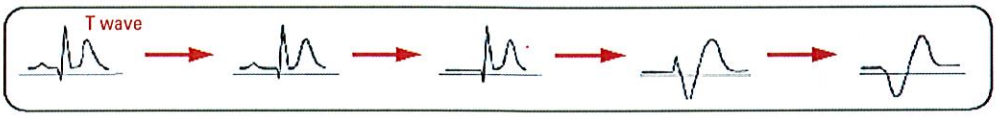


Figure 11. Hyperkalemia

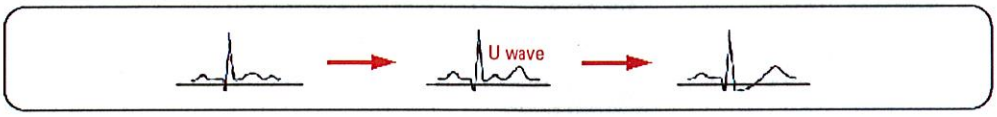


Figure 12. Hypokalemia

Hypothermia

- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves: "hump-like" waves at the junction of the J point and the ST segment

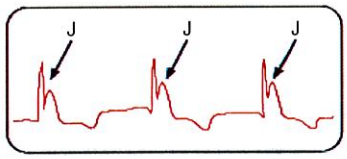


Figure 13. Osborne J waves of a hypothermic patient

Pericarditis

- early: diffuse ST segment elevation ± PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- ± tachycardia

Drug Effects

- digitalis (cardiac glycoside) poisoning rare in 2021; <1/1000 cardiac patients overall
  - therapeutic levels may be associated with "digitalis effect"
    - ST downsloping or "scooping"
    - T wave depression or inversion
    - QT shortening ± U waves
    - slowing of ventricular rate in AFib
    - most common rhythm disturbance: PVCs
  - toxic levels associated with:
    - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, VT (see *Arrhythmias, C19*)
    - "regularization" of ventricular rate in AFib due to complete heart block with junctional escape rhythm
- amiodarone, quinidine, phenothiazines, mood stabilizing medications (including tricyclic antidepressants and antipsychotics), some antihistamines, antifungals, and some antibiotics
  - prolonged QT interval, U waves

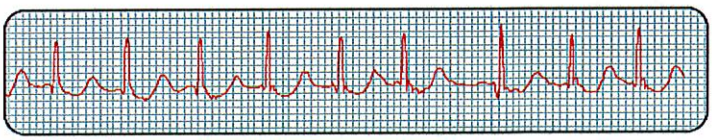


Figure 14. AFib, ST change due to digitalis ("digitalis effect")



Digitalis Side Effects
Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion, and depression

Pulmonary Disorders

- cor pulmonale (often secondary to COPD)
  - low voltage, right axis deviation (RAD), poor R wave progression in precordial leads
  - RAE and RVH with strain
  - multifocal atrial tachycardia
- massive pulmonary embolism
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain
  - most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III) but rather uncommon

Alternative PQRSTU Approach to ECGs

Note: the PQRSTU Approach is organized a different way based on the anatomy of the ECG

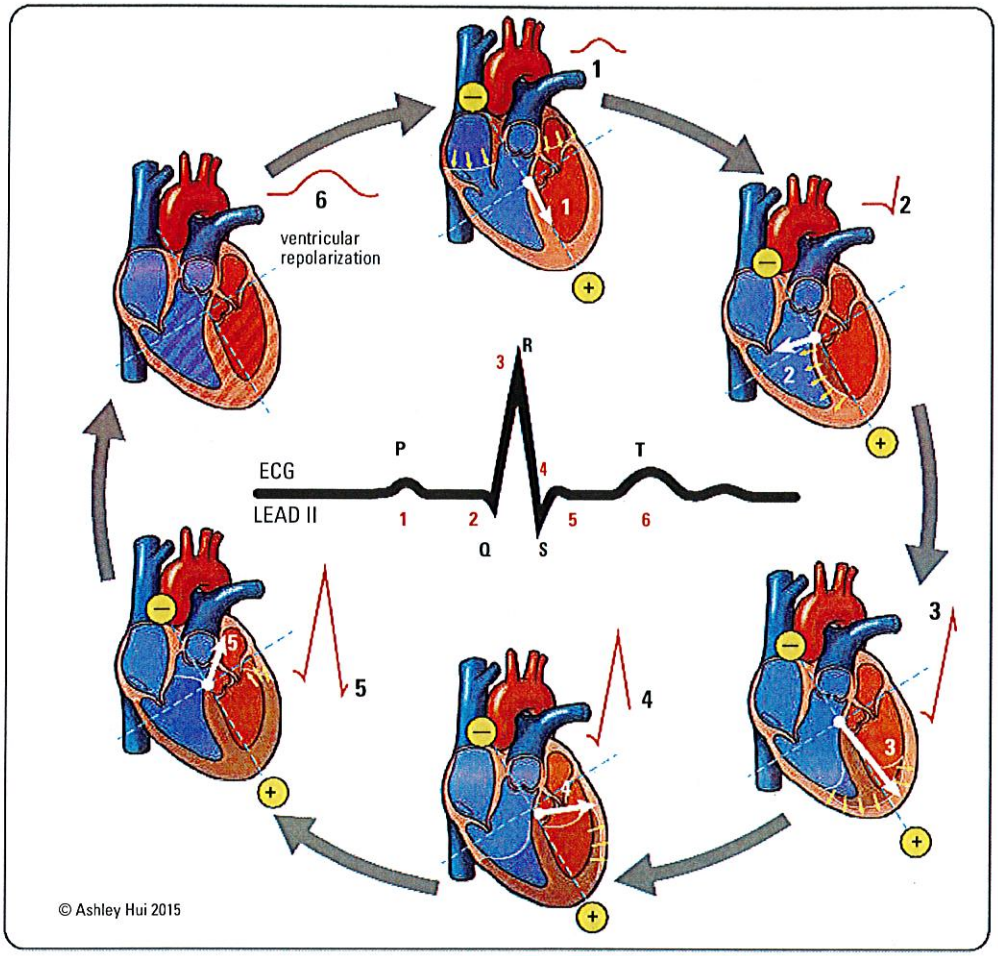


Figure 15. ECG correlations with heart activity

PQRSTU Approach to ECGs
P wave
P-R interval
QRS complex
ST segment
T wave
Q-T interval
U wave

P WAVE

- the P wave represents atrial contraction, best seen in leads: II and V1
  - lead II: the P wave should be rounded, <120 msec and <2.5 mm in height
  - lead V1: the P wave is biphasic with a positive phase, followed by a negative phase
- atrial flutter: "sawtooth" P wave with continuous atrial activity at 300 bpm indicates the interval (Hints: flip the ECG upside-down and check inferior leads (II, III, and aVF) to see it better)
- AFib: absent P wave, may have fibrillatory wave, irregularly irregular ventricular rhythm
- RAE: tall P wave (>2.5 mm) in II or V1 (P pulmonale)
- LAE: biphasic P wave with negative deflection >1 mm deep or >1 mm wide in V1, wide (>100 msec) notched P wave in II may be present (P mitrale)

P-R INTERVAL

- the P-R interval indicates the interval between sinus node activation and the start of ventricular depolarization
  - includes the impulse traveling through the atria, the AV node, and the bundle of His. The magnitude of the conduction velocity is referred to as "dromotropy" (faster = positive dromotropy, slower = negative dromotropy)
  - positive dromotropy associated with increased conduction velocity (e.g. sympathetic stimulation), while negative dromotropy is associated with decreased velocity (e.g. vagal stimulation)
- P-R interval should be 120-200 msec
- long P-R interval (>200 msec)
  - heart block (may be due to disease, delay in the AV node, or delay in distal (His-Purkinje) conduction system)
    - first degree: fixed, prolonged P-R interval (though every P wave has a QRS following)
    - second and third degree AV block: some P waves are NOT followed by a QRS
    - second degree Mobitz I (Wenckebach): gradual prolongation of the P-R interval precedes a dropped P wave
    - second degree Mobitz II (Hay): fixed P-R interval with ratio of atrial to dropped ventricular beats (e.g. for every 3 atrial beats, there is one ventricular beat (3:1))
    - third degree/complete: constant P-P and R-R intervals but variable P-R intervals

Significant ECG Changes

Look for ST changes starting at 60 msec from J point

J point = the junction between the QRS complex and the ST segment

ST elevation: at least 1 mm in 2 adjacent limb leads, or at least 1-2 mm in adjacent precordial leads

ST depression: downsloping or horizontal

Q Wave: pathological if Q wave ≥1 small square (≥40 msec) or >1/3 of the total QRS amplitude

- hypokalemia
- "trifascicular" block: long PR segment (first degree AV block) and bifascicular block

• short P-R interval (<120 msec)
- pre-excitation syndrome (delta wave: upsloping of the first part of the QRS complex) due to accessory pathways
- low atrial rhythm, P waves inverted in II, III, and aVF

QRS COMPLEX

• represents ventricular contraction
• rate: check if R-R interval matches the P-P interval
• amplitude: check for hypertrophy (see *Table 2, C8*)
• narrow QRS (<120 msec) means that the His-Purkinje system is being used
• wide QRS (>120 msec) means that the His-Purkinje system is being bypassed or is diseased
- BBB, VT, ventricular hypertrophy, cardiomyopathy, WPW, ectopic ventricular beat, hyperkalemia, or drugs (e.g. tricyclic antidepressants, antiarrhythmics)

• Q wave: the first downward deflection of the QRS complex
- significant Q wave (>40 msec or >1/3 of total QRS amplitude) indicates myocardial necrosis (new or old)

• R and S wave abnormalities typically show pathology in terms of BBB or intraventricular abnormalities

Insignificant Q Wave
- Septal depolarization by the left bundle
- Seen in leads I, II, III, aVL, V5, and V6
- <40 msec
- Q wave <1/3 of the total QRS amplitude

ST SEGMENT

• located between QRS complex and the beginning of T wave
- corresponds to the completion of ventricular depolarization

• normally at the same level as baseline (T-P segment)
• ST elevation: see *Infarction, C9*
• ST depression: ischemia
- ischemia that causes ST depression can result in myocardial damage (NSTEMI)
- lateral ST depression (leads I, aVL, V5, V6) may actually indicate a STEMI in the right heart
- ST depression may be nonspecific, or associated with remote MI or ischemia

T WAVE

• repolarization phase of ventricles (repolarization of the atria is obscured by the QRS complex)
• typically positive (except in aVR and V1) on ECG but normal isolated negative T waves may be present (especially in V1 and V2)
• T wave variation in consecutive leads may indicate pathology
- inversion: BBB, ischemia, hypertrophy, drugs (e.g. digitalis), pulmonary embolism (lead III as part of S1Q3T3 sign)
- elevation: infarction (STEMI, Prinzmetal, hyperacute), hyperkalemia (wider, peaked)
- flattened: hypokalemia, pericarditis, drugs (e.g. digitalis), pericardial effusion
  - flat T waves are nonspecific with no clinical significance (common)
- variations: T wave alternans; beat-to-beat variations due to PVC overlap (R on T phenomenon which may precipitate VT or VFib)

• appropriate T wave discordance: in BBB, T wave deflection should be opposite to that of the terminal QRS deflection (i.e. T wave negative if ends with R or R'; positive if ends with S)
- inappropriate T wave concordance suggests ischemia or infarction

Differential Diagnosis of ST Segment Changes

ST Elevation – I HELP A PAL
Ischemia with reciprocal changes
Hypothermia (Osborne waves)
Early repolarization (normal variant, need old ECGs to confirm)
LBBB
Post-MI
Acute STEMI
Prinzmetal's (Vasospastic) angina
Acute pericarditis (diffuse changes)
Left/right ventricular aneurysm

ST Depression – WAR SHIP
WPW syndrome
Acute NSTEMI
RBBB/LBBB
STEMI with reciprocal changes
Hypertrophy (LVH or RVH) with strain
Ischemia
Post-MI

Q-T INTERVAL

• duration of ventricular depolarization plus repolarization; often difficult to interpret
• corrected QT (QTc) corrects for the repolarization duration (since QT interval normally shortens with increased HR)
- QTc = QT ÷ √RR (Bazett's formula. NOTE: Bazett formula is inaccurate at rapid rates (e.g. >100/min))

• normal QTc is 360-450 msec for males and 360-460 msec for females
- increased (>450 msec for males and >460 msec for females): risk of Torsades de Pointes (lethal tachyarrhythmia; rare if <520 msec)
  - genetic long QT syndrome (often a channelopathy)
  - drugs: antiarrhythmics (classes I and III), antipsychotics (haloperidol, ziprasidone), antidepressants (citalopram), antibiotics (erythromycin, azithromycin)
  - electrolytes: low Ca^{2+}, low K^{+}, low Mg^{2+}
  - others: hypothyroidism, hypothermia, cardiomyopathy
- decreased (<360 msec): risk of VFib (very rare)
  - electrolytes: high Ca^{2+}
  - drugs: digoxin
  - others: hyperthyroidism

U WAVE

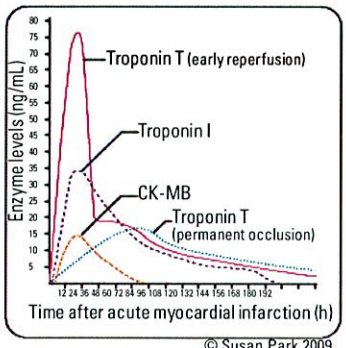
• origin unclear but may be repolarization of Purkinje fibres or delayed/prolonged repolarization of the myocardium
• more visible at slower heart rates
• deflection follows T wave with <25% of the amplitude
• variations from norm could indicate pathologic conditions
- prominent (>25% of T wave): electrolyte (low K^{+}), drugs (digoxin, antiarrhythmics)
- inverted (from T wave): ischemia, volume overload

Cardiac Biomarkers

- provide diagnostic and prognostic information in acute coronary syndromes and in HF

Table 4. Cardiac Enzymes

Enzyme	Peak	Duration Elevated	DDx of Elevation
Troponin I, Troponin T	12-24 h	Up to 2 wk	MI, CHF, AFib, acute PE, aortic dissection, myocarditis, pericarditis, endocarditis, cardiac defibrillation, myocardial damage, infiltrative cardiomyopathy, ischemic stroke, intracranial hemorrhage, acute hypotension, chronic renal insufficiency, sepsis, hypovolemia, acute respiratory distress syndrome, chronic hypertension, diabetes mellitus, hypothyroidism, rhabdomyolysis
Creatine Kinase-MB (CK-MB)	1 d	3 d	MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, chronic renal insufficiency



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Figure 16. Cardiac enzymes

- timing for troponin measurements is dependent on the assay used
  - high-sensitivity troponin I and T assays detect elevations in cardiac troponin earlier than traditional assays
- new CK-MB elevation can be used to diagnose re-infarction
- other biomarkers of cardiac disease
  - CK-MB, AST, and lactate dehydrogenase (LDH) also increases in MI (low specificity)
  - BNP and N-terminal prohormone of BNP (NT-proBNP): secreted by ventricles in response to increased end-diastolic pressure and volume
    - DDx of elevated BNP: CHF, AFib, PE, pulmonary HTN

Ambulatory ECG

- description
  - provides a view of two or three leads of electrocardiographic data over an extended period of time
  - permits evaluation of changing dynamic cardiac electrical phenomena
  - the choice of monitor depends on the patient's reported symptom frequency
    - if daily symptoms, use a 24 h or 48 h continuous ECG (Holter) monitor
    - if less frequent (i.e. weekly or monthly), use prolonged continuous monitoring (1-2 wk) or an event monitor
  - **continuous ambulatory monitor**: a small, lightweight, battery-operated recorder (box or patch) which records two or three channels of electrocardiographic data
    - patient activated event markers
    - minimum of 24-72 h, up to 14 d
  - **implantable loop recorder (ILR):** subcutaneous monitoring device for the detection of cardiac arrhythmias
    - typically implanted in the left pectoral region and stores events when the device is activated automatically according to programmed criteria or manually with magnet application
    - generally used for months to years
    - note: devices implanted for bradyarrhythmias (pacemakers) or tachyarrhythmias (defibrillators) also record rhythm continuously and have algorithms for automatic rhythm detection and storage
  - **external event monitor**
    - post-event monitoring device: placed on patient's chest after symptom onset and records "real-time" rhythm for a specified period (e.g. 30-150 s)
    - event/loop recorder: constantly records patient's rhythm for a period of time but only saves the data when the patient experiences symptoms and presses the event button (usually 30-60 s recall)
    - auto-triggered event recorder: uses programmed algorithms to auto-detect, capture, and save asymptomatic arrhythmias in addition to patient-triggered events
  - **patient administered single lead ECG**
    - wrist or finger electrodes, commercially available direct to consumer (e.g. Apple Watch, Kardia Mobile)
- **indications**
  - evaluation of cardiac rhythm abnormalities, especially as they correlate with symptoms and provoking factors
  - has also been used for assessing pacemaker and implantable cardioverter-defibrillator function, evidence of myocardial ischemia, late potentials, and HR variability

ALGrawany

Echocardiography

Transthoracic Echocardiography

- **description**
  - non-invasive ultrasound directed across the chest wall to obtain real time images of the heart
- **indications**
  - evaluation of cardiac anatomy and functioning including: chamber size, wall thickness, wall motion, valve morphology, proximal great vessel morphology, and LVEF
  - evaluation of clinical cardiac abnormalities including: chest pain with hemodynamic instability, peripheral edema with elevated JVP, murmurs, unexplained hypotension, and syncope with suspected structural cardiac cause
  - evaluation of suspected cardiac diseases including: aortic dissection, congenital heart disease, LV thrombus, MI, pericardial effusion, and pericardial tamponade

Transesophageal Echocardiography

- **description**
  - ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
  - better visualization of posterior structures, including LA, mitral, aortic valves, and inter-atrial septum
- **indications**
  - initial test in certain life-threatening situations (e.g. aortic dissection) when other tests contraindicated (e.g. CT angiography in patient with renal failure or when TTE is technically inadequate
  - key indication is to evaluate valvular morphology, vegetation (e.g. infective endocarditis), and function (e.g. stenosis and regurgitation) especially of the aortic, mitral, and prosthetic valves if present
  - evaluate cardiac disease including: aortic dissection, aortic atheromas, intracardiac thrombi, tumours, and shunts
  - evaluation for left atrial thrombus/left atrial appendage thrombus in a patient with AFib/atrial flutter to facilitate clinical decision making regarding electrical cardioversion or ablation
- **risks**
  - serious complications are extremely rare (<1 in 5000)
  - esophageal perforation
  - gastrointestinal bleeding
  - pharyngeal hematoma

Stress Echocardiography

- **description**
  - echocardiography using exercise (treadmill or bicycle) or pharmacologic agents (dobutamine or adenosine) as physiological stressor
- **indications**
  - when other stress imaging modalities are unequivocal or when ECG is non-diagnostic
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS to decide on potential efficacy of revascularization (i.e. myocardial viability)
  - evaluate the clinical significance of valvular heart disease: AS, MS, MR, or AR
  - evaluation of cardiac disease: LV systolic dysfunction of unclear etiology, latent or established pulmonary HTN, LVOT obstruction in HCM, and syncope of unclear etiology
  - dobutamine
    - pharmacologic stress for patients physically unable to exercise; same indications as exercise stress echocardiogram
    - low dose dobutamine stress echocardiogram can be used to assess myocardial viability and to assess AS with LV systolic dysfunction
- **contraindications**
  - absolute contraindications to exercise testing (see below)
  - contraindications to dobutamine stress echocardiography: tachyarrhythmias and systemic hypertension
  - relative contraindications to both exercise and dobutamine stress echocardiography: AAA, electrolyte abnormalities, left main CAD, and moderate stenotic valvular disease

Contrast Echocardiography with Agitated Saline Contrast

- **description**
  - improves visualization and provides real-time assessment of intracardiac blood flow
  - conventional agent is agitated saline (contains microbubbles of air)
  - visualization of right heart and intracardiac shunts, most commonly PFO and intrapulmonary shunt
  - in a normal heart, microbubbles are still seen but only in the right heart and eventually diffuse into lungs after travelling through pulmonary circulation

- **indications**
  - detection of right-to-left shunts the presence of microbubbles in the left heart chambers indicates a right-to-left intracardiac or extracardiac shunt
  - Doppler signal enhancement agitated saline enhances tricuspid Doppler signals; this could be used to assess transvalvular velocity and to estimate right ventricular systolic pressure
  - diagnosis of persistent left superior vena cava if contrast injected in left arm vein appears in the coronary sinus before the RA

Contrast Echocardiography with Transpulmonary Contrast Agents

- **description**
  - newer contrast agents such as Definity® contrast can cross the pulmonary bed and achieve left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders, enhance evaluation of LVEF , wall motion abnormalities (in patients with technically inadequate echocardiograms), and intracardiac mass (e.g. LV thrombus)
- **risks**
  - major complications (e.g. risk of non-fatal MI and death are rare)
  - ultrasound contrast agents may cause back pain, headache, urticaria, and anaphylaxis
  - caution in patients with significant intra-cardiac shunts

Stress Testing

EXERCISE TESTING

- **description**
  - cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring for the detection of inducible myocardial ischemia, exercise related symptoms (e.g. arrhythmias), or objective measures of exercise tolerance
  - exercise test results stratify patients into 3 risk groups:
    1. low-risk: can treat medically without invasive testing
    2. intermediate-risk: may need additional testing in the form of exercise imaging studies or cardiac catheterization
    3. high-risk: refer for cardiac catheterization
- **indications**
  - patients with intermediate (10-90%) pretest probability of myocardial ischemia (usually due to CAD) based on age, gender, and symptoms
  - ST depression <1 mm at rest, LBBB, digoxin or estrogen use make the ST changes difficult to interpret however, graded exercise stress test can still be valuable
  - important prognostic and diagnostic information (beyond ST changes) is obtained from symptoms, total exercise time, HR, and BP response to exercise, if arrhythmia is provoked
    - note: this is a diagnostic test with false positives and false negatives. Management needs to take into account symptoms and exercise tolerance
- **absolute contraindications**
  - acute MI (within 2 d) or unstable angina pectoris
  - uncontrolled arrhythmias causing symptoms of hemodynamic compromise
  - symptomatic severe valvular stenosis
  - uncontrolled symptomatic HF
  - active endocarditis, acute myocarditis, or pericarditis
  - acute aortic dissection
  - acute pulmonary or systemic embolism
  - acute non-cardiac disorders that may affect exercise performance or may be aggravated by exercise
  - termination of exercise testing
    - target HR achieved
    - patient's desire to stop
    - drop in sBP of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
    - moderate to severe angina
    - ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
    - increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
    - signs of poor perfusion (cyanosis or pallor)
    - technical difficulties in monitoring ECG or sBP
    - sustained VT
- **risks**
  - death, MI, arrhythmia, hemodynamic instability, and orthopedic injury (<1-5/10000 supervised tests)



Most Commonly Used Treadmill Stress Test Protocols

The Bruce Protocol: 7 stage test with each stage lasting 3 min. With each successive stage, the treadmill increases in both speed (2.7 km/h to 9.6 km/h) and grade (10% with a 2% increase per stage up to 22%)

The Modified Bruce, Modified Naughton Protocol: for older individuals or those with limited exercise capacity



Important Contraindications to Exercise Testing

- Acute MI, aortic dissection, pericarditis, myocarditis, PE
- Severe AS, arterial HTN
- Inability to exercise adequately



Important Prognostic Factor
Duke Treadmill Score (DTS) Weighted Index Score

Treadmill exercise time using standard Bruce protocol
Maximum net ST segment deviation (depression or elevation)
Exercise-induced angina provides diagnostic and prognostic information (such as 1 yr mortality)

DTS = exercise time – (5 x MaxST) – (4 x angina index)
Angina index: 0 (no angina), 1 (angina but not exercise-limiting), 2 (exercise-limiting angina)
DTS ≥5: 0.25% 1 yr mortality
DTS 4 to -10: 1.25% 1 yr mortality
DTS ≤ -11: 5.25% 1 yr mortality
Ann Intern Med 1987;106:793-800



Patients with normal imaging (nuclear perfusion or stress echo) studies at peak stress have a <1%/yr incidence of death or nonfatal MI and are thus often spared further invasive evaluation

NUCLEAR CARDIOLOGY

- **description**
  - MPI with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
  - evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
  - predicts the likelihood of future cardiac event rates independent of the patient's history, examination, resting ECG, and stress ECG
  - often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
  - stress with either treadmill or IV vasodilator stress (e.g. dipyridamole, adenosine, regadenoson)
  - images of the heart obtained during stress and at rest 3-4 h later
  - tracers
    - Thallium-201 (^{201}Tl, a K^+analogue)
    - Technetium-99 (^{99}Tc)-labeled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)
- **indications**
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarker
  - exercise MPI
    - when ECG cannot be interpreted appropriately due to LBBB or abnormal baseline ECG
    - intermediate pre-test probability with normal/equivocal exercise ECG
    - in patients with previous imaging whose symptoms have changed
    - to diagnose ischemia
  - dipyridamole/adenosine MPI
    - exercise testing is always preferred
    - pharmacological stress imaging test for patients who cannot exercise or do not want to hold cardiac medications (β-blockers/CCBs)
    - same indication as exercise MPI
- **contraindications**
  - vasodilators (i.e. adenosine, regadenoson, and dipyridamole) are contraindicated in patients with hypotension, sick sinus syndrome, high-degree AV block (in the absence of backup pacemaker capability), and reactive airways disease
  - pregnancy
- **risks**
  - radiation exposure

STRESS ECHOCARDIOGRAPHY

- see *Echocardiography, C14*

Cardiac Catheterization and Angiography

Right Heart Catheterization (Swan-Ganz Catheter)

- **description**
  - also known as pulmonary artery catheterization
  - obtain direct measurements of central venous, right-sided intracardiac, pulmonary artery, and pulmonary artery occlusion pressures
  - can estimate CO, SVR, and PVR as well as mixed venous oxyhemoglobin saturation, oxygen delivery, and oxygen uptake
  - right atrial, right ventricular, and pulmonary artery pressures are recorded
  - can also be used to measure the Cardiac Index (CI), a measure of cardiac function
    - CI = CO/body surface area
    - 2.6-4.2 L/min/$m^2$is considered normal while <1.8 L/min/m^2usually means cardiogenic shock
  - PCWP
    - obtained by advancing the catheter to wedge in the distal pulmonary artery
    - records pressure measured from the pulmonary venous system
    - in the absence of pulmonary venous disease, reflects left atrial pressure
- **indications**
  - unexplained or unknown volume status in shock
  - severe cardiogenic shock (e.g. acute valvular disease, suspected pericardial tamponade)
  - suspected or known pulmonary artery HTN
  - severe underlying cardiopulmonary disease (e.g. congenital heart disease, left-to-right shunt, severe valvular disease, pulmonary HTN) and undergoing surgery (e.g. corrective)
- **contraindications**
  - infection at the insertion site
  - presence of a right VAD
  - insertion during cardiopulmonary bypass

- **risks**
  - complications for diagnostic catheterization: <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - complications of insertion: atrial and/or ventricular arrhythmias (~3% of patients)
  - catheter misplacement or knotting (uncommon)
  - perforation of a cardiac chamber and rupture of a cardiac valve or the pulmonary artery (rare)
  - complications of catheterization: pulmonary artery rupture, pulmonary infarction, thromboembolic events, infection, and data misinterpretation
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)

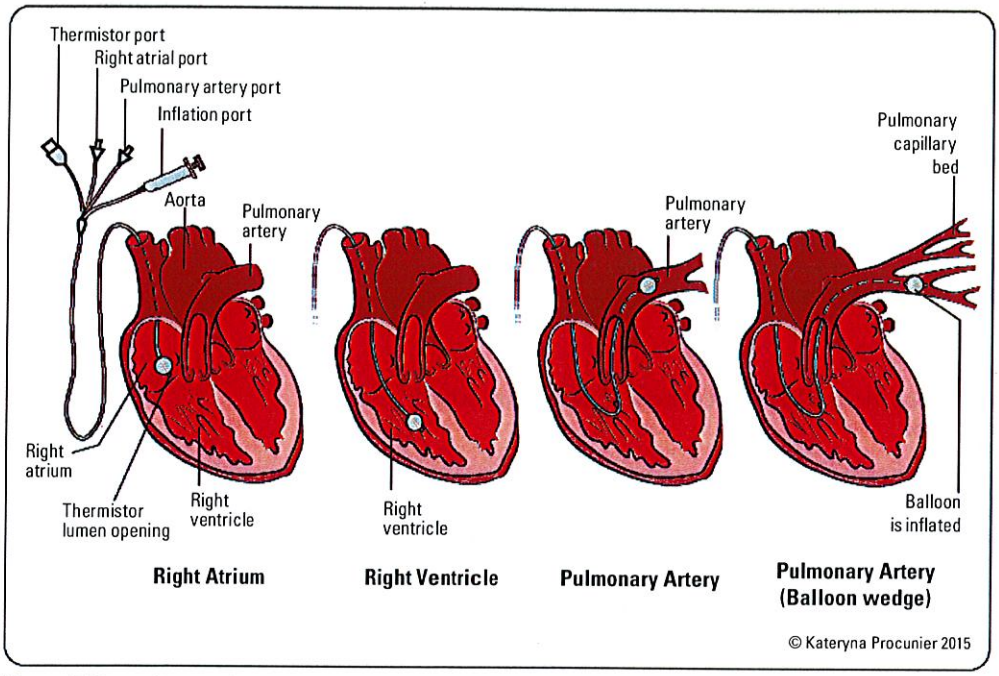


Figure 17. Swan-Ganz catheter placement

Left Heart Catheterization

- **description**
  - accomplished by introducing a catheter into the radial, brachial, or femoral artery and advancing it through the aorta, across the aortic valve, and into the LV
  - evaluates mitral and aortic valvular defects and myocardial disease
  - systolic and end-diastolic pressure tracings recorded
  - LV size, wall motion, and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
- **indications**
  - identification of the extent and severity of CAD and evaluation of left ventricular function
  - assessment of the severity of valvular or myocardial disorders (e.g. AS or insufficiency, MS or insufficiency, and various cardiomyopathies) to determine the need for surgical correction
  - collection of data to confirm and complement non-invasive studies
  - investigating CAD in patients with confusing clinical features or chest pain of uncertain origin
- **contraindications**
  - severe uncontrolled HTN
  - ventricular arrhythmias
  - acute stroke
  - severe anemia
  - active gastrointestinal bleeding
  - allergy to radiographic contrast
  - acute renal failure
  - uncompensated congestive failure (patient cannot lie flat)
  - unexplained febrile illness or untreated active infection
  - electrolyte abnormalities (e.g. hyperkalemia)
  - severe coagulopathy
- **risks**
  - major complications of diagnostic catheterization (i.e. death, MI, stroke): <3 in 1000
  - minor complications (e.g. vascular access issue, kidney dysfunction): <1 in 100
  - inadequate diagnostic procedures occur in <1% of cases

Chambers	Pressure (systolic; mmHg)
Right atrium/central venous	1-8
Right ventricle	1-8 (15-30)
Pulmonary artery	4-12 (15-30)
Left atrium/pulmonary capillary wedge	4-12
Left ventricle end diastolic	4-12

Coronary Angiography

- **description**
  - radiographic visualization of the coronary vessels after injection of radiopaque contrast media
  - coronary vasculature accessed via the coronary ostia
- **indications**
  - to define the coronary anatomy and the degree of luminal obstruction of the coronary arteries
  - to determine the presence and extent of obstructive CAD
  - to assess the feasibility and appropriateness of various forms of therapy, such as revascularization by percutaneous or surgical interventions
  - can be used when the diagnosis of CAD is uncertain and cannot be excluded by non-invasive techniques
- **contraindications**
  - severe renal failure due to contrast agent toxicity (must check patient's renal status)
- **risks**
  - major complications of diagnostic catheterization (i.e. death, MI, stroke): <3 in 1000
  - minor complications (e.g. vascular access issue, kidney damage): <1 in 100

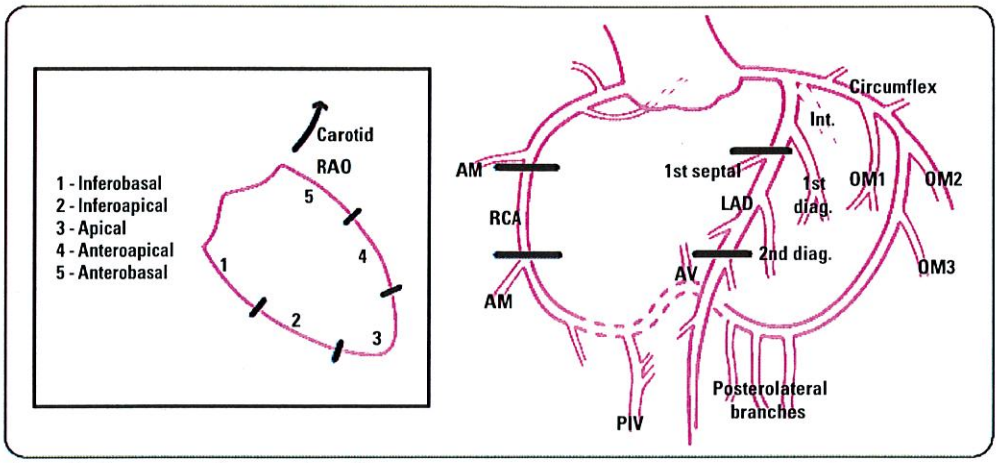


Figure 18. Coronary angiogram schematic
AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal; RAO = right anterior oblique; RCA = right coronary artery

Diagnostic Catheterization

- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, CCBs, adenosine, nitric oxide, prostacyclin)

Contrast-Enhanced CT Coronary Angiography

- **description**: fast ECG-synchronized multi-slice CT image acquisition in the heart to enable non-invasive imaging of the coronary arterial tree
- **indications**: often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis
- **contraindications**: allergy to contrast dye; severe renal dysfunction; irregular heart rhythm or tachycardia which may impact image quality
- **risks**: radiation exposure; and contrast induced nephropathy

Magnetic Resonance Imaging

- **description**
  - offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
  - often used with gadolinium injection to assess myocardial scar
- **indications**
  - valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, assessment of viable myocardium, and assessment of cardiomyopathies
    - most accurate measure of ejection fraction
    - especially valuable for assessing RV

ACC/AHA 2011 Recommended Indications for Coronary Angiography

- Disabling chronic stable angina (CCS classes II and IV) despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing

Coronary Angiography
Gold standard for localizing and quantifying CAD

Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter

- **contraindications**
  - metallic foreign bodies/implants (e.g. pacemaker, ICD, CRT, cerebral aneurysm clips, metal shrapnel, piercings)
  - kidney dysfunction due to gadolinium contrast medium
- **risks**
  - hazards posed by certain metallic devices inside patients

CARDIAC DISEASE

Arrhythmias

Mechanisms of Arrhythmias

Alterations in Impulse Formation

A. Normal Automaticity

- impulses from the SA node, caused by spontaneous depolarization, result in the basic cardiac pacemaker function. "Downstream" cells in the AV node and Purkinje fibres also depolarize spontaneously, but at a slower rate; they serve as the "backup" pacemaking cells if the upstream rate is slower than the more distal spontaneous rate
- normal automaticity is influenced by:
  - neurohormonal tone (sympathetic tone increases and parasympathetic tone decreases spontaneous firing rate and thus HR)
  - myocardial ischemia/infarction or other cardiac pathology (e.g. HF) may alter HR via these mechanisms
  - abnormal metabolic conditions (e.g. hypoxia, acidosis, hypothermia)
  - electrolyte abnormalities, especially hyperkalemia which slows HR
  - drugs (e.g. digitalis, β-blockers, CCB)
  - athletic training: endurance athletes often have sinus bradycardia
  - age: elderly often have sinus bradycardia
  - increased circulatory demand can result in sinus tachycardia (e.g. pregnancy, anemia, exercise)



Sinus Arrhythmia

- Normal P waves, with variation of the P-P interval, especially with respiration, due to varying rate of SA node depolarization

Respiratory SA

- Seen more often in young adults
- Normal, physiologic results from changes in autonomic tone during respiratory cycle
- Rate increases with inspiration, slows with expiration

Non-Respiratory SA

- Seen more often in the elderly
- Can occur in the normal heart; if marked may be due to sinus node dysfunction (e.g. in heart disease or after digitalis toxicity)
- Usually does not require treatment

B. Abnormal Automaticity due to Triggered Activity (due to Afterdepolarizations)

1. Early Afterdepolarizations

- during the terminal plateau or repolarization phases of action potential
- consequence of the membrane potential transiently becoming more positive during repolarization (depolarization interrupting repolarization)
  - these are called EADs and DADs (early and delayed afterdepolarization, respectively)
- may result in self-maintaining oscillations of depolarization, giving rise to action potentials thereby generating a tachyarrhythmia (e.g. new baseline voltage is greater than threshold, which automatically triggers a new action potential after the refractory period ends)
- EADs are the basis for the arrhythmias associated with QT prolongation, either congenital or acquired; termed "Torsades de Pointes"

2. Delayed Afterdepolarizations

- occur after the action potential has fully repolarized, but before the next usual action potential
- commonly occurs in situations of high intracellular calcium (e.g. digitalis intoxication, ischemia) or during enhanced catecholamine stimulation (e.g. "twitchy" pacemaker cells)

Alterations in Impulse Conduction

A. Re-Entry Circuits

- the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium (see *Figure 29, C24*, for an example in the context of AV nodal re-entrant tachycardia)
- the conditions necessary for re-entry include block of an impulse into a region of the heart that is refractory (non-excitable tissue or because of local functional block, where the impulse encounters tissue still in its refractory period), followed by "re-entry" of the impulse around a region of block to the site of origin, forming a complete re-entry circuit
  - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits
  - most sustained tachyarrhythmias are due to re-entry

B. Conduction Block

- ischemia, fibrosis, trauma, and drugs can cause transient or permanent, unidirectional or bidirectional block
- most common cause of block is "functional block" due to refractory myocardium (cardiomyocytes are in refractory period) or "anatomical block" (area of myocardium unexcitable due to fibrosis); cells in the conduction system distal to the block can assume pacemaking control if the block occurs along the specialized conduction system
- the consequence of conduction block are re-entry arrhythmias (tachyarrhythmias - see above) or failure of impulses to conduct to ventricular cells (bradycardia)
- conduction block in the AV node or His Purkinje tissue can lead to bradycardia

C. Bypass Tracts

- normally, the only electrical connection between atria and ventricles is the AV node and connected penetrating Bundle of His;
- an accessory bypass tract is a direct connection between A and V, histologically similar to atrial tissue, through the valve ring which is normally impenetrable to electrical impulses (hence "accessory atrio-ventricular bypass tract")
  - see *Pre-Excitation Syndromes, C25*

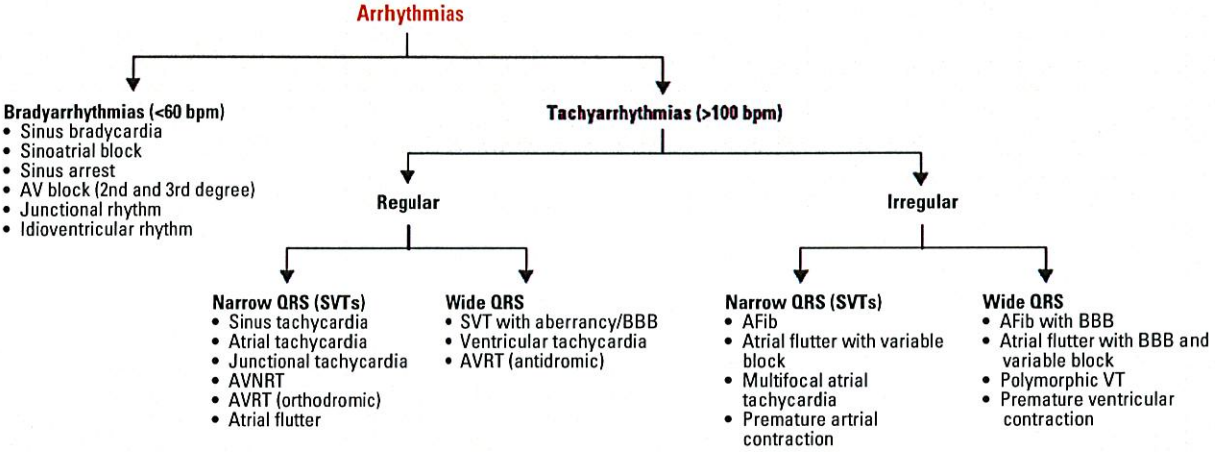


Figure 19. Clinical approach to arrhythmias

Bradyarrhythmias

Table 5. Types of Bradyarrhythmias

1. SA NODAL DYSFUNCTION

- P axis normal (P waves positive in I and aVF)
- Rate <60 bpm; marked sinus bradycardia (<50 bpm)
- May be seen in normal adults, particularly athletes, and in elderly individuals
- Increased vagal tone or vagal stimulation
- Drugs (e.g. β-blockers, CCB)
- Ischemia/infarction

Atropine; pacing for sick sinus syndrome

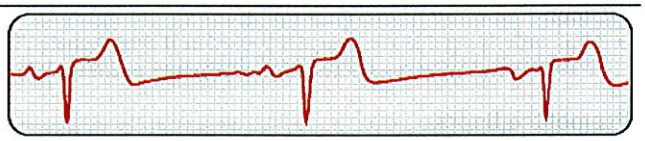


Figure 20. Sinus bradycardia

2. AV CONDUCTION BLOCKS

A. First Degree AV Block

- Prolonged PR interval (>220 msec)
- Frequently found among otherwise healthy adults

No treatment required

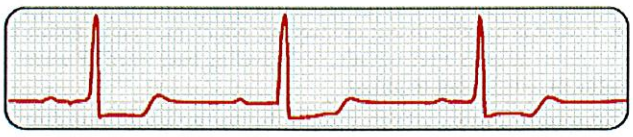


Figure 21. First degree AV block

B. Second Degree AV Block: Type I (Mobitz I)

- Gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
- AV block is usually in AV node (proximal) triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia

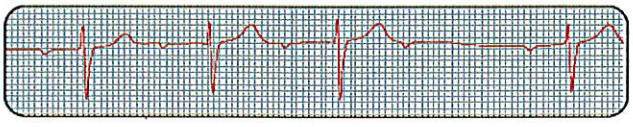


Figure 22. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V1)

Table 5. Types of Bradyarrhythmias

C. Second Degree AV Block: Type II (Mobitz II)

- The PR interval is constant; there is an abrupt failure of conduction of a P wave
- Often associated with distal conduction system disease (BBB)
- AV block is usually distal to the AV node (i.e. bundle of His); increased risk of high grade or third degree AV block

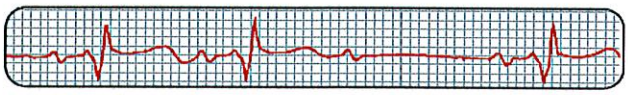


Figure 23. Second degree AV block (Mobitz II) (3:2 conduction) (lead V1)

D. Third Degree AV Block

- Complete failure of conduction of the supraventricular impulses to the ventricles
- Ventricular depolarization initiated by an escape pacemaker distal to the block
- Wide or narrow QRS, P-P and R-R intervals are constant, variable PR intervals
- No relationship between P waves and QRS complexes (P waves "marching through")

Management (see *Electrical Pacing, C29*)

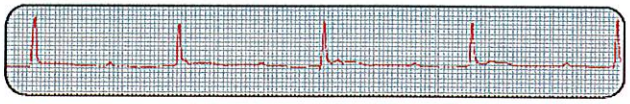


Figure 24. Third degree AV block (complete heart block) (lead II)

Supraventricular Tachyarrhythmias

Presentation for SVT (and Pre-Excitation Syndromes)

- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate CHF, hypotension, or ischemia in patients with underlying cardiovascular disease
- untreated tachycardias of long duration (i.e. days) can cause tachycardia- induced cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- arrhythmias involving the AV node (i.e. AVNRT and AVRT) may terminate spontaneously, after vagal stimulation, or after adenosine treatment

Supraventricular Tachyarrhythmias

- tachyarrhythmias that originate in the atria or involve the AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS unless there is pre-existing BBB or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

1. Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- causes:
  - anxiety, exercise
  - metabolic (e.g. thyrotoxicosis, pheochromocytoma)
  - systemic demand (e.g. pregnancy, anemia, exercise, pain, fever, hypotension, hypovolemia, anemia, CHF, MI, shock, PE)
  - pharmacologic (e.g. cocaine, caffeine, alcohol, β-adrenergic agonists, anticholinergic drugs)
  - idiopathic (i.e. IST–idiopathic/inappropriate sinus tachycardia) or POTS (postural orthostatic tachycardia syndrome)
- treatment:
  - treat underlying disease; consider β-blocker if symptomatic, CCB if β-blockers contraindicated; ivabradine may be considered as an alternative agent for inappropriate sinus tachycardia

2. Premature Beats

- premature atrial contraction
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
- junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually absent or inverted, which may come before or closely follow the QRS complex (referred to as a retrograde, or "traveling backward" P wave)
- treatment usually not required

3. Atrial Flutter

- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly RA involving isthmus of tissue between tricuspid annulus and inferior vena cava (IVC))
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (e.g. 2:1, 3:1, 4:1, etc.) or variable
- etiology: HTN, cardiomyopathy, in association with AFib, age
  - less often: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis, in association with long term endurance sport/exercise
- ECG: "sawtooth" flutter waves (most common type of flutter, called "isthmus-dependent, typical flutter") in inferior leads, II, III, aVF; narrow QRS (unless aberrancy); commonly seen as 2:1 block with HR of 150
- in atrial flutter with 2:1 block, carotid sinus massage (after checking for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and allow flutter waves to be more easily seen

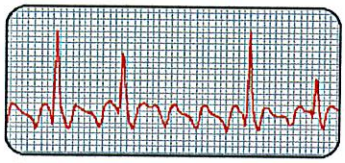


Figure 25. Atrial flutter with variable block

- treatment of acute atrial flutter
  - if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable:
    1. rate control: β-blocker, diltiazem, verapamil, or digoxin
    2. chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
    3. anticoagulation guidelines same as for patients with AFib
- long-term treatment of atrial flutter to prevent recurrences includes antiarrhythmics and radiofrequency (RF) ablation (for isthmus dependent, typical flutter, treatment of choice is RF ablation)

4. Multifocal Atrial Tachycardia (MAT)

- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm
  - 3 or more distinct P wave morphologies
  - PR intervals vary
  - some P waves may not be conducted
- more common in patients with COPD or hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline use, or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil); β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics, or ablation

5. Atrial Fibrillation

- see CCS Atrial Fibrillation Guidelines 2020 for details (free mobile app iCCS available on iOS and Android)
- the most common sustained arrhythmia
- risk factors: older age, hypertension, heart failure, valvular disease (especially leading to dilated LA), recent cardiac surgery, lung disease, excessive alcohol consumption, sepsis (particularly pneumonia)
- symptoms: palpitations, exercise intolerance, fatigue, dyspnea, dizziness, syncope, may precipitate or worsen HF. May also be completely asymptomatic
- **classification**
  - "lone": generally occurs in persons <65 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease (usually MS), or prosthetic heart valves, or valve repair
    - valvular disease is observed in patients/people with MS, prosthetic heart valves, or those who have undergone valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: AFib sustained for more than 7 d or AFib that terminates only with cardioversion
  - permanent/chronic: continuous AFib that is unresponsive to cardioversion or in which clinical judgement has led to a decision not to pursue cardioversion
  - recurrent: two or more episodes of AFib
  - secondary: caused by a separate underlying condition or event (e.g. MI, cardiac surgery, pulmonary disease, hyperthyroidism)
- **initiation**
  - single circuit re-entry and/or ectopic foci, mostly arising from the pulmonary veins, act as aberrant generators producing atrial tachycardia (350-600 bpm)
    - this leads to multiple re-entry circuitry (microre-entry)
  - impulses are conducted irregularly across the atrial myocardium to give rise to fibrillation
  - in most cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated
- maintenance
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib, the more difficult it is to restore normal sinus rhythm
- **consequences**
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response (usually <200 bpm); tachycardia leads to suboptimal CO
    - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation
      - AFib is an important risk factor for stroke or thromboembolic events (stroke risk can be assessed by CHADS2 score in AFib; CHADS2-VASc if the former gives a score of 0 or 1)
      - all valvular Afib (those with mechanical valves or MS) need anticoagulation but CHADS determines treatment for AS and MR

Table 6. CHADS2 Risk Prediction for Non-Valvular AFib

Risk Factor	Points	CHADS2 Score	Stroke Risk (%/Yr)
Congestive HF	1	0	1.9 (low)
HTN	1	1	2.8 (low-mod)
Age >75	1	2-3	4.0-5.9 (mod), need anticoagulation
Diabetes	1	4-6	8.5-18.2 (high), need anticoagulation
Stroke/TIA (prior)	2		

Can J Cardiol 2014;30:1114-30

- ECG findings
  - no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline

- irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
- loss of atrial contraction, thus no "A" wave seen in JVP, no S4 on auscultation

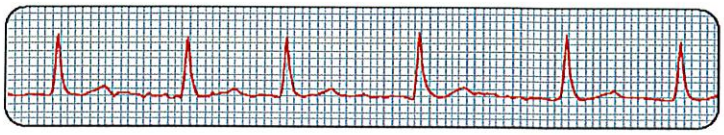


Figure 26. AFib (lead II)

- management (adapted from CCS Atrial Fibrillation Guidelines 2020)
  - primary goal is symptom control
  - stroke prevention is crucial, since patients who are not anticoagulated for AFib have, on average, a 4-5% annual stroke risk
  - all patients should be assessed for stroke risk and receive anticoagulation independent of the rate or rhythm treatment
  - **newly discovered AFib**
    - if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
    - if AFib persists, consider one of the following:
      1. rate control and anticoagulation (as indicated below)
      2. cardioversion (as indicated below)
    - an initial rhythm control strategy for patients with newly diagnosed AFib (i.e. within past year), is associated with reduced cardiovascular death and stroke rate
  - **recurrent or permanent AFib**
    - if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
    - patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence; permanent AFib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations
    - if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
  - **drug selection for rhythm control**
    - no or minimal heart disease: flecainide, propafenone once proven to have no underlying CAD (may consider exercise stress testing)
    - LV dysfunction: amiodarone
    - CAD: β-blockers, amiodarone
    - if antiarrhythmic drugs fail or are not tolerated, can consider RF ablation for rhythm/symptom control
  - **treatment of AFib (RACE):** all patients with AFib (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and risk of bleeding, and patients should receive an oral anticoagulant (OAC) if indicated
    1. **R**ate control: β-blockers, diltiazem, verapamil (in patients with HF: digoxin, amiodarone)
       - digoxin can be used to achieve rate control in patients whose response to β-blockers and/or CCB is inadequate, contraindicated, or not tolerated
    2. **A**nticoagulation: use either warfarin or DOACs (e.g. apixaban, dabigatran, rivaroxaban, edoxaban) to prevent thromboembolism
       - DOAC use is preferred to warfarin
       - for patients with non-valvular AFib (NVAF), OAC use is recommended for those >65 yr and/or with a CHADS2 ≥1. NVAF is defined as AF *not* due to mechanical valve or moderate-severe mitral stenosis
       - ASA 81 mg is recommended only for patients with none of the risks outlined in the CCS algorithm (age <65 and no CHADS2 risk factors) who also have arterial disease (coronary, aortic, or peripheral)
    3. **C**ardioversion (electrical)
       - if AFib <48 h, can usually cardiovert without anticoagulation (<12 h if high stroke risk)
       - if AFib >48 h, anticoagulate 3 wk before and 4 wk after cardioversion due to risk of unstable intra-atrial thrombus
       - if patient is unstable (hypotensive, active angina due to tachycardia, uncontrolled HF), cardiovert immediately
    4. **E**tiology
       - HTN, obesity, sleep apnea, CAD, heart failure, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, postoperative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
       - may present in young patients without demonstrable disease ("lone AFib") and in the elderly without underlying heart disease
       - studies of patients with AFib suggest that there is no difference in long-term survival when treating patients with a rhythm-control vs. rate-control strategy (recent large study suggests benefit of rhythm control for recent onset AF- see above)
       - many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate AFib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible



The 2020 Canadian Cardiovascular Society/ Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation
Can J Cardiol 2020;36:1847-1948
Rate and Rhythm Control: Long-term rate control therapy in AFib patients is recommended to reduce symptoms and prevent CV events. Based on the paucity of data informing HR targets, it is recommended to titrate rate-controlling agents to achieve a resting HR <100 bpm during AFib. Rhythm control with long-term antiarrhythmic drug therapy might not completely suppress AFib, and thus should be focused on symptom relief, improving functional capacity, and reducing healthcare utilization. Rhythm control strategies are recommended for patients with established AFib who remain symptomatic with rate control therapy, or in whom rate control therapy is unlikely to control symptoms. In patients with newly diagnosed AFib, an initial strategy of rhythm control has been associated with reduced CV death and reduced incidence of stroke. It is recommended to consider catheter ablation of AFib as a reasonable alternative to pharmacologic rate or rhythm control.
Antithrombotic Therapy in AFib: In patients with AFib and coronary or arterial vascular disease, the choice of antithrombotic therapy should be based on a balanced risk assessment of AFib-related stroke, ischemic coronary events, and clinically relevant bleeding. If an oral anticoagulant is indicated, non-Vitamin K antagonist oral anticoagulants (NOACs) are recommended over warfarin.

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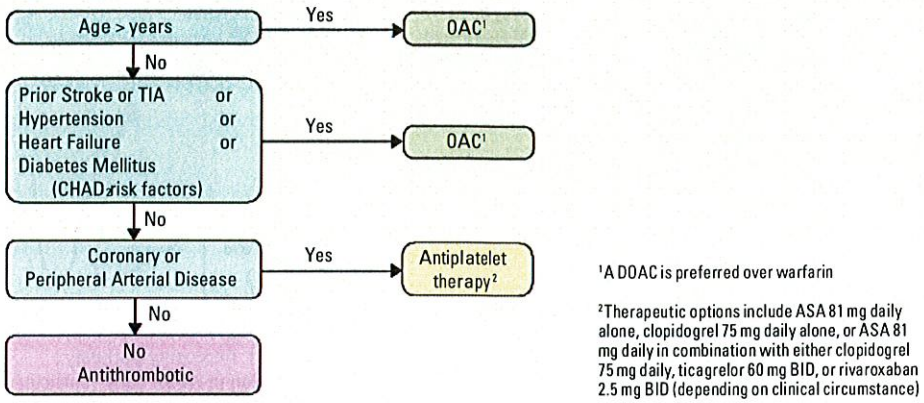


Figure 27. CHADS-65: CCS algorithm for oral anticoagulation therapy in AFib

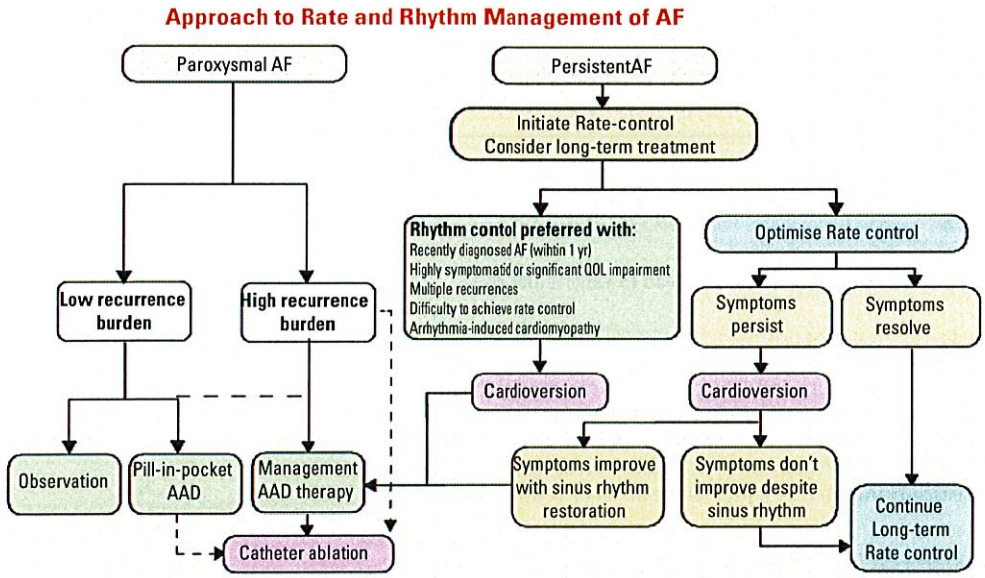


Figure 28. Approach to management of AFib

- **surgical management in AFib ablation**
  - sutured lesion
    - Cox-maze III: definitive surgical treatment of chronic AFib; indicated in patients who have failed maximal medical therapy and have had embolic events or are symptomatically compromised by AFib; 90-95% postoperative freedom from AFib; less likely to be successful in patients with large left atria (>5 cm) or with longstanding AFib (>5 yr)
    - modified maze and pulmonary vein isolation: more limited patient sets but takes less time to perform than classical maze procedure; selected cases can be done off bypass with concomitant OPCAB; 60-75% postoperative freedom from AFib
  - energy lesion
    - cryoablation: see *Catheter Ablation, C29*
    - radiofrequency ablation: see *Catheter Ablation, C29*
    - current experimental trials include use of laser ablation, microwave ablation, and ultrasound ablation

6. AV Nodal Re-Entrant Tachycardia

- re-entrant circuit using dual pathways (fast conducting β-fibres and slow conducting α-fibres) within or near the AV node; often found in the absence of structural heart disease
  - cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset with patients often describing "neck pounding" and "shirt flapping"
- fast regular rhythm of 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex
- treatment
  - acute: Valsalva maneuver or carotid sinus pressure technique, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina, or CHF)
  - long-term: 1st line radiofrequency ablation (>98% cure rate and < < 1% complication rate), β-blocker, diltiazem, digoxin; 2nd line flecainide, propafenone

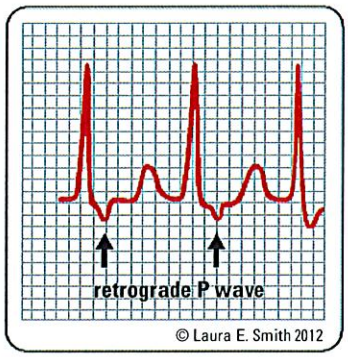


Figure 29. AVNRT

N.B. Refer to ECG Made Simple for further discussion and an animation of the mechanism (www.ecgmadesimple.com)

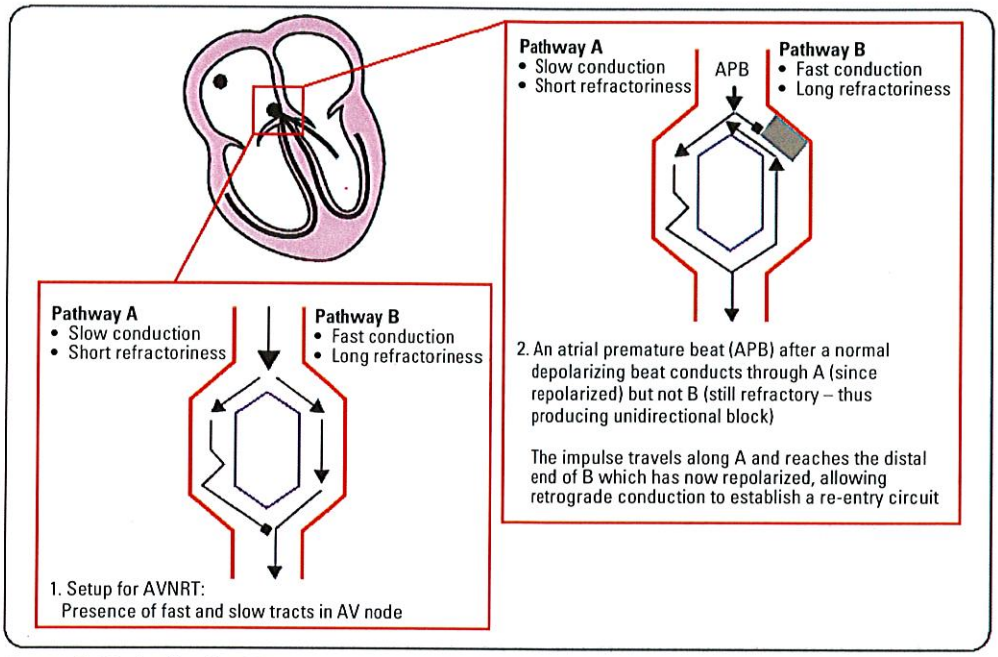


Figure 30. Mechanism for AVNRT

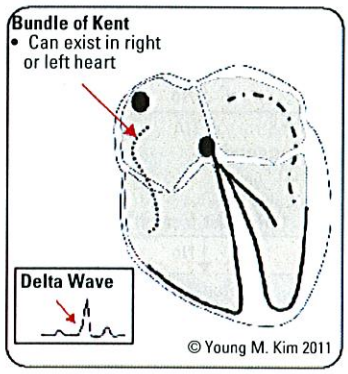


Figure 31. Accessory pathway conduction in WPW. Early ventricular activation leads to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction across the AV node

Pre-Excitation Syndromes

- refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

AV Re-Entrant (or Reciprocating) Tachycardia (AVRT)

- re-entrant loop in antegrade via normal conduction system and retrograde via accessory pathway
- often in patients with an antegradely conducting bypass tract (WPW); may also occur if there is an exclusively retrogradely conducting (i.e. concealed) bypass tract - in these cases the ECG is normal and there are no delta waves. Note that most AVRT is orthodromic, therefore, retrograde conduction up the pathway is most common mechanistically initiated by a premature atrial or ventricular complex
- treatment
  - acute: treatment is similar to AVNRT but avoid long-acting AV nodal blockers (e.g. digoxin and verapamil)
  - long-term: for recurrent arrhythmias, ablation of the bypass tract is recommended
  - drugs such as flecainide and procainamide can be used

Wolff-Parkinson-White Syndrome

- congenital defect present in 1.5-2/1000 of the general population
- an accessory conduction tract (bundle of Kent; can be in RA or LA) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the bundle of Kent thereby effectively 'bypassing' AV node
  - since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex the so-called "delta wave"
- atrial impulses that conduct to the ventricles through both the bundle of Kent and the normal AV node/His-Purkinje system generate a broad "fusion complex"
- ECG features of WPW
  - PR interval <120 msec
  - delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  - widening of the QRS complex due to premature activation
  - secondary ST segment and T wave changes
  - tachyarrhythmias may occur most often AVRT and AFib
- orthodromic AVRT: the most common arrhythmia in WPW stimulus from a premature complex travels up the bypass tract (ventricles to atria) and down the AV node (atria to ventricles) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
  - comprises 95% of the re-entrant tachycardias associated with WPW syndrome
- antidromic AVRT: more rarely, the stimulus goes up the AV node (ventricles to atria) and down the bypass tract (atria to ventricles); wide and abnormal QRS as ventricular activation is only via bypass tract

AFib in WPW Patients

- AFib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - usually intermittent rather than persistent or permanent
- rapid atrial depolarizations in AFib are conducted antegradely through the bypass tract which is not able to filter impulses like the AV node can and thus the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens ("pre-excited AFib")
- treatment: electrical cardioversion, IV procainamide, or IV amiodarone
  - do not use drugs that slow AV node conduction during pre-excited AFib (e.g. digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and increase the risk of VFib
    - note: even without drug administration, AFib with WPW can lead to VFib and would be an indication for an urgent EPS and ablation (especially with very rapid ventricular rates during AFib)
  - long-term: ablation of bypass tract

Ventricular Tachyarrhythmias

Premature Ventricular Contraction or Ventricular Premature Beat

- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
- PVCs may be benign, but are usually significant in the following situations:
  - consecutive (≥3 = VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat ("R on T phenomenon"): may precipitate VT or VFib
- risk of sustained arrhythmia depends on the clinical situation (i.e. MI, HF), not the PVCs themselves
- **treatment**
  - lifestyle changes (e.g. limiting or eliminating alcohol, caffeine, and stimulants) may be sufficient in patients with mild symptoms
  - in patients with more severe symptoms or underlying structural disease, β-blockers, catheter ablation, or antiarrhythmic therapy may be indicated

Accelerated Idioventricular Rhythm

- ectopic ventricular rhythm with rate of 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (i.e. cardiomyopathy, HTN, valvular heart disease) but it does not affect prognosis and does not usually require treatment

Ventricular Tachycardia

- 3 or more consecutive ectopic ventricular complexes
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate approximately 300 bpm and monomorphic sinusoidal pattern
  - "sustained VT" if it lasts longer than 30 s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec)
  - AV dissociation, bizarre QRS pattern
  - also favour diagnosis of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally, during VT, supraventricular impulses may be conducted to the ventricles; these impulses generate QRS complexes with normal/aberrant supraventricular morphology (i.e. "ventricular capture") or summation pattern (i.e. "fusion complexes")
  - by itself, nonsustained VT (<30 s without hemodynamic collapse) independently increases mortality and cardiovascular events such as stroke; it can also indicate higher than usual risk of subsequent sustained VT, especially with structural heart disease
- **monomorphic VT**
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - can degenerate into polymorphic VT or VFib
  - typically result from intraventricular re-entry circuit, especially in patients with RV/LV dysfunction, may be idiopathic without any structural heart disease
  - potential causes: chronic infarct related scarring, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- **polymorphic VT**
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm)
  - potential causes: acute MI, severe or silent ischemia, valvular heart disease, HCM, dilated cardiomyopathies, myocarditis, congenital heart disease, WPW with anterograde accessory pathway, electrolyte or acid-base disturbances, and predisposing factors for QT prolongation

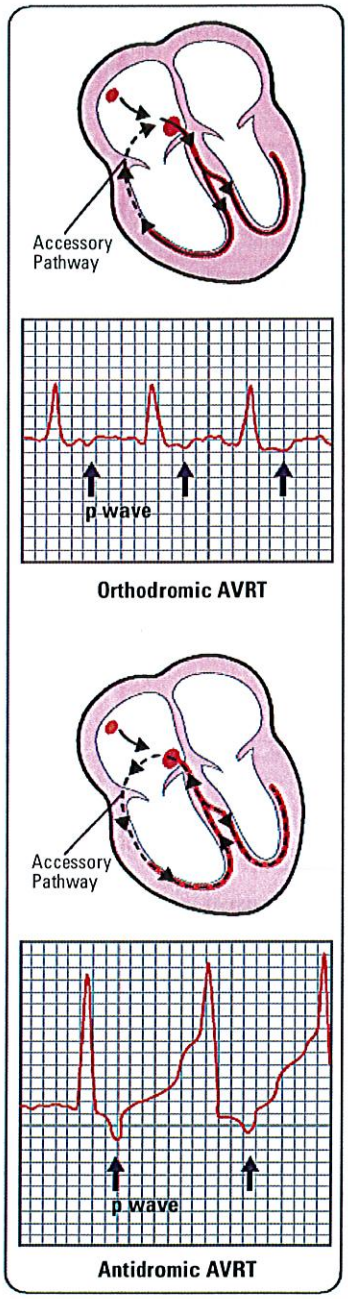


Figure 32. Orthodromic vs. antidromic AVRT

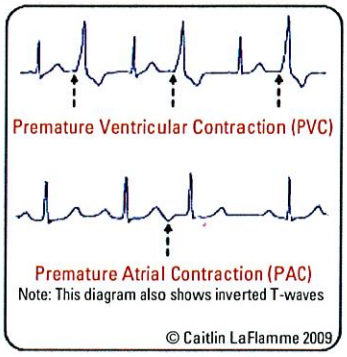


Figure 33. PVC (with bigeminy pattern) and PAC. Note the difference between the normal QRS/T wave and the PVC-generated QRS/T wave

- **treatment**
  - sustained VT (>30 s) is an emergency requiring immediate treatment
  - hemodynamic compromise: treat VT with electrical cardioversion and ACLS
  - no hemodynamic compromise: treat VT with electrical cardioversion, amiodarone, Type IA agents (e.g. procainamide, quinidine)
  - every patient with sustained VT/VFib and comorbid structural heart disease, in the absence of reversible causes, should be considered for ICD implantation to prevent SCD

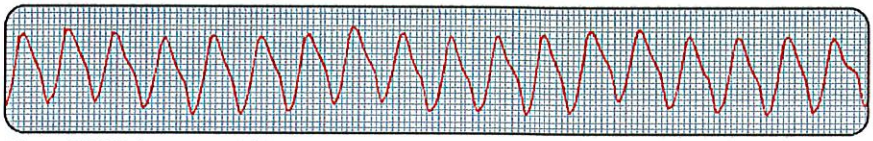


Figure 34. VT (monomorphic)

Table 7. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy*

Clinical Clues		ECG Clues	
Presenting symptoms	Not helpful	AV dissociation	VT
History of CAD and previous MI	VT	Capture or fusion beats	VT
Physical exam		QRS width >140 msec	VT
Cannon "a" waves Variable S1	VT	Extreme axis deviation (left or right superior axis)	VT
Carotid sinus massage/adenosine terminates arrhythmia	SVT**	Positive QRS concordance (R wave across chest leads)	VT
		Negative QRS concordance (S wave across chest leads)	May suggest VT
		Axis shift during arrhythmia	VT (polymorphic)

*If patient >65 yr and previous MI or structural heart disease, then chance of VT >95%
**May terminate VT in some patients with no structural heart disease

Arrhythmias that may present as a Wide QRS Tachycardia

- VT (this is most common, especially in older patients or those with structural heart disease)
- SVT with aberrant conduction (rate related)
- SVT with pre-existing BBB or nonspecific intraventricular conduction defect
- AV conduction through a bypass tract in WPW patients during an atrial tachyarrhythmia (e.g. atrial flutter, atrial tachycardia)
- Antidromic AVRT in WPW patients (see *Pre-Excitation Syndromes, C25*)

Torsades de Pointes

- a variant of polymorphic VT that occurs in patients with baseline QT prolongation "twisting of the points"
- looks like usual VT except QRS complexes "rotate around the baseline," changing their axis and amplitude
- usually starts following a post extrasystolic pause ("pause dependent")
- ventricular rate >100 bpm, usually 150-300 bpm
  - usual onset after a post-PVC pause associated with "pause dependent" QT prolongation)
- etiology: occurs in association with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing ß blocker, correct the underlying cause of prolonged QT
  - electrical cardioversion and ACLS if hemodynamic compromise

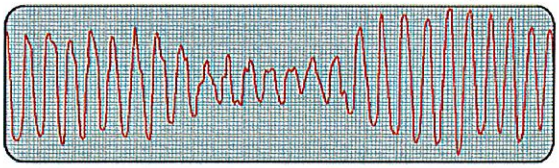


Figure 35. Torsades de pointes

Ventricular Fibrillation

- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology without clear QRS complexes
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and CO, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines

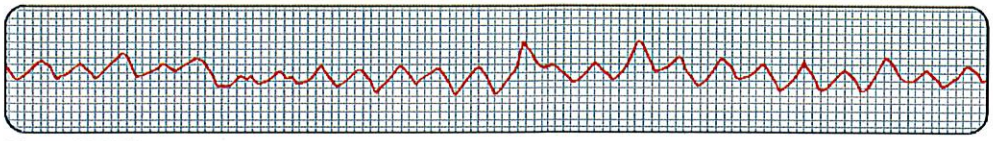


Figure 36. VFib

Sudden Cardiac Arrest

Definition

- cessation of cardiac electrical activity with circulatory collapse (loss of pulses) and gasping respirations or lack of spontaneous breathing
- patient becomes suddenly unresponsive
- presenting rhythms may be PEA, asystole, VFib (less commonly pulseless VT)

Etiology

- the likelihood of an underlying cardiac cause is proportional to age at time of arrest
  - cardiac causes (especially CAD) are more likely in older adults
  - non-cardiac causes are more likely in children and young adults (<35 yr)

Table 8. Etiology of Cardiac Arrest

Cardiac Causes		Non-Cardiac Causes	
myocardial Ischemia	STEMI NSTEMI Coronary spasm coronary dissection Anomalous coronary artery	**Vascular**	Pulmonary embolism Aortic dissection Aortic rupture Stroke
Ischemic Cardiomyopathy	HF Scar	**Neurologic**	Sudden unexplained death in epilepsy Neurogenic
Non-Ischemic Cardiomyopathy	Dilated CM Hypertrophic CM Infiltrative CM myocarditis Arrhythmogenic RV CM Hypertensive CM VHD with LV failure	**Hemorrhagic**	Subarachnoid Intracranial Gastrointestinal
Valvular Heart Disease	AS MR	**Infection**	Sepsis Pneumonia
Heritable ion channel disorders	Long QT syndrome Brugada syndrome	**Respiratory**	Respiratory arrest Tension pneumothorax
Primary Arrhythmogenic	Acquired QT prolongation Idiopathic Complete heart block WPW	**Other**	Substance overdose Ketoacidosis Trauma
Congenital Heart Disease	Tetralogy of Fallot VSD Post-Surgical scar		

Management

- acute: resuscitate according to ACLS guidelines (see Anesthesia, A32)
  - resuscitation can be grouped into those with and without shockable rhythms
  - activation of emergency systems and high-quality chest compressions are essential for any bystander
- investigate underlying causes using cardiac catheterization, electrophysiologic studies, echocardiography
  - patients with ST-elevation require emergent coronary angiography and revascularization
  - patients without ST-elevation can still have clinically relevant coronary lesions and therefore benefit from coronary angiography on a non-emergent basis
- initiate targeted temperature management to optimize neurologic recovery regardless of presenting rhythm
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone, lidocaine, β-blockers
- ICD for secondary prevention



See Landmark Cardiology and Cardiac Surgery Trials table for more information on COACT, which details the 1-yr clinical outcomes of angiography timing on survival in resuscitated cardiac arrest patients without STEMI.

Electrophysiologic Studies

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block (rarely performed)
- tachyarrhythmias: map for possible ablation, assess inducibility of VT prior to ICD implant

Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia with intermittent bradycardia precluding rate limiting medications

Pacemaker Indications

- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

Pacemaker Complications

- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas, and infection; rarer complications include venous stenosis or thrombosis, and tricuspid regurgitation
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome, lead fractures, and pacemaker-mediated tachycardia (note: PMT is benign and self-limited, though may be bothersome to patients)

Pacing Techniques

- temporary: transvenous (jugular, subclavian, femoral) or external (transcutaneous) pacing
- permanent: transvenous into RA, apex of RV, or both
- single or dual chamber: can sense and pace atrium, ventricle, or both
- rate responsive, able to respond to physiologic demand
- biventricular pacing (cardiac resynchronization therapy): leads are guided to RV and LV to stimulate both ventricles

Implantable Cardioverter Defibrillators

- SCD usually results from VFib, sometimes preceded by monomorphic or polymorphic VT
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention and selected patients for primary prevention
- CRT-D may be of benefit in patients with LBBB, prolonged QRS, and LVEF <35%
- see *Heart Failure, C40* for current treatment recommendations

Catheter Ablation

Modalities

- radiofrequency (RF) ablation: a low-voltage high-frequency form of electrical energy (similar to cautery); RF ablation produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth
- cryoablation: technology which uses a probe with a tip that decreases in temperature to -20°C and -70°C; small necrotic lesions are produced in a similar fashion to RF ablation; when brought to -20°C, the catheter tip reversibly freezes the area; when brought to -70°C for 5 min, it permanently scars the tissue
  - advantage: can "test" areas before committing to an ablation
  - disadvantage: takes much longer than RF (5 min per cryoablation vs. 1 min per RF ablation)
  - cryoablation is most commonly used for AFib

Indications

- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases; slow AV nodal pathway is targeted for ablation in these cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm with an accessory AV connection as one of the limbs
  - corrected by targeting the accessory pathway
- atrial flutter: re-entry circuit in RA
- AFib: primarily isolation of pulmonary vein triggers, usually with additional ablation in the atrial chambers
- idiopathic VT: focus arises from the right ventricular outflow tract or left ventricular outflow tract and less commonly originates in the inferoseptal LV near the apex
  - scar mediated VT most commonly due to scarring from previous MI or other cardiomyopathies; ablation less often successful and not first line therapy
  - significant benefit was seen with catheter ablation vs. antiarrhythmic drug escalation among patient with amiodarone-resistant VT, in contrast to non-amiodarone resistant VT

Major Complications
- cardiac: high grade AV block requiring permanent pacemaker (less risk with cryoablation), new or worsening arrhythmia, tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: PE

Ischemic Heart Disease

Epidemiology
- refer to CCS guidelines - 2014 Stable Ischemic Heart Disease Guidelines for Diagnosis and Management for more information
- most common cause of cardiovascular morbidity and mortality
- patients may have asymptomatic or symptomatic disease
- silent myocardial ischemia may be a predictor of adverse coronary events and cardiac mortality
  - needs to be monitored via intracardiac monitoring of physiological and hemodynamic parameters, metabolic indicators of ischemia in the coronary sinus, and hemodynamic factors
  - optimal medical therapy (reduction of HR and BP) and myocardial revascularization
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- M:F=2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
  - CHD incidence in women triples shortly after menopause
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease see Family Medicine, FM8

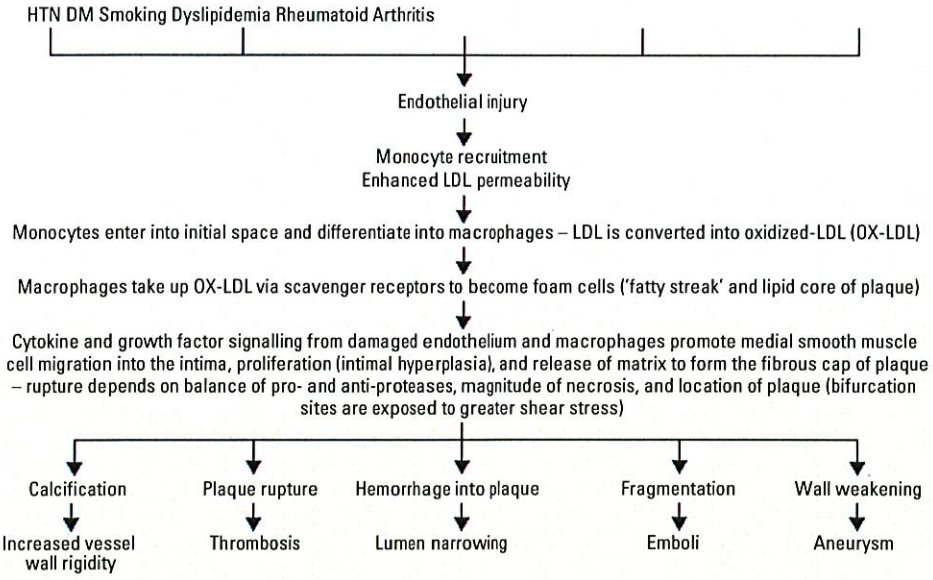


Figure 37. Pathophysiology of atherosclerosis

Table 9. Risk Factors and Markers for Atherosclerotic Heart Disease

Non-Modifiable Risk Factors	Modifiable Risk Factors §	Markers of Disease
Age	Hyperlipidemia*	Elevated high-sensitivity C-reactive protein (hsCRP)
Male, postmenopausal female	HTN*	Coronary artery calcification
Family history (FHx) of MI*	DM*	Carotid IMT/plaque
First degree male relative <55 yr	Cigarette smoking*	Ankle-brachial index
First degree female relative <65 yr	Psychosocial stress	
	Abdominal obesity	
	Sedentary lifestyle	
	Heavy alcohol intake	
	Not consuming fruits and vegetables daily	
	Elevated lipoprotein(a)	
	Hyperhomocysteinemia	

* Major risk factors
§ Modifiable risk factors account for >90% of MIs

Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA)
NEJM 2020;382:1395-1407
Purpose: Assess clinical outcomes in stable coronary disease treated with invasive plus medical therapy vs. medical therapy alone.
Methods: 5179 patients were randomized to invasive therapy (angiography and revascularization) plus medical therapy or medical therapy alone plus angiography upon failure of initial conservative approach. The primary outcome was a composite of mortality from CV causes, MI, hospitalization for UA, HF or resuscitated cardiac arrest.
Results: Over a median of 3.2 yr, 318 and 352 primary outcome events occurred in the invasive-strategy and conservative-strategy groups, respectively. At 5 yr, the cumulative event rate was 16.4% and 18.2% in the invasive-strategy and conservative-strategy groups, respectively.
Conclusion: In patients with chronic stable coronary disease, there was no evidence that an initial invasive strategy reduced ischemic CV events or death from any cause over a median of 3.2 yr, compared with initial conservative medical therapy.

Chronic Stable Angina

Definition

- symptom complex resulting from an imbalance between oxygen supply and myocardial oxygen demand in the myocardium

Etiology and Pathophysiology

- factors that decrease myocardial oxygen supply:
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased SaO_2: hypoxemia
  - congenital anomalies
- factors that increase myocardial oxygen demand:
  - increased HR: hyperthyroidism, exercise, anemia, pregnancy
  - increased contractility: hyperthyroidism
  - increased wall stress: myocardial hypertrophy, AS

Chronic stable angina is most often due to a fixed stenosis caused by an atheroma
ACSs are the result of plaque rupture which causes a cascade resulting in thrombosis

Signs and Symptoms

- typical
  1. retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
  2. predictably precipitated by the "3 Es": exertion, emotion, eating
  3. brief duration, lasting <10-15 min and typically relieved by rest and nitrates
- atypical/probable angina (meets 2 of the above)
- non-cardiac chest pain (meets none or 1 of the above)
- Levine's sign: clutching fist over sternum when describing chest pain
- anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema
- ischemia may present differently in understudied populations

Canadian Cardiovascular Society (CCS) Functional Classification of Angina

Class I: ordinary physical activity (walking, climbing stairs) does not cause angina; angina with strenuous, rapid, or prolonged activity

Class II: slight limitation of ordinary activity: angina brought on at >2 blocks on level or climbing >1 flight of stairs, or by emotional stress

Class III: marked limitation of ordinary activity: angina brought on at <2 blocks on level or climbing <1 flight of stairs

Class IV: inability to carry out any physical activity without discomfort; angina may be present at rest

Clinical Assessment

- history including directed risk factor assessment and physical exam
- labs: Hb, fasting glucose, fasting lipid profile, HbA1c, renal function tests, liver function tests, and thyroid function test
- 12-lead ECG (at rest and during episode of chest pain if possible)
- CXR (suspected HF, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs/symptoms of pulmonary disease)
- stress testing (see *Stress Testing, C15*) or angiography
- echo for other causes of chest pain:
  - aortic dissection
  - valvular heart disease
  - HCM
  - LV dysfunction and/or wall motion abnormality
  - pericardial disease/effusion

Differential Diagnosis

- see *Differential Diagnoses of Common Presentations, C5*

Aspirin in the Primary Prevention of Cardiovascular Disease on Diabetic Patients: Systematic Review and Meta-analysis
Primary Care Diabetes. 2020;14(3):213-21
Purpose: This study sought to conduct a systematic review of all randomized controlled trials that assessed the clinical effects of aspirin in diabetic patients for primary prevention purposes.
Methods: A comprehensive search was conducted in MEDLINE, EMBASE, and CENTRAL for RCTs examining the effects of aspirin in diabetic patients for primary prevention. The primary outcomes were all-cause mortality and the composite outcome of major adverse cardiovascular events.
Results: No significant reduction in all-cause mortality was found (RR 0.96, 95% CI 0.90-1.03; 7 RCTs; 27595 patients). However, there was an 8% risk reduction in major adverse cardiovascular events (RR 0.92, 95% CI 0.84-0.999; 8 RCTs; 29814 patients). The risks of major bleeding (RR 1.30, 95% CI 1.10-1.53; 2 RCTs, 18019 patients) and major gastrointestinal bleeding (RR 1.39, 95% CI 1.08-1.80; 2 RCTs, 18019 patients) were significantly increased.
Conclusions: The use of aspirin in primary prevention for diabetic patients was linked to an increased risk of major bleeding, a modest reduction in major adverse cardiovascular events, and no observed benefit in terms of mortality

Treatment of Chronic Stable Angina

- refer to 2019 European Society of Cardiology guidelines for more information

1. General Measures

- goals: to reduce myocardial oxygen demand and/or increase oxygen supply
- lifestyle modification (diet, exercise, smoking cessation)
- treatment of risk factors: e.g. statins (see Endocrinology, E5, Family Medicine, FM11 for target lipid guidelines), antihypertensives
- pharmacological therapy to stabilize the coronary plaque which will prevent rupture and thrombosis

2. Antiplatelet Therapy (first-line therapy)

- ASA
- clopidogrel when ASA contraindicated
- low dose rivaroxaban in combination with ASA (based on COMPASS trial)

3. β-blockers (first-line therapy improves survival in patients with HTN)

- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)
- avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand

4. Nitrates (symptomatic control, no clear impact on survival)
- decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
- maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

5. Calcium Channel Blockers (CCBs, second-line or combination)
- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block
- contraindicated in patients with LV systolic dysfunction

6. Renin-Angiotensin-Aldosterone System Blockade
- angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. HTN, DM, proteinuric renal disease, previous MI with LV dysfunction)
- ARB can be considered in patients intolerant to ACEI
- benefit in all patients at high-risk for CV disease (e.g. those with concomitant DM, renal dysfunction, or LV systolic dysfunction)

7. Invasive Strategies
- revascularization (see *Coronary Revascularization, C37*)

Variant Angina (Prinzmetal's Angina)
- Myocardial ischemia secondary to coronary artery vasospasm with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 am, unrelated to exercise, relieved by nitrates
- typically ST elevation is observed on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs
- strongly recommend patient to stop smoking

Syndrome X
- Typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis

Acute Coronary Syndromes

Definition
- ACS includes the spectrum of UA, NSTEMI, and STEMI; this distinction aids in providing the appropriate therapeutic intervention
  - UA is clinically defined by any of the following:
    - accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
    - angina at rest
    - new-onset angina
    - angina post-MI or post-procedure (e.g. PCI, CABG)
  - MI (STEMI/NSTEMI) is defined by evidence of myocardial necrosis and is diagnosed by a rise/fall of serum markers plus any one of:
    - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
    - ECG changes (ST-T changes, new BBB, or pathological Q waves)
    - imaging evidence (myocardial loss of viability, wall motion abnormality, or intracoronary thrombus)
    - if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
  - NSTEMI meets criteria for MI without ST elevation or BBB
  - STEMI meets criteria for MI characterized by ST elevation or new BBB
- possible ACS in women, diabetics, and older adults is more likely to present with "atypical" symptoms such as dyspnea or weakness even in the presence of acute coronary-related ischemia



Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction (COLCOT)
NEJM 2019;381:2497-2505
Purpose: To determine if colchicine lowers risk of future CV events following MI.
Methods: Patients (n=4745) who had an MI within the last 30 d were randomized to colchicine once daily or placebo. The primary efficacy endpoint was a composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina.
Results: Median follow-up was 22.6 mo. The primary endpoint occurred in 5.5% and 7.1% of patients in the colchicine and placebo groups, respectively (P=0.02). Pneumonia was observed in 0.9% of the patients in the colchicine group and in 0.4% of patients in the placebo group (P=0.03).
Conclusion: In patients with recent MI, colchicine lowered the risk of subsequent CV events as compared to placebo.

Investigations
- history and physical
  - note that up to 30% of MIs are unrecognized or "silent" due to atypical symptoms that are more common in women, patients with DM, elderly, post-heart transplant (because of denervation)
- ECG
- CXR

- labs
  - serum cardiac biomarkers for myocardial damage (use of high-sensitive cardiac troponin (hs-cTn) with a validated 0 h/2 h algorithm recommended blood sampling at 0 h and 2 h) (see *Cardiac Biomarkers, C13*)
  - CBC, International Normalized Ratio (INR)/prothrombin time test (PTT), electrolytes, magnesium, creatinine, urea, glucose, and serum lipids
  - draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General Measures
- ABCs: assess and correct hemodynamic status first
- bed rest, cardiac monitoring, oxygen
- nitroglycerin sublingual (SL) followed by IV
- morphine IV

2. Antiplatelet and Anticoagulation Therapy
- see also 2018 CCS/CAIC Antiplatelet Guidelines, 2012 and 2010 CCS Antiplatelet Guidelines, and 2009 CCS Position Statement on Dual Antiplatelet Therapy in Patients Requiring Urgent CABG for details (free mobile apps available on iOS and Android platforms in the CCS app stores). Also see 2020 ESC guidelines on ACS management in patients without persistent ST-segment elevation, 2017 ESC guidelines on STEMI management, and 2019 CCS guidelines on acute STEMI management (focused update on regionalization and reperfusion)
- ASA chewed
- NSTEMI
  - ticagrelor + ASA + LMWH/IV unfractionated heparin (UFH), unless contraindications
    - LMWH, except in renal failure or if CABG is planned, within 24 h
    - fondaparinux also commonly used in Canada for initial medical management of NSTEMI/UA based on OASIS-5 results
  - clopidogrel used if patient ineligible for ticagrelor
- if PCI is planned: ticagrelor or prasugrel and consider IV glycoprotein IIb/IIIa inhibitor (e.g. eptifibatide, tirofiban)
  - clopidogrel used if patient ineligible for ticagrelor and prasugrel
  - prasugrel contraindicated in those with a history of stroke/TIA, and its avoidance or lower dose is recommended for those >75 yr or weighing <60 kg (TRITON-TIMI 38)
- anticoagulation options depend on reperfusion strategy:
  - primary PCI: UFH during procedure; bivalirudin is a possible alternative
  - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
  - no reperfusion: LMWH (enoxaparin) until discharge from hospital
- continue LMWH or UFH followed by oral anticoagulation at discharge if at high-risk for thromboembolic event (large anterior MI, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)
  - in patients with AFib (CHA2DS2-VASc score ≥1 in men and ≥2 in women), use triple antithrombotic therapy for up to 1 wk and then transition to dual antithrombotic therapy (using a NOAC and an antiplatelet agent (preferably clopidogrel))

3. β-blockers
- STEMI: contraindications include signs of HF, low output states, risk of cardiogenic shock, heart block, asthma, or airway disease; initiate orally within 24 h of diagnosis when indicated
- if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine CCB (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (CCB do not prevent MI or decrease mortality)

4. Invasive Strategies and Reperfusion Options
- UA/NSTEMI: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  - diagnosis of NSTEMI
  - recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  - CHF or LV dysfunction
  - hemodynamic instability
  - high (≥3) Thrombolysis in Myocardial Infarction (TIMI) risk score (tool used to estimate mortality following an ACS)
  - GRACE risk score >140
  - sustained ventricular tachycardia
  - dynamic ECG changes, transient ST-elevation
  - high-risk findings on non-invasive stress testing
  - PCI within the previous 6 mo
  - repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high-risk features
  - note: thrombolysis is NOT administered for UA/NSTEMI



Complete Revascularization with Multivessel PCI for Myocardial Infarction (COMPLETE)
NEJM 2019;381:1411-1421
Purpose: To determine if PCI of non-culprit lesions, in addition to culprit lesions, further reduces the risk of CV events or MI in patients with STEMI.
Methods: Patients with STEMI and multivessel CAD who had undergone culprit-lesion PCI (n=4041) were randomized to either complete revascularization with PCI (of significant non-culprit lesions) or no further revascularization. The two main outcomes measured included: 1) the composite of CV death or MI, and 2) the composite of CV death, MI, or ischemia-driven revascularization.
Results: The first outcome was observed in 7.8% of the complete revascularization group and 10.5% of the culprit-lesion-only PCI group (P=0.004). The second outcome was observed in 8.9% of the complete revascularization group and 16.7% of the culprit-lesion-only PCI group (P<0.001).
Conclusions: In patients with STEMI and multivessel CAD, complete revascularization by PCI further reduced the risk of CV death or MI as compared to culprit-lesion-only PCI.



TIMI Risk Score for UA/NSTEMI

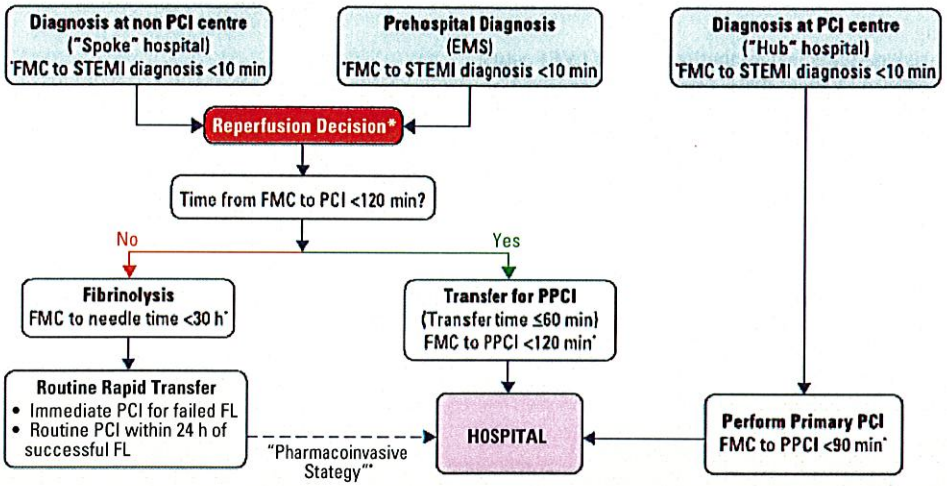
Characteristics	Points
Historical	
Age ≥65 yr	1
≥3 risk factors for CAD	1
Known CAD (stenosis ≥50%)	1
Aspirin ® use in past 7 d	1
Presentation	
Recent (≤24 h) severe angina	1
ST-segment deviation ≥0.5 mm	1
Increased cardiac marker	1

Risk Score = Total Points
If TIMI risk score ≥3 , consider early LMWH and angiography
TIMI = thrombolysis in myocardial infarction
UA = unstable angina
JAMA 2000;284:835-842

ALGrawany

- STEMI
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis ("EMS-to-needle") within 30 min or primary PCI ("EMS-to-balloon") within 90 min (if available)
  - PCI
    - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intracranial hemorrhages and recurrent MIs
    - primary PCI: without prior thrombolytic therapy method of choice for reperfusion in experienced centres
    - rescue PCI: following failed thrombolytic therapy (diagnosed when ST segment elevation fails to resolve below half its initial magnitude after thrombolysis and patient still has chest pain)

    thrombolysis
    - assuming no contraindications, use if <12 h since symptom onset and primary PCI cannot be conducted within 120 min of STEMI diagnosis
    - note: benefit of thrombolysis is inversely proportional to time from symptom onset; in patients meeting the above criteria, the later the presentation (>3 h), the more one should consider using primary PCI instead (depending on clinical circumstances)



*Also consider clinical factors such as symptom duration and presence of contraindications to fibrinolysis
EMS = emergency medical services; FL = fibrinolysis; FMC = first medical contact; PCI = percutaneous coronary intervention; PPCI = primary percutaneous coronary intervention. Guideline based recommendations: strong = '; weak = #

Figure 38. Reperfusion strategy in STEMI

Table 10. Contraindications for Thrombolysis in STEMI

Absolute	Relative
Prior intracranial hemorrhage	Chronic, severe, poorly controlled HTN
Known structural cerebral vascular lesion	Uncontrolled HTN (sBP >180, dBP >110)
Known malignant intracranial neoplasm	Current anticoagulation
Significant closed-head or facial trauma (≤3 mo)	Noncompressible vascular punctures
Ischemic stroke (≤3 mo)	Ischemic stroke (≥3 mo)
Active bleeding	Recent internal bleeding (≤2-4 wk)
Suspected aortic dissection	Prolonged CPR or major surgery (≤3 wk)
	Pregnancy
	Active peptic ulcer disease



Newer, more accurate risk quantification scores for UA/NSTEMI exist, such as the GRACE Risk Score; however, TIMI is still used most often

Long-Term Management of ACS

- risk of progression to MI, or recurrence of MI, or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre-discharge workup: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

1. General Measures

- education
- risk factor modification

2. Antiplatelet and Anticoagulation Therapy
- see also CCS Antiplatelet Guidelines 2018 for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
- ECASA 81 mg daily
- ticagrelor 90 mg BID or prasugrel 10 mg daily (at least 1 mo, up to 9-12 mo; if stent placed at least 12 mo)
- clopidogrel 75 mg daily can be used as alternatives to ticagrelor and prasugrel when indicated
- ± warfarin x 3 mo if high-risk (high-risk patients include those with large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)
- rivaroxaban 2.5 mg BID (based on COMPASS trial)

3. β-Blockers (e.g. metoprolol 25-50 mg BID or atenolol 50-100 mg daily)

4. Nitrates
- alleviate ischemia but do not improve outcome
- use with caution in right-sided MI patients who have become preload dependent

5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to β-blockers)

6. ACEIs
- prevent adverse ventricular remodelling
- recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
- recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
- use ARBs in patients who are intolerant of ACEI; avoid combining ACEI and ARB

7. ± Aldosterone Antagonists
- if already on ACEI and β-blockers, with and LVEF <40% and CHF or DM
- significant mortality benefit shown with eplerenone by 30 d

8. Lipid Lowering Therapy Statins (e.g. atorvastatin 80 mg daily)
- second line add-on therapy: ezetimibe or PCSK9 inhibitor
- as per CCS 2022 Dyslipidemia Guidelines, decision on which therapy to initiate can be based on achieved LDL (target is <1.8 mmol/L)

9. Invasive Cardiac Catheterization if indicated (risk stratification)

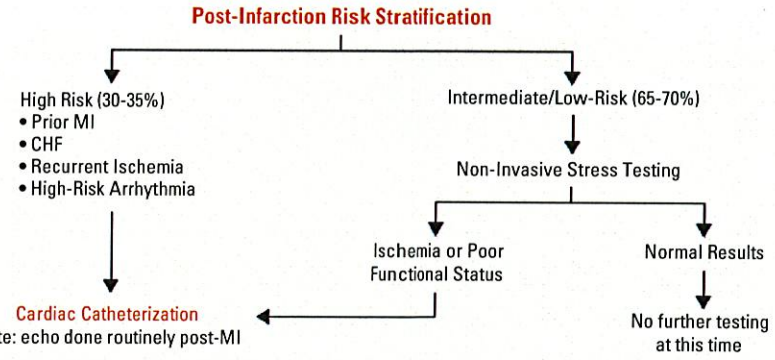


Figure 39. Post-MI risk stratification

Prognosis following STEMI
- 5-15% of hospitalized patients will die
  - risk factors
    - infarct size/severity
    - age
    - comorbid conditions
    - development of HF or hypotension
- post-discharge mortality rates
  - 6-8% within first year, half of these within first 3 mo
  - 4% per year following first yr
  - risk factors
    - LV dysfunction
    - residual myocardial ischemia
    - ventricular arrhythmias
    - history of prior MI

Is this Patient having a MI?
From The Rational Clinical Examination
JAMA 1998;381(14):1256-1263
Study: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of an acute MI.
Results: In patients with normal or non-diagnostic ECG, no established CAD, and prolonged or recurrent chest pain typical of their usual discomfort, radiation of pain to the shoulder OR both arms had the highest positive likelihood ratio (+LR) of 4.1 and a negative likelihood ratio (-LR) of 0.68. Radiation to the right arm had a +LR of 3.8 and –LR of 0.86, vomiting had a +LR of 3.5 and –LR of 0.87, while radiation to the left arm only had a +LR of 1.3 and a –LR of 0.9.
Conclusions: The most compelling features that increase likelihood of an MI are ST-segment and cardiac enzyme elevation, new Q-wave, and presence of an S3 heart sound. In patients where the diagnosis of MI is uncertain, radiation of pain to the shoulder OR both arms, radiation to the right arm, and vomiting had the best predictive values, while radiation to the left arm is relatively non-diagnostic.

Complications of MI

CRASH PAD
Cardiac Rupture
Arrhythmia
Shock
Hypertension/Heart failure
Pericarditis/Pulmonary embolism
Aneurysm
DVT

Resting LVEF is a useful prognostic factor

Table 11. Complications of MI

Complication	Etiology	Presentation	Therapy
Arrhythmia			See *Arrhythmias, C19*
1. Tachycardia	Sinus, AFib, VT, VFib	First 48 h	
2. Bradycardia	Sinus, AV block	First 48 h	
Myocardial Rupture			
1. LV free wall	Transmural infarction	1-7 d	Surgery
2. Papillary muscle (→ MR)	Inferior infarction	1-7 d	Surgery
3. Ventricular septum (→ VSD)	Septal infarction	1-7 d	Surgery
Shock/CHF	Infarction or aneurysm	Within 48 h	Inotropes, intra-aortic balloon pump
Post-Infarct Angina	Persistent coronary stenosis	Anytime	Aggressive medical therapy
	Multivessel disease		PCI or CABG
Recurrent MI	Reocclusion	Anytime	Aggressive medical therapy
			PCI or CABG
Thromboembolism	Mural/apical thrombus DVT	7-10 d, up to 6 mo	Anticoagulation
Pericarditis	Inflammatory	1-7 d	ASA
Dressler's Syndrome	Autoimmune	2-8 wk	

Treatment of NSTEMI

BEMOAN
β-blocker
Enoxaparin
Morphine
O_2
ASA
Nitrates

Treatment Algorithm for Acute Coronary Syndrome

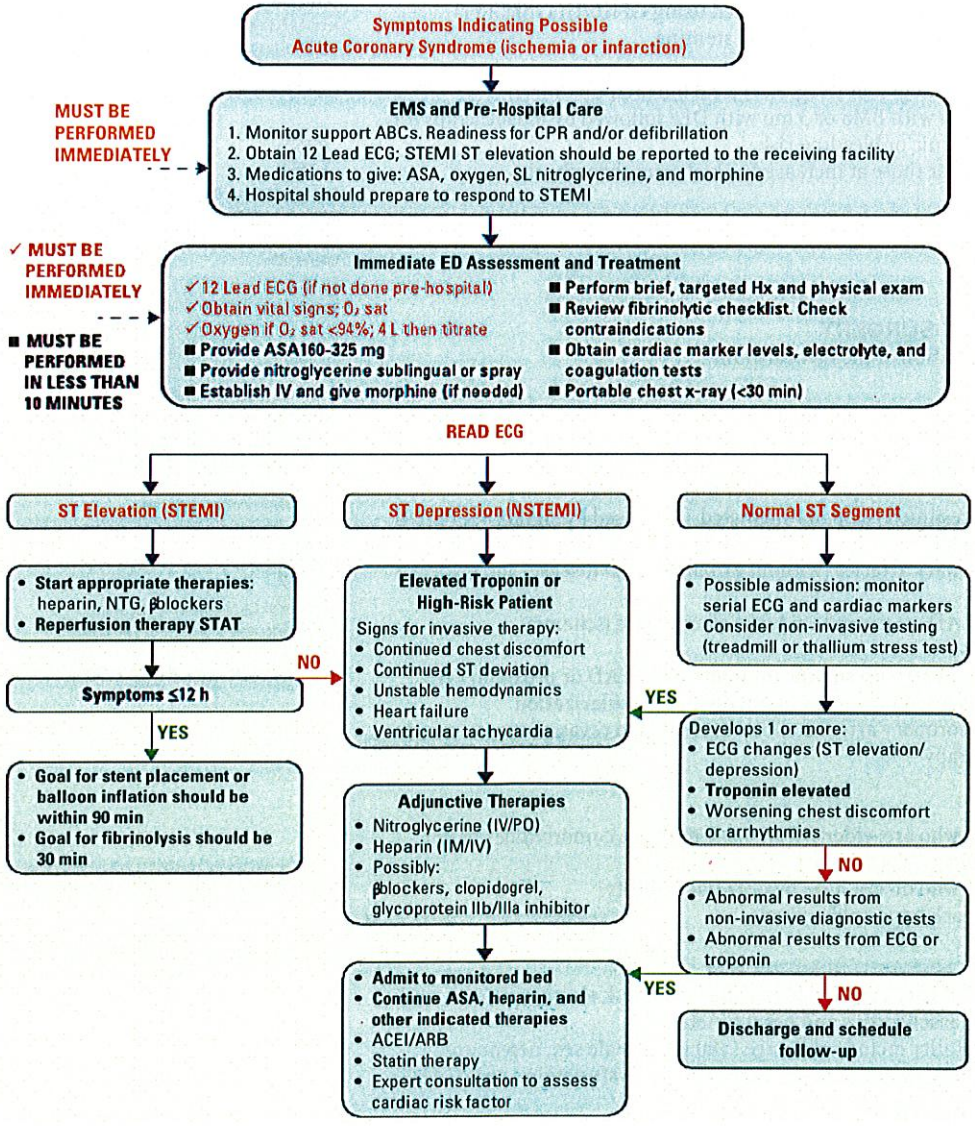


Figure 40. AHA ACLS acute coronary syndrome algorithm
Adapted from: Jeffery Media Productions 2016. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. Circulation. 2014 Jan 1:CIR-0000000000000134

Contraindications to nitrates: severe aortic stenosis, hypertrophic cardiomyopathy, suspected right ventricular infarct, hypotension, marked bradycardia or tachycardia, and recent use of phosphodiesterase 5 inhibitors.

Coronary Revascularization

PERCUTANEOUS CORONARY INTERVENTION

- interventional cardiology technique aimed at relieving significant coronary artery stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

Indications

- medically refractory angina
- NSTEMI/UA with high-risk features (e.g. high TIMI risk score)
- primary/rescue PCI for STEMI
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG

Balloon Angioplasty and Intracoronary Stenting

- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), thought to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
  - bare metal stent (BMS) vs. drug-eluting stents: PRAMI trial demonstrated stenting non-culprit lesions results in 14% absolute risk reduction of cardiac death, nonfatal MI, or refractory angina
  - coated with antiproliferative drugs (sirolimus, paclitaxel, everolimus, zotarolimus)
  - reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
  - complication: late stent thrombosis (5 events per 1000 stents implanted)

Adjunctive Therapies

- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel or ticagrelor) for 6 mo (and up to 1 yr)
  - consider short-duration DAPT for 1 mo with BMS or 3 mo with DES followed by monotherapy for 12 mo among patients with high ischemic or bleeding risk
  - ASA and prasugrel can be considered for those at increased risk of stent thrombosis

Procedural Complications

- mortality and emergency bypass rates <1%
- nonfatal MI: approximately 2-3%

CORONARY ARTERY BYPASS GRAFT SURGERY

- objective of CABG is complete revascularization of the myocardium

Indications

- ≥50% diameter stenosis in the left main coronary artery
- ≥70% diameter stenosis in three major coronary arteries
- ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
- survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
- ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
- multivessel CAD in patients with diabetes
- LV systolic dysfunction (LVEF 35% to 50%) and with significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- one or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

Contraindications

- CABG may be contraindicated in patients who are: elderly/frail, have multiple comorbidities or, for any other reason, may not survive surgery
- CABG may be contraindicated in patients who do not have myocardial viability
- CABG is contraindicated in patients that lack bypassable vessels

Results

- perioperative and in-hospital mortality rate after CABG: ~1% for the lowest risk elective patients, and 2% for all patients (depends on patient characteristics and heart function)
- predictive variables for early hospital mortality include older age (>80 yr), female sex, urgency of operation, left main stem disease, increasing extent of CAD, increasing LV dysfunctions, redo CABG



See Landmark Cardiology and Cardiac Surgery Trials table for more information on EXCEL which details the long-term efficacy profile of CABG vs. PCI in patients with left main CAD.



Ticagrelor with or without Aspirin® in High-Risk Patients after PCI
NEJM 2019;381:2032-2042
Purpose: To determine if monotherapy with ticagrelor, a P2Y12 inhibitor, after a period of dual antiplatelet therapy reduces the risk of bleeding following PCI.
Methods: Patients who were at high-risk for bleeding or an ischemic event underwent PCI and 3 mo of treatment with ASA plus ticagrelor. Patients (n=7119) were then randomized to receive either ticagrelor plus ASA or ticagrelor plus placebo for a year. The primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding.
Results: The primary endpoint was observed in 4.0% of patients in the ticagrelor plus placebo group and 7.1% of patients in the ticagrelor plus ASA group (P<0.001). The incidence of death from any cause, nonfatal MI, or nonfatal stroke was 3.9% in both groups (P<0.001 for noninferiority).
Conclusion: Among high-risk bleed patients who received PCI and 3 mo of dual antiplatelet therapy, additional ticagrelor monotherapy was associated with lower incidence of bleeding and the same risk of death, as compared to ticagrelor plus ASA therapy.



Safety and Efficacy Outcomes of Double vs. Triple Antithrombotic Therapy in Patients with Atrial Fibrillation Following Percutaneous Coronary Intervention
Eur Heart J 2019; 40:3757-3767
Purpose: To evaluate the safety and efficacy of double vs. triple antithrombotic therapy (DAT vs. TAT) in patients with AFib and ACS following PCI.
Methods: Systematic review and meta-analysis of 4 trials with a total of 10234 patients.
Conclusions: DAT was associated with lower risk of bleeding, but higher risk of stent thrombosis and MI compared to TAT. There was no significant difference in all-cause and cardiovascular death, stroke, and major adverse cardiovascular events.



See Landmark Cardiology and Cardiac Surgery Trials table for more information on SYNTAX, which details all-cause mortality, stroke, MI or repeat revascularization 12 mo following PCI vs. CABG.

Table 12. Choice of Revascularization Procedure

	PCI	CABG
Advantages	Less invasive technique Decreased periprocedural morbidity and mortality Shorter periprocedural hospitalization	Greater ability to achieve complete revascularization Decreased need for repeated revascularization procedures
Factors favouring Revascularization Procedure	**Clinical characteristics** Severe comorbidity Advanced age/frailty/reduced life expectancy Restricted mobility and conditions that affect rehabilitation **Anatomical and technical aspects** MVD with SYNTAX score <23 Anatomy likely resulting in incomplete revascularization with CABG due to poor quality or missing conduits Severe chest deformation or scoliosis Sequelae of chest radiation Porcelain aort	**Clinical characteristics** Diabetes Reduced LV function (EF ≤35%) Contraindications to DAPT Recurrent diffuse in-stent restenosis **Anatomical and technical aspects** MVD with SYNTAX score ≥23 Anatomy likely resulting in incomplete revascularization with PCI Severely calcified coronary artery lesions limiting lesion expansion Need for concomitant interventions Ascending aortic pathology with indication for surgery Concomitant cardiac surgery

Note: Table reflects guidelines from the European Society of Cardiology that have been taught to Canadian cardiac surgery residents

Table 13. Conduits for CABG

Graft	Occlusion/Patency Rate	Considerations
Saphenous Vein Grafts (SVG)	At 10 yr: 50% occluded, 25% stenotic, 25% angiographically normal	Used to be commonly used, but arterial conduits have proven to be superior
Left Internal Thoracic/Mammary Artery (LITA/LIMA)	90-95% patency at 15 yr	Considered the standard conduit for CABG Excellent patency Almost always used to bypass LAD Improved event-free survival (angina, MI) Decreased late cardiac events
Right Internal Thoracic/Mammary Artery (RITA/RIMA)	Pedicled RIMA patency comparable to LIMA Lower rate of free RIMA patency	Used in bilateral ITA/IMA grafting Patients receiving bilateral ITAs/IMAs have less risk of recurrent angina, late MI, angioplasty
Radial Artery (free graft)	85-95% patency at 5 yr	Prone to severe vasospasm postoperatively due to vascular muscular wall
Right Gastroepiploic Artery	80-90% patency at 5 yr	Primarily used as an *in situ* graft to bypass the RCA Use limited because of the fragile quality of the artery, technical issues, increased operative time (laparotomy incision), and incisional discomfort with associated ileus
Complete Arterial Revascularization		For younger patients (<60 y/o) Preferred due to longer term graft patency
Redo Bypass Grafting		Indications for redo CABG: symptomatic patients (disabling angina) who have failed medical therapy, have stenotic vessels, have viable myocardium, have suitable distal targets Risk factors for redo CABG: poor control of HTN/hypercholesterolemia/smoking, normal LV, 1 or 2 vessel disease, no use of IMA/ITA in initial CABG, incomplete revascularization in initial CABG, young age Operative mortality 2-3 times higher than first operation 10% perioperative MI rate Reoperation undertaken only in symptomatic patients who have failed medical therapy and in whom angiography has documented progression of the disease Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA/ITA, and other bypass grafts, uncontrollable hemorrhage, arterial bleeding and VFib, venous bleeding, or failure to arrest heart

Adapted from: Chikwe J, Beddow E, Glenville B. Cardiothoracic Surgery, 1st ed. Oxford, UK: Oxford UP. 2006.

Operative Issues

- LV function is an important determinant of outcome for all heart diseases
- patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, stress echo, positron emission tomography (PET) scanning, or MRI



Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients with Three-vessel or Left Main Coronary Artery Disease

Lancet 2019;394:1325-34

Purpose: Report 10-yr all-cause mortality results as a 10-yr follow-up to the 2009 SYNTAX trial.

Methods: Adult patients with established left main CAD or three-vessel coronary disease were randomized to receive either PCI or CABG in a 1:1 ratio. Patients with a prior history of MI, PCI or CABG were excluded. The primary study endpoint was 10-yr all-cause mortality.

Results: 10-yr all-cause mortality rates were 28% and 24% for PCI- and CABG-treated patients, respectively (hazard ratio 1.19; 95% CI 0.99 to 1.43; P=0.066). In subgroup analysis, 10-yr all-cause mortality was 28% and 21% in PCI and CABG patients with three-vessel disease, respectively (hazard ratio 1.42; 95% CI 1.11 to 1.81). The same primary endpoint occurred in patients with left main coronary disease at a rate of 27% and 28% in PCI and CABG patients, respectively (hazard ratio 0.92; 0.69 to 1.22; P=0.023).

Conclusions: CABG provided a significant all-cause survival benefit in patients with three-vessel disease, compared to PCI in the same population. This effect was not observed in patients with left main CAD or in the pooled study sample.



Duration of Dual Antiplatelet Therapy Following Drug-eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with Longer Follow up

Catheter Cardiovasc. Interv. 2017; 90:31-7

Purpose: Conduct an updated meta-analysis to compare the efficacy and safety of short-term dual antiplatelet therapy (S-DAPT) vs. long-term DAPT (L-DAPT) in patients who underwent drug-eluting stent (DES) implantation.

Methods: RCTs comparing efficacy and/or safety outcomes for different DAPT durations after coronary DES implantation were searched in PubMed, CINAH, Cochrane CENTRAL, EMBASE, Scopus, and Web of Science. S-DAPT was defined as ≤12 mo duration of aspirin plus P2Y12 receptor inhibitor, while L-DAPT was defined as the same combination for >12 mo duration after DES implantation.

Results: 5 RCTs met all eligibility criteria and were included in the final meta-analysis. Outcomes of interest included all-cause mortality, cardiac mortality, myocardial infarction, stent thrombosis, target vessel revascularization, stroke, or major bleeding. Compared with L-DAPT, S-DAPT did not significantly increase the rate of stent thrombosis (OR 1.59; 95% CI 0.77 to 3.27). All-cause mortality, cardiac mortality, target vessel revascularization and stroke were also not significantly different between groups. However, S-DAPT was associated with an increased risk of MI (OR 1.48; 95% CI 1.04 to 2.10) and a lowered risk of major bleeding (OR 0.64; 95% CI 0.41 to 0.99).

Conclusions: In this meta-analysis with a longer follow-up time of ≥24 mo, S-DAPT compared to L-DAPT was associated with increased risk of MI but lower rates of major bleeding. No significant differences were found for all-cause mortality, cardiac mortality, stent thrombosis, target vessel revascularization, or stroke.

CABG and Antiplatelet Regimens

- refer to CCS guidelines 2018 update on antiplatelet therapy for more information
- prior to CABG, clopidogrel and ticagrelor should be discontinued for 5 d, and prasugrel for 7 d before surgery
- dual antiplatelet therapy should be continued for 12 mo in patients with ACS within 48-72 h after CABG
- ASA (81 mg) continued indefinitely (can be started 6 h after surgery)
- patients requiring CABG after PCI should continue their dual antiplatelet therapy as recommended in the post-PCI guidelines

Table 14. Risk Factors for CABG Mortality and Morbidity

Risk Factors for CABG Mortality	Risk Factors for CABG Postoperative Morbidity or Increased Length of Stay
Urgency of surgery (emergent or urgent)	Reoperation
Reoperation	Emergent procedure
Older age	Preoperative intra-aortic balloon pump (IABP)
Poor LV function (see below)	CHF
Female gender	CABG + valve surgery
Left main disease	Older age
Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, DM, cerebrovascular disease, and peripheral vascular disease	Renal dysfunction
	COPD
	DM
	Cerebrovascular disease

Note: risk factors are listed in decreasing order of significance

Procedural Complications

- CABG using CPB (see *Cardiopulmonary Bypass, C69*)
- stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
- immunosuppression
- deep sternal wound infection
- bleeding
- systemic inflammatory response leading to:
  - myocardial dysfunction
  - renal dysfunction
  - neurological injury
  - respiratory dysfunction
  - coagulopathies

OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Procedure

- avoids the use of CPB by allowing surgeons to operate on a beating heart
  - stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - procedure is safe and well tolerated by most patients; however, this surgery remains technically more demanding

Indications/Contraindications

- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe PVD, severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah's Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- absolute contraindications: hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels, and calcified coronary vessels
- relative contraindications: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

Outcomes

- OPCAB surgery decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
  - OPCAB has been associated with lower graft patency



See Landmark Cardiology and Cardiac Surgery Trials table for more information on ROOBY, which details the 5-year clinical outcomes in patients undergoing on-pump vs. off-pump CABG.

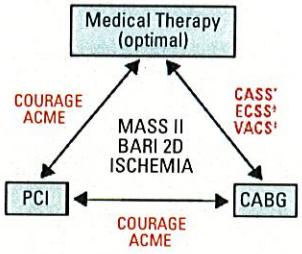


Figure 41. Clinical trials comparing strategies for stable CAD
Figure recreated with permission from Dr. Chris Overgaardn

Heart Failure

- see also CCS Heart Failure Guidelines 2021 for details (free mobile apps available on iOS and Android platforms in the CCS app stores) as well as the Canadian Cardiovascular Society (CCS) Heart Failure Guidelines Compendium available at CCS.ca

Congestive Heart Failure

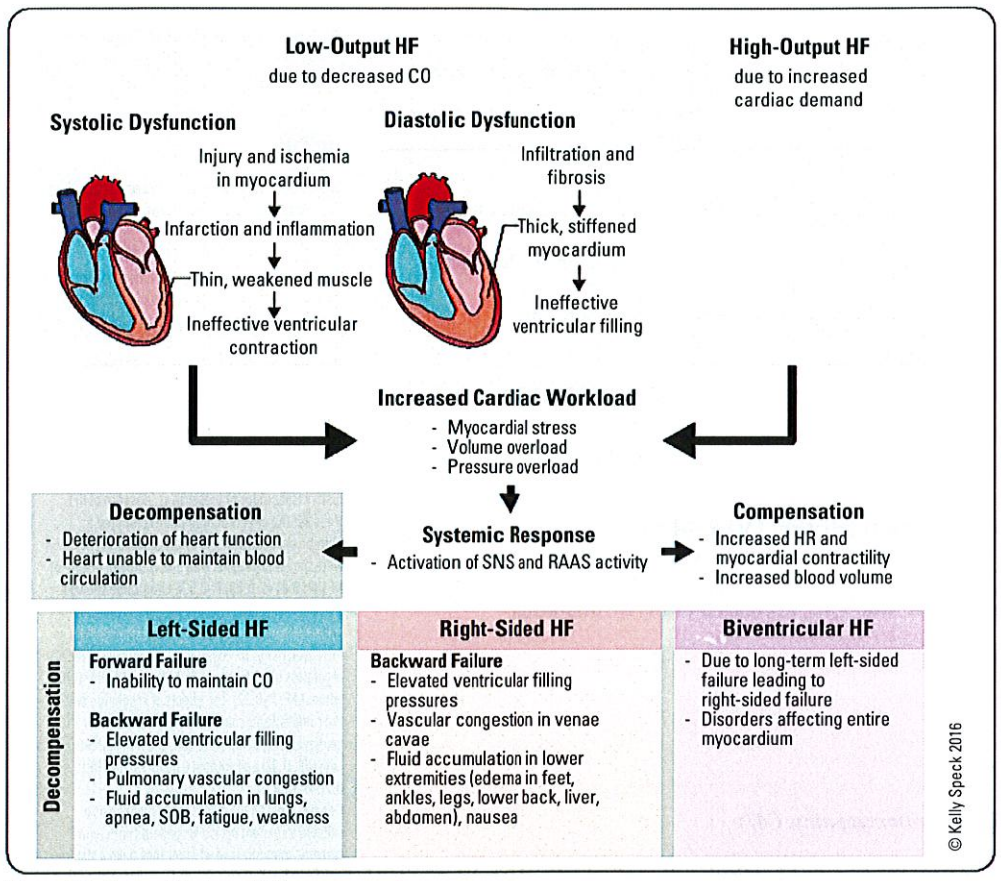


Figure 42. Congestive heart failure

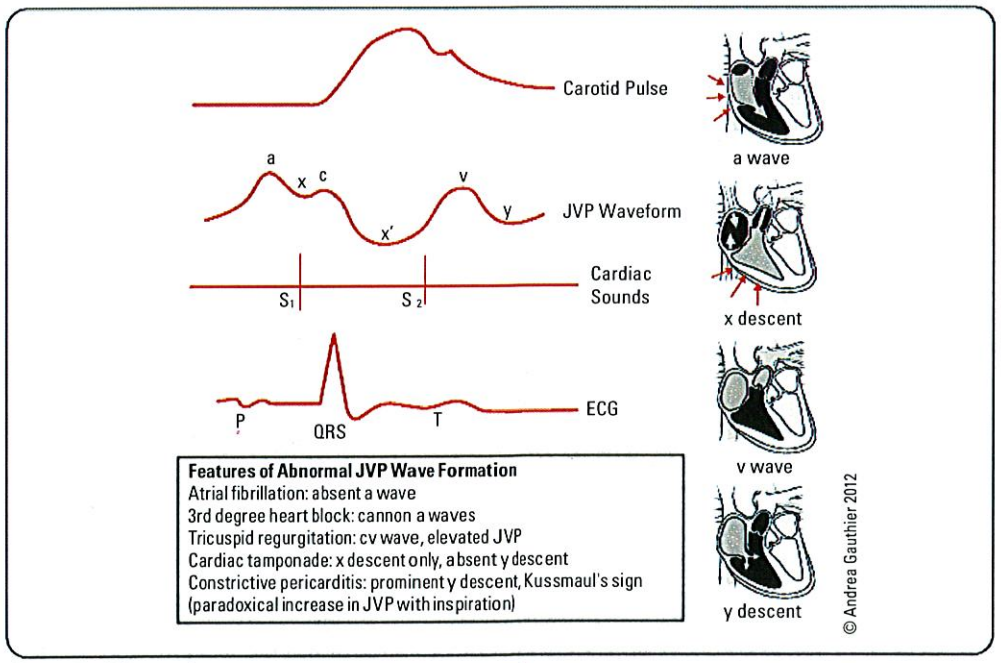


Figure 43. JVP waveform

Does this Dyspneic Patient in the Emergency Department have Congestive Heart Failure?
JAMA 2005;294:1944-1956

	LR+ (95% CI*)	LR− (95% CI*)
Initial clinical judgment	4.4 (1.8-10.0)	0.45 (0.28-0.73)
PMHx		
HF	5.8 (4.1-8.0)	0.45 (0.38-0.53)
MI	3.1 (2.0-4.9)	0.69 (0.58-0.82)
CAD	1.8 (1.1-2.8)	0.68 (0.48-0.96)
Symptoms		
PND	2.6 (1.5-4.5)	0.7 (0.54-0.91)
Orthopnea	2.2 (1.2-3.9)	0.65 (0.45-0.92)
SOBOE	1.3 (1.2-1.4)	0.48 (0.35-0.67)
Physical Exam		
Third heart sound	11 (4.9-25)	0.88 (0.83-0.94)
Jugular venous distension	5.1 (3.2-7.9)	0.66 (0.57-0.77)
Rales	2.8 (1.9-4.1)	0.51 (0.37-0.70)
Lower extremity edema	2.3 (1.5-3.7)	0.64 (0.47-0.87)
Chest Radiograph		
Pulmonary venous congestion	12 (6.8-21)	0.48 (0.28-0.83)
Interstitial edema	12 (5.2-27)	0.68 (0.54-0.85)
Cardiomegaly	3.3 (2.4-4.7)	0.33 (0.23-0.48)
ECG		
AFib	3.8 (1.7-8.8)	0.79 (0.65-0.96)
Any abnormal finding	2.2 (1.6-3.1)	0.64 (0.47-0.88)

* CI = confidence interval

Dichotomies of HF
Forward vs. backward
Left-sided vs. right-sided
Systolic vs. diastolic dysfunction
Low output vs. high output

Use EF to Grade LV Dysfunction
Grade I (EF >60%) (Normal)
Grade II (EF = 40-59%)
Grade III (EF = 21-39%)
Grade IV (EF ≤20%)

Table 15. Signs and Symptoms of Left vs. Right HF

	Left Failure	Right Failure
Low CO (Forward)	Fatigue Syncope Systemic hypotension Cool extremities Slow capillary refill Peripheral cyanosis Pulsus alternans MR S3	Left failure symptoms if decreased RV output leads to LV underfilling TR S3 (right-sided)
Venous Congestion (Backward)	Dyspnea, orthopnea, PND Cough Crackles	Peripheral edema Elevated JVP with abdominojugular reflux ± Kussmaul's sign Hepatomegaly Pulsatile liver

Pathophysiology

- most common causes are ischemic heart disease, risk factors for CAD, LVH (HTN), valvular heart disease, and tachyarrhythmia
- myocardial insult causes pump dysfunction/impaired filling leading to myocardial remodeling and the following maladaptive changes:
  - pressure overload (e.g. AS or HTN) leads to compensatory hypertrophy (i.e. concentric remodeling) and eventually interstitial fibrosis
  - volume overload (e.g. aortic insufficiency) leads to dilatation (i.e. eccentric remodeling)
- remodeling results in decreased forward CO resulting in activation of the SNS and RAAS
- SNS causes tachycardia
- RAAS causes Na^+ and water retention to increase preload and afterload
- net result is increased cardiac demand leading to eventual decompensation

Heart Failure with Reduced Ejection Fraction (HFrEF: LVEF ≤40%)

- impaired myocardial contractile function → decreased LVEF and SV → decreased CO
- volume overload is the typical phenotype
- findings: apex beat displaced, S3, cardiothoracic ratio >0.5, decreased LVEF, LV dilatation
- causes
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - EtOH (and other toxins)
    - myocarditis
    - DCM (multiple causes see *Dilated Cardiomyopathy, C47*)
    - tachycardia-induced

Heart Failure with Mid-Range Ejection Fraction (HF-mrEF: LVEF 41-49%)

- includes patients who are recovering from HFrEF, declining from HFpEF, and transitioning to HFpEF
- characterization of HFmEF ongoing; guideline management does not currently exist

Heart Failure with Preserved Ejection Fraction (HFpEF: LVEF ≥50%)

- previously known as "diastolic HF"
- concentric remodelling with a "stiff" LV is the typical phenotype
- 50% of patients with HF have preserved EF; confers similar prognosis to HFrEF; more common in the elderly and females
- reduced LV compliance causes increased LV filling pressures, increased LA pressure/volume, and pulmonary congestion
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal EF
- causes
  - transient: ischemia (e.g. CAD, MI)
  - permanent: severe hypertrophy (HTN, AS, HCM), RCM (e.g. amyloid), MI

High-Output Heart Failure

- caused by demand for increased CO
- often exacerbates existing HF or decompensates a patient with other cardiac pathology
- DDx: anemia, thiamine deficiency (beriberi), hyperthyroidism, arteriovenous (A-V) fistula or left to right (L-R) shunting, Paget's disease, renal disease, hepatic disease

Precipitants of Symptomatic Exacerbations

- consider natural progression of disease vs. new precipitant
- always search for reversible cause



See Landmark Cardiology and Cardiac Surgery Trials table for more information on DAPA-HF which details the efficacy of SGLT2 inhibition in patients with HFrEF and without T2DM.



See Landmark Cardiology and Cardiac Surgery Trials table for more information on PARADIGM-HF which details the survival outcomes of HFrEF patients treated with an ACEI or an angiotensin-neprilysin inhibitor.



Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure

J Am Coll Cardiol 2020; 75 (10) 1128–1141

Purpose: This study aimed to examine the impact of liraglutide on cardiovascular events and mortality among participants of the LEADER trial, based on their history of HF.

Methods: The LEADER trial included 9340 high-risk patients with type 2 diabetes who were assigned to receive liraglutide or placebo. The primary outcome was the occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Post hoc analyses were conducted based on baseline HF history (subgroups of presence vs. absence of HF).

Results: The effects of liraglutide compared to placebo on major adverse cardiovascular events were similar in patients with and without a history of HF (HR: 0.81 vs. 0.88, P=0.53). Liraglutide showed a reduction in deaths in both subgroups (HR:0.89 with HF; HR: 0.83 without HF; P=0.63). There was no increased risk of HF hospitalization with liraglutide, regardless of HF history (HR: 0.98 with HF; HR: 0.78 without HF; P=0.22). The effects of liraglutide on the composite outcome of HF hospitalization or cardiovascular death were consistent in patients with (HR: 0.92) and without a history of HF (HR: 0.77, P=0.19).

Conclusions: Liraglutide is recommended as a suitable treatment option for patients with type 2 diabetes, regardless of whether they have a history of New York Heart Association functional class I to III heart failure.



A Validated Clinical and Biochemical Score for the Diagnosis of Acute Heart Failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score

Am Heart J 2006;151:48-54

Predictor	Possible Score
Age >75 yr	1
Orthopnea present	2
Lack of cough	1
Current loop diuretic use (before presentation)	1
Rales on lung exam	1
Lack of fever	2
Elevated NT-proBNP (>450 pg/mL if <50 yr, >900 pg/mL if >50 yr)	4
Interstitial edema on CXR	2
Total	/14

Likelihood of HF
Low = 0-5
Intermediate = 6-8
High = 9-14

- DDx can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease, cardiotoxic chemotherapy
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection
  - medication non-compliance
  - dietary indiscretion (e.g. salt intake)
  - obstructive sleep apnea

Investigations
- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), blood urea nitrogen (BUN), Cr, fasting blood glucose, HbA1c, lipid profile, LFTs, serum TSH ± ferritin, BNP (>100 pg/mL), NT-ProBNP (>300 pg/ml), uric acid
- urinalysis
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchiolar-alveolar cuffing
- echo: systolic function (LVEF), diastolic function (E/A ratio, E/e'), cardiac dimensions, wall motion abnormalities, RV systolic pressure (from TR jet), valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

Additional Diagnostic Investigations
- cardiac catheterization
- cardiopulmonary exercise testing
- other tests (CMR, MPI, MUGA, CT scan)

Acute Treatment of Pulmonary Edema
- treat acute precipitating factors (e.g. ischemia, arrhythmias)
  - **L** Lasix® (furosemide) 40-500 mg IV
  - **M** morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
  - **N** nitroglycerin: topical/IV/SL - use with caution in preload-dependent patients (e.g. right HF or RV infarction) as it may precipitate CV collapse
  - **O** oxygen: in hypoxemic patients
  - **P** positive airway pressure (continuous positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP)): decreases preload and need for ventilation when appropriate
  - **P** position: sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOPP: other interventions may be necessary
  - nitroprusside IV
  - hydralazine PO
  - sympathomimetics
    - dopamine
      - low dose: selective renal vasodilation (high potency D1 agonist)
      - medium dose: inotropic support (medium potency β1 agonist)
      - high dose: increases SVR (low potency β1 agonist), which is undesirable
    - dobutamine
      - β1-selective agonist causing inotropy, tachycardia, hypotension (low dose) or HTN (high dose); most serious side effect is arrhythmia, especially AFib

      phosphodiesterase inhibitors (milrinone)
      - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor PCWP if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - IABP - reduces afterload via systolic unloading and improves coronary perfusion via diastolic augmentation
  - LVAD/RVAD
  - cardiac transplant

Long-Term Management
- overwhelming majority of evidence-based management applies to HFrEF
- currently no proven pharmacologic therapies shown to reduce mortality in HFpEF; control risk factors for HFpEF (e.g. HTN)
- prevent fluid overload with appropriate diuretic strategies

Conservative Measures
- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease EtOH consumption, patient education, sodium, and fluid restriction
- multidisciplinary HF clinics: for management of individuals at higher risk, or with recent hospitalization



BNP is secreted by Vs due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into Vs, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP. The above scoring algorithm developed by Baggish et al. is commonly used. A score of <6 has a negative predictive value of 98%, while scores ≥6 had a sensitivity of 96% and specificity of 84% (P<0.001) for the diagnosis of acute HF



NYHA Functional Classification of HF
- **Class I**: ordinary physical activity does not cause symptoms of HF
- **Class II**: comfortable at rest; ordinary physical activity results in symptoms
- **Class III**: marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- **Class IV**: inability to carry out any physical activity without discomfort; symptoms may be present at rest



Five Most Common Causes of CHF

CAD (60-70%)
HTN
Idiopathic (often DCM)
Valvular (e.g. AS, AR, and MR)
EtOH (DCM)



Precipitants of HF

HEART FAILED
HTN (common)
Endocarditis/environment (e.g. heat wave)
Anemia
Rheumatic heart disease and other valvular disease
Thyrotoxicosis
Failure to take medications (very common)
Arrhythmia (common)
Infection/Ischemia/Infarction (common)
Lung problems (PE, pneumonia, COPD)
Endocrine (pheochromocytoma, hyperaldosteronism)
Dietary indiscretions (common)



The most common cause of right HF is left HF

Non-Pharmacological Management

- from 2021 CCS guidelines
- restrict salt intake to 2-3 g/d
- monitor daily weight for patients with HF, fluid retention, or congestion that is difficult to control with diuretics or renal dysfunction
- restrict daily fluid intake to approximately 2 L/d for patients with fluid retention or congestion that is difficult to control with diuretics
- cardiac rehabilitation: participation in a structured exercise program for NYHA class I-III after clinical status assessment to improve quality of life (HF-ACTION trial)

Pharmacological Therapy

- **ACEI/ARB:** RAAS blockade
  - ACEI: slows progression of LV dysfunction and improves survival
    - all symptomatic patients functional class II-IV
    - all asymptomatic patients with LVEF <40%
    - post-MI
  - angiotensin II receptor blockers
    - second-line to ACEI (if ACEI not tolerated), or as adjunct to ACEI if β-blockers not tolerated
    - combination of β-blockers with ACEI is not routinely recommended and should be used with caution as it may precipitate hyperkalemia, renal failure, and the need for dialysis (CHARM, ONTARGET)

- **antiarrhythmic drugs**: for use in CHF with arrhythmia
  - can use amiodarone, β-blocker, or digoxin

- **anticoagulants**: DOACs or vitamin K antagonist (warfarin) for prevention of thromboembolic events
  - prophylactic indications:
    - AFib
    - LV thrombus
    - Prior thromboembolic event

- **ARNI**: combination angiotensin receptor-neprilysin inhibitors - slows down progression of LV dysfunction and improves survival
  - RAAS inhibitor prevents volume overload and neprilysin inhibitor enhances effects of BNP
  - first line therapy or if switching from an ACEI or ARB among patients with residual NYHA II-IV symptoms and LVEF <40%

- **β-blockers**: slow progression and improve survival
  - β-adrenergic blocking agents blocks effects of epinephrine to reduce rate and force of myocardial contraction
  - indicated for class I-III with LVEF <40% and stable class IV patients
  - carvedilol improves survival in class IV HF (COMET)
  - caution: should be used cautiously; titrate slowly because may initially worsen CHF

- **diuretics**: management of fluid overload and symptom control (e.g. dyspnea and PND)
  - furosemide (40-500 mg QD) for potent diuresis
  - metolazone once weekly may be used with furosemide to increase diuresis if patient becomes refractory to furosemide
  - furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by β-blockers, ACEI, ARBs, and aldosterone antagonists

- **digoxin and cardiac glycosides**: increase myocardial contractility but decrease rate
  - improves symptoms and decreases hospitalizations; no effect on mortality
  - indications: patient in sinus rhythm and symptomatic on ACEI or CHF and AFib
  - caution: patients on digitalis glycosides may worsen if these are withdrawn

- **hydralazine plus isosorbide dinitrate**: combination antihypertensive and vasodilator
  - consider for symptom control and mortality benefit in Black patients with symptomatic HFrEF despite guideline-directed medical therapy (GDMT)
  - also consider for HFrEF patients with drug intolerance to ACEIs, ARBs, or ARNI

- **ivabradine**: selective inhibition of the If current
  - recommended for CV death and hospitalization prevention in patients with HFrEF and symptomatic despite:
    - treatment with appropriate doses of GDMT, resting HR >70 bpm, and in sinus rhythm
  - weaker level of evidence than either ARNI or SGLT2 inhibitor

- **mineralocorticoid receptor (aldosterone) antagonists**: spironolactone or eplerenone
  - mortality benefit in symptomatic HF and severely depressed EF
  - for symptomatic HF in patients already on ACEI, β-blocker, and loop diuretic
  - caution: potential for life threatening hyperkalemia
    - monitor K^+ after initiation and avoid if Cr >220 μmol/L or K^+ >5.2 mmol/L

Measuring NT-proBNP

BNP is secreted by Vs due to LV stretch and wall tension

Cardiomyocytes secrete BNP precursor that is cleaved into proBNP

After secretion into Vs, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP portion

	NT-proBNP levels (pg/mL)
Age	HF very likely
<50	>450
50-75	>900
>75	>1800

Limitations: Age, body habitus, renal function, PE

Features of HF on CXR

HERB-B

Heart enlargement (cardiothoracic ratio >0.50)

Pleural Effusion

Re-distribution (alveolar edema)

Kerley B lines

Bronchiolar-alveolar cuffing

Patients on β-blocker therapy who have acute decompensated HF should continue β-blockers where possible (provided they are not in cardiogenic shock or in severe pulmonary edema)

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure with Reduced Ejection Fraction

Can J Cardiol 2021;37:531-46

Management of HFrEF: It is recommended that, in the absence of contraindications, HFrEF patients be treated with combination therapy including 1 drug from each of the following categories: ARNI (or ACEI/ARB), β-blocker, mineralocorticoid receptor antagonist (MRA), and SGLT2 inhibitor. It is recommended that patients admitted with acute decompensated HFrEF be switched to an ARNI from an ACEI/ARB when stabilized. It is recommended that β-blockers be initiated as soon as possible after HF diagnosis, not waiting until hospital discharge to initiate treatment in stabilized patients. MRA treatment is recommended for patients with acute MI, LVEF <40%, and HF symptoms or DM to reduce CV mortality and hospitalization for CV events. SGLT2 inhibitors should be used in patients with HFrEF, with or without concomitant T2DM, to improve symptoms and reduce hospitalizations.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on DAPA-HF which details the efficacy of SGLT2 inhibition in patients with HFrEF and without T2DM.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on PARADIGM-HF which details the survival outcomes of HFrEF patients treated with an ACEI or an angiotensin-neprilysin inhibitor.

ALGrawany

- **SGLT2 inhibitor**: empagliflozin, canagliflozin, dapagliflozin
  - recommended for treatment of patients with stable HFrEF, irrespective of T2DM
  - recommended in mild to moderate HFrEF with concomitant T2DM to improve symptoms and reduce mortality

HFrEF Management

1. ARNI (or if on ACEI/ARB substitute to ARNI)
2. β-blockers
3. MRA
4. SGLT2 inhibitor

HFpEF Management

1. ARB
2. Systolic/Diastolic Hypertension Management according to CHEP Guidelines (2017)
3. MRA (if serum K^+<5.0 mmol/L and eGFR >30 mL/min)

Surgical Management

- revascularization is the most frequently performed operation in HF patients with the aim to restore blood flow to hibernating myocardium (<10% operative mortality in some patient groups)
- mitral valve surgery for the treatment of MR secondary to ischemic LV dilation
- LV remodeling (Batista procedure - partial left ventriculectomy; Dor procedure - left ventricular restoration) improves ventricular function by reducing ventricular radial dimensions and thus decreasing wall tension via Laplace's law
- VADs (see *Cardiac Transplantation, C50*)
- heart transplantation (see *Cardiac Transplantation, C50*)

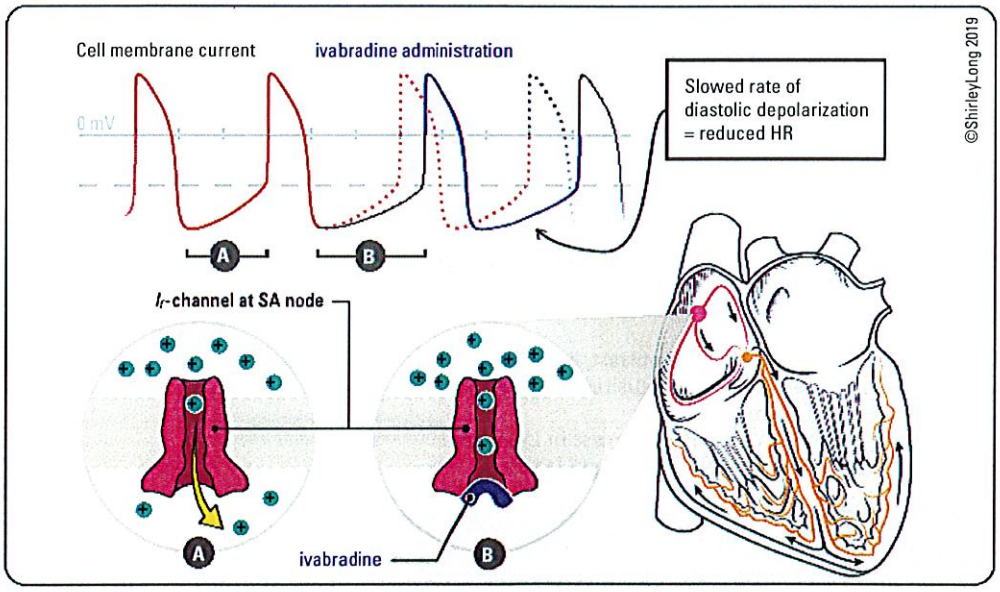


Figure 44. Ivabradine mechanism of action

Procedural Interventions

- resynchronization therapy: symptomatic improvement with CRT-P or CRT-D
  - consider if QRS >130 msec with LBBB morphology, LVEF <35%, and persistent symptoms despite OMT
  - greatest benefit likely with marked LV enlargement, MR, QRS >150 msec
  - CRT-P is indicated for patients eligible for resynchronization therapy but not ICD; if the patient is also eligible for an ICD the decision for CRT-D is individualized in accordance with overall goals of care
- ICD: mortality benefit in 1° prevention of SCD
  - consider if: prior MI, OMT, LVEF <30%, clinically stable
  - consider if: prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see *Ventricular Assist Devices, C52*)
- cardiac transplantation (see *Cardiac Transplantation, C50*)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see *Valvular Heart Disease, C54*)

Chronic Treatment of CHF

ACEI*
β-blockers*
± Mineralocorticoid receptor antagonists*
Diuretic
ARNI
± Inotrope
± Antiarrhythmic
± Anticoagulant
SGLT2 inhibitors
*Mortality benefit

SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis
EClinicalMedicine 2021;36:100933
Study: Systematic review and meta-analysis of placebo-controlled, randomized trials
Population: Patients with HF
Outcome: The primary endpoints were all-cause and cardiovascular mortality.
Results: In a meta-analysis of 15 trials with20251 patients, SGLT2 inhibitors showed significant benefits. All-cause mortality was reduced by 14% (HR 0.86, 95% CI 0.79-0.94, P=0.0007) and cardiovascular mortality by 14% (HR 0.86, 95% CI 0.78-0.96, P=0.006). The composite outcome of cardiovascular mortality, heart failure hospitalizations, or urgent visits was significantly reduced in various subgroups.
Conclusions: SGLT2 inhibitors demonstrate significant reductions in both all-cause and cardiovascular mortality when compared to placebo in patients with heart failure.

Higher New York Heart Association Classes and Increased Mortality and Hospitalization in Patients with Heart Failure and Preserved Left Ventricular Function
Am Heart J 2006;151:444-450
Purpose: To establish the association between NYHA class and outcomes with HF and preserved systolic function.
Methods: Retrospective follow-up study (median 38.5 mo) of 988 patients with HF with EF >45%. Estimated risks of various outcomes using Cox proportional hazard models.
Results: Adjusted HR for all-cause mortality for NYHA class II, III, IV patients was 1.54, 2.56, and 8.46, respectively. Adjusted HR for all-cause hospitalization for NYHA class II, III, IV patients was 1.23, 1.71, and 3.4, respectively.
Conclusions: Higher NYHA classes were associated with poorer outcomes in patients with HF and preserved systolic function.
Proportions of NYHA I, II, III, and IV patients who died of all causes during the study were 14.3%.

NYHA	Proportion of All-Cause Hospitalization	Proportion of All-Cause Mortality
I	60.7%	14.3%
II	65.2%	21.3%
III	77.7%	35.9%
IV	75.0%	58.3%

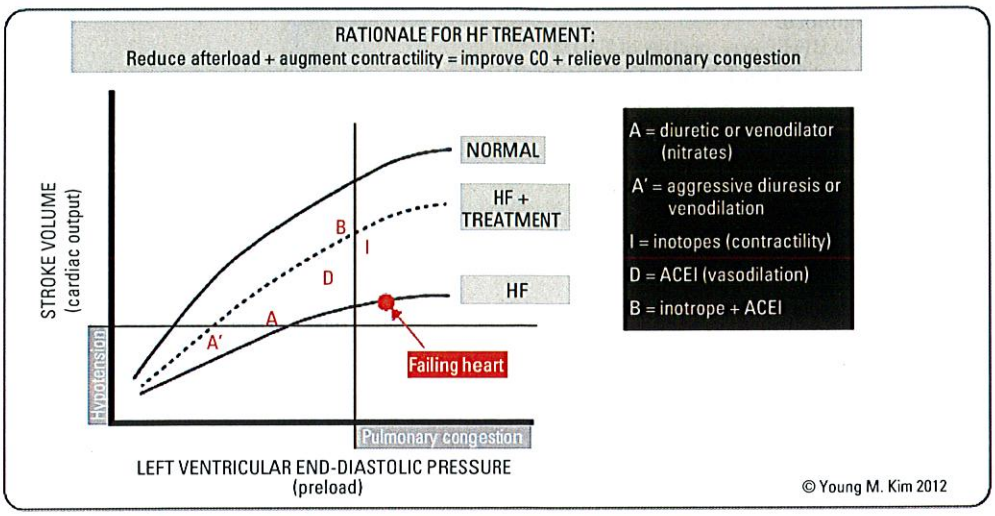


Figure 45. Effect of HF treatment on the Frank-Starling curve

Sleep-Disordered Breathing

- patients with CHF can have sleep disturbances; 40% of patients have central sleep apnea with Cheyne-Stokes breathing and 11% of patients have obstructive sleep apnea
- associated with a worse prognosis and greater LV dysfunction
- nasal CPAP may be effective to treat symptoms of sleep apnea with secondary benefits to cardiac function

Cardio-oncology

- cardiotoxicity of chemotherapeutic agents is a leading cause of long-term morbidity and mortality among cancer survivors
- dose-dependent LV systolic dysfunction with anthracyclines and potentially reversible decline in LVEF with trastuzumab
- evaluate CV risk factors and optimize treatment of pre-existing CV disease before, during, and after receiving cardiotoxic cancer therapy
- follow patient using same imaging modality and methods (e.g. echo with contrast, echocardiographic global longitudinal strain (GLS), 3 dimensional echo, or multiple-gated acquisition (MUGA) scan) to assess LV function before, during, and upon completion of chemotherapy
- recommended that clinical HF or an asymptomatic decline in LVEF (>10% decrease in LVEF from baseline or LVEF <53%) during or after treatment is managed according to CCS guidelines

Myocardial Disease

Definition of Cardiomyopathy

- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
  - results in both morphologic and functional abnormalities
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction secondary to MI, often termed "ischemic cardiomyopathy," is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD



Cardiomyopathy

HARD
Hypertrophic cardiomyopathy (HCM)
Arrhythmogenic right ventricular cardiomyopathy
Restrictive cardiomyopathy (RCM)
Dilated cardiomyopathy (DCM)

Table 16. Comparison of Cardiomyopathies, Secondary Causes, and Consequent HF Phenotypes

Heart Failure Reduced Ejection Fraction (HFrEF)		Heart Failure Preserved Ejection Fraction (HFpEF)		
Dilated Cardiomyopathy (DCM)	**Secondary Causes**	**Hypertrophic Cardiomyopathy (HCM)**	**Restrictive Cardiomyopathy (RCM)**	**Secondary Causes**
Idiopathic, infectious (e.g. myocarditis), EtOH, familial, collagen vascular disease	CAD, MI, DM, valvular (e.g. AR, MR)	Genetic disorder affecting cardiac sarcomeres (most common cause of SCD in young athletes)	Amyloidosis, sarcoidosis, scleroderma, hemochromatosis, Fabry's, Pompe's Disease, Loeffler's	HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia

Myocarditis

Definition
- inflammatory process involving the myocardium ranging from acute to chronic
- important cause of DCM
- spectrum of severity ranging from non-specific symptoms such as fatigue to cardiogenic shock

Etiology
- idiopathic
- infectious
  - viral (most common overall cause): coxsackie A and B, parvovirus B19, adenoviruses, influenza, echovirus, poliovirus, HIV, mumps, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  - bacterial: *S. aureus, Streptococcus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia*
  - fungi
    - spirochetal (Lyme disease *Borrelia burgdorferi*)
  - Chagas disease (*Trypanosoma cruzi*), *Toxoplasma gondii*
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity/eosinophilic: drugs (e.g. antibiotics, diuretics, lithium, clozapine), insect/snake bites, mRNA vaccines (rare)
- systemic diseases: collagen vascular diseases (e.g. SLE, rheumatoid arthritis), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

Signs and Symptoms
- constitutional symptoms
- acute CHF: dyspnea, tachycardia, elevated JVP
- cardiogenic shock
- chest pain: due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- presyncope/syncope/sudden death

Investigations
- ECG: non-specific ST-T changes and/or conduction defects (used for initial screening and risk stratification)
  - echocardiography: lack of cardiac dilation and increased thickness of septum (fulminant myocarditis), spherical ventricle that remodels to elliptical after some months (acute myocarditis)
- blood work
  - increased creatine kinase (CK), cardiac troponins (cTnI and cTnT), NT-proBNP (if LV dysfunction occurs), LDH, and AST with acute myocardial necrosis ± increased WBC, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody test (ANA), rheumatoid factor, complement levels
  - blood culture, viral titres, and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- TTE: systolic dysfunction (dilated, hypokinetic chambers, segmental wall motion abnormalities) and/or diastolic dysfunction
- CMR: functional and morphological abnormalities as well as tissue pathology (gadolinium enhancement)
- endomyocardial biopsy: only done in certain clinical scenarios (e.g. on inotropic and/or mechanical circulatory support)
- coronary angiography: to exclude ischemic heart disease

Management
- supportive care
- mechanical circulatory support and inotropic support if cardiogenic shock
- restrict physical activity during early recovery
- treat CHF per current HF guidelines
  - guideline-directed medical therapy
  - advanced therapies such as ventricular assist and transplantation
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

Prognosis
- often unrecognized and may be self-limited
- myocarditis treatment trial showed 5 yr mortality between 25-50%
- giant cell myocarditis, although rare, can present with fulminant CHF and be rapidly fatal, with 5 yr mortality >80%
- sudden death in young adults
- may progress to DCM

Dilated Cardiomyopathy

Definition
- unexplained dilation and impaired systolic function of one or both ventricles
- if present, comorbid CAD is unable to fully account for extent of dysfunction observed

Major Risks Factors for DCM
FMHx, EtOH, cocaine,

Etiology
- familial/genetic ~60%
- EtOH ~20-30%
- myocarditis
- infectious: viral (coxsackie B, HIV, SARS-CoV-2), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- idiopathic (presumed viral or idiopathic)
- uncontrolled tachycardia (e.g. persistent, rapid AFib)
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), anti-retrovirals, chloroquine, clozapine, TCA
- radiation

Abnormal Labs in DCM
- High BNP
- High Cr
- High LFTs
- Low bicarbonate
- Low Na+

Signs and Symptoms
- may present as:
  - systolic HF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

Investigations
- blood work: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, total iron binding capacity (TIBC)
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (e.g. non-sustained VT)
- CXR: global cardiomegaly (i.e. globular heart), signs of CHF, pleural effusion
- echo: systolic dysfunction (chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi)
- cardiac MRI: myocardial fibrosis
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in select patients to exclude ischemic heart disease

Management
- treat underlying disease: e.g. abstinence from EtOH
- treat CHF as per current guidelines (see *Heart Failure, C40*)
  - includes medical management and devices (ICD and CRT)
- advanced therapies considered for medication-refractory disease
  - e.g. LVAD, transplant, and volume reduction surgery
- thromboembolism prophylaxis: anticoagulation with warfarin
  - indicated for: AFib, history of thromboembolism or documented thrombus
- treat symptomatic or serious arrhythmias
- immunize against influenza and S. pneumoniae
- indication to screen first-degree relatives when unclear etiology

Prognosis
- depends on etiology, often parallels prognosis of systolic HF
- better with reversible underlying cause; worst with infiltrative diseases, HIV, drug-induced
- early reverse remodelling with optimal HF management (i.e. medications and devices) improves prognosis
- myocardial fibrosis increases SCD risk
- cause of death usually CHF (due to pump failure) or sudden death secondary to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in first yr, 10% per year thereafter

Hypertrophic Cardiomyopathy

- see 2020 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy for details

Definition

- unexplained left ventricular hypertrophy (LVH)
- LVH can occur in any distribution
  - asymmetric septal hypertrophy is most common
- systolic anterior motion of mitral valve and hyperdynamic LV are common but non-diagnostic

Etiology

- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins
  - >400 mutations associated with autosomal dominant inheritance, incomplete penetrance, variable age of onset
  - 70% of pathogenic variants occur within 2 genes: β-myosin heavy chain 7 (MYH7) and myosin-binding protein C3 (MYBPC3)
- prevalence of 1 in 500 to 1 in 1000 in general population
  - equally prevalent in men and women although women are diagnosed less often
- generally presents in early adulthood

Pathophysiology

- histopathologic features include myocyte disarray, myocyte hypertrophy, dysplastic arterioles and interstitial fibrosis
- dynamic obstruction of LVOT (LVOTO) due to both septal hypertrophy and systolic anterior motion (SAM) of mitral leaflets
- diastolic dysfunction due to LVH, ischemia, and interstitial fibrosis
- myocardial ischemia due to supply-demand mismatch
- autonomic dysfunction, inappropriate vasodilation during exercise, and abnormal HR recovery

Hemodynamic Classification

- HOCM (hypertrophic obstructive cardiomyopathy): defined as peak LVOT gradient of at least 30 mmHg either at rest or with provocation
  - peak LVOT gradient of at least 50 mmHg at rest or provoked is the typical threshold for considering invasive septal reduction in patients with insufficient response to medical management
- non-obstructive HCM (one-third): no LVOT obstruction

Signs and Symptoms

- clinical manifestations: asymptomatic (common, therefore screening is important), SOBOE, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- pulses: rapid upstroke, "spike and dome" pattern in carotid pulse (in HCM with outflow tract obstruction)
- precordial palpation: PMI localized, sustained, double impulse, 'triple ripple' (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOTO as compared to AS); often with pansystolic murmur due to MR

Investigations

- 3-generation family history
  - first-degree relatives receive directed cascade genetic testing and routine TTE and ECG screening
  - first-degree relatives are screened every 1-3 yr as children and every 3-5 yr as adults provided they are asymptomatic and initial assessment is negative
- TTE for initial diagnosis, monitoring every 1-2 yr and evaluating clinical concerns
  - for patients not meeting LVOTO criteria (LVOT gradient of at least 50 mmHg) at rest, a provocative maneuver and/or exercise stress test is performed to assess for dynamic LVOTO development
- TEE for preoperative planning of septal reduction, assessment of MR etiology, SAM, and LVOTO
- cardiac MRI to clarify inconclusive echocardiogram results or determine method of septal reduction
- ECG/holter monitor for initial workup, regular follow-up, and assessment of SCD risk
  - LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- cardiac catheterization (only when patient being considered for invasive therapy)
- genetic studies to clarify uncertain diagnoses and facilitate screening of family members

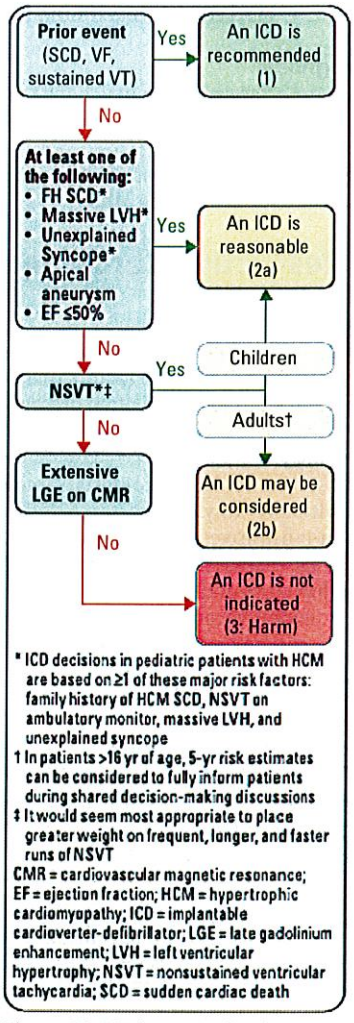


Figure 46. ICD implantation in HCM

Management
- avoid factors which increase obstruction (e.g. volume depletion)
  - avoidance of high-intensity competitive sports unless exceptional circumstances
  - mild-to-moderate-intensity exercise is safe
- treatment of HOCM
  - medical agents: β-blockers, verapamil or diltiazem (started only in monitored settings), disopyramide, phenylephrine (in setting of cardiogenic shock), mavacamten
  - avoid digoxin and vasodilators (e.g. nitrates, dihydropyridine calcium channel blockers, and ACEi/ARB) as they are inotropic and afterload reducing, respectively
- patients with HOCM and drug-refractory symptoms require septal reduction therapy at experienced centres
  - surgical myectomy
  - alcohol septal ablation - percutaneous intervention that ablates the hypertrophic septum with 100% ethanol via the septal artery
  - dual chamber pacing (rarely done)
- treatment of non-obstructive HCM
  - symptomatic: β-blockers or non-dihydropyridine calcium channel blockers and diuretics if refractory symptoms
- comorbid atrial fibrillation: direct oral anticoagulant or warfarin regardless of CHA2DS2-VASc score
- consequent systolic dysfunction: consider candidacy for transplant
- treatment of patients at high-risk of sudden death: ICD (see *Figure 46, ICD implantation in HCM, C48*)
  - history of survived cardiac arrest/sustained VT
  - FMHx of premature sudden death
  - other factors associated with increased risk of SCD
    - syncope (presumed to be arrhythmic in origin)
    - LVEF <50%
    - LV apical aneurysm
    - non-sustained VT on ambulatory monitoring
    - marked LVH (maximum wall thickness ≥30 mm)

Prognosis
- life expectancy may or may not be reduced
  - the majority of those with HCM do not experience severe symptoms or require aggressive treatments
- potential complications: AFib, stroke, CHF (diastolic and systolic), VT, SCD (1% risk/yr; most common cause of SCD in young athletes)



Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM): A Randomized, Double Blind, Placebo-Controlled, Phase 3 Trial
The Lancet 2020 Sep 12;396(10253):759-69.
Purpose: Assess the safety and efficacy of mavacamten, a cardiac myosin inhibitor, in symptomatic HOCM.
Methods: Patients with HOCM (LVOT>50mmHg, NYHA II-III) from 68 clinical centers in 13 countries were randomized to mavacamten or placebo for 30 wk. The primary endpoint was a >1.5mL/kg/min increase in peak O2 consumption and at least one NYHA class reduction, or >3.0mL/kg/min increase in peak O2 consumption with no NYHA class reduction.
Results: 45 (37%) of 123 patients on mavacamten vs. 22 (17%) of 128 on placebo met the primary endpoint. Patients on mavacamten had greater reductions in post-exercise LVOT gradient and greater increase in peak O2 consumption. 34% more patients in the mavacamten group improved by at least 1 NYHA class. Safety and tolerability were comparable to placebo.
Conclusion: Mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with HOCM.

Restrictive Cardiomyopathy

Definition
- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)
- biatrial enlargement is often present despite normal AV valve functioning

Etiology
- most commonly: amyloidosis, sarcoidosis, and hemochromatosis
- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis, diabetic cardiomyopathy
- storage diseases: hemochromatosis, Fabry's disease, Gaucher's disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis (late presentation), Loeffler's endocarditis, or eosinophilic endomyocardial disease
  - radiation heart disease
  - carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

Clinical Manifestations
- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul's sign
- S3, S4, MR, TR
- thromboembolic events

Investigations
- ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
- CXR: mild cardiomegaly due to biatrial enlargement
- echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
- cardiac MRI: assessment of myocardial fibrosis, determination of etiology, and exclusion of constrictive pericarditis
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)



RCM vs. Constrictive Pericarditis
Present similarly but constrictive pericarditis is treatable with surgery

RCM	Constrictive Pericarditis
Family history	Prior surgical history in some cases
No pulsus paradoxus	Pulsus paradoxus may be present
Systolic murmurs	Pericardial rub
Lvh	No lvh
Normal pericardium (intracardiac pathology)	Pericardial calcification and pericardial thickening
Myo- and endocardial later gadolinium enhancement (lge)	Pericardial late gadolinium enhancement (lge)
Elevated bnp	Reduced bnp

Management
- exclude constrictive pericarditis
- control HR, anticoagulate if AFib
- treat underlying disease: (e.g. cardiac amyloidosis, cardiac sarcoidosis, hemochromatosis)
- supportive care and treatment for CHF, arrhythmias, and prevention of SCD when indicated
  - judicious use of diuretics (excess volume reduction reduces filling pressures versus pathologic requirements triggering hypoperfusion)
- cardiac transplant: might be considered for CHF refractory to medical therapy

Prognosis
- depends on etiology

Key Investigations

Echo: may show respiratory variation in blood flow in constrictive pericarditis

CT: may show very thickened pericardium and calcification in constrictive pericarditis

MRI: best modality to directly visualize pericardium and myocardium

Left Ventricular Noncompaction Cardiomyopathy

Definition
- failure of LV compaction leading to endomyocardial trabeculations that increase in number and prominence
- characterized by abnormal trabeculations in the LV, most frequently at the apex

Etiology
- genetics are incompletely understood
- mutations have been mainly observed in genes coding sarcomeric, cytoskeletal, and mitochondrial proteins
- can occur in healthy individuals (e.g. athletes and pregnancy) as well as concomitantly with congenital heart diseases and other cardiomyopathies (i.e. HCM, RCM, DCM, ARVC)
- can be reversible

Clinical Manifestations
- if occurring in absence of concomitant cardiomyopathy and congenital heart disease, LV non-compaction can be benign
- symptoms range from SOBOE to rest symptoms
  - many patients are asymptomatic
- ventricular arrhythmias or complete AV block (presents as syncope and sudden death)
- thromboembolic events
  - more likely when systolic dysfunction and LV dilatation are present

Investigations
- directed by primary pathology when LV non-compaction is comorbid with congenital disease or other cardiomyopathies
- TTE and cardiac MRI
  - most common diagnostic method is the ratio of the thickness of the non-compacted layer to that of the compacted layer (greater than 2:1 at the end of diastole)
- role of routine genetic screening remains in question
  - typically performed in the setting of LV non-compaction with comorbid cardiomyopathy

Management
- at-risk first-degree relatives are recommended to undergo screening
- therapy is largely driven by concomitant myocardial dysfunction, arrhythmias, and congenital heart disease
- ICD is an option if patients have syncope, documented VT, or LV systolic dysfunction
- antiplatelets or systemic anticoagulation should be considered in adults, especially when the LV or atria are dilated

Prognosis
- dependent on LV function and presence of comorbid conditions (e.g. congenital heart disease and cardiomyopathy)

Cardiac Transplantation

- treatment for end-stage heart failure
- median survival is 12.5 yr, extending to 14.8 yr among 1-year survivors
- matching is according to blood type, body size and weight (should be within 25%), HLA tissue matching, and geographical considerations (to minimize ischemic time)

Indications for Surgery
- severe cardiac disability despite maximal medical therapy (e.g. recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker) with a life expectancy of 12-18 mo
- symptomatic cardiac ischemia refractory to conventional treatment (e.g. unstable angina not amenable to CABG or PCI with LVEF <20-25%; recurrent, symptomatic ventricular arrhythmias)

- high-risk HFSS
  - HFSS is an algorithm that incorporates the patient's HR, serum sodium, ischemic cardiomyopathy, LVEF, peak myocardial oxygen consumption, MAP, interventricular conduction delay
  - patients with medium-risk (HFSS 7.2-8.1, 73% 1-yr survival) and high-risk (HFSS <7.2, 43% 1-yr survival) benefit from cardiac transplant
- cardiogenic shock requiring IV inotropic agents or mechanical circulatory support to sustain organ perfusion
- exclusion of all surgical alternatives to cardiac transplantation

Absolute Contraindications
- active alcohol use disorder or substance use disorder
- actively smoking
- coagulopathy
- incurable malignancy
- irreversible major organ disease
- irreversible pulmonary HTN (i.e. >5 Wood units, transpulmonary gradient <18 mmHg, or systolic pulmonary artery pressure >60 mmHg)
- major systemic illness
- mental illness or other cognitive factors likely to affect ability to adhere to post-transplant regimens
- repeated non-adherence to medications
- severe COPD (i.e. FEV 1 <1L)
- severe symptomatic cerebrovascular disease

Relative Contraindications
- active systemic infection
- acute PUD
- age >70 yr
- DM with end-organ disease
- lack of family/social support
- obesity (>35 kg/m ^{2})
- significant symptomatic carotid disease or PVD

Prerequisites
- psychosocial stability
- medically compliant and motivated

Complications
- rejection
  - declining incidence with improved post-transplant immunosuppression regimens: <13% experience an episode that needs to be treated and <5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - risk of acute rejection is greatest during the first 3 mo after transplant
  - hyperacute rejection (minutes to hours after transplant) due to ABO mismatch, acute rejection (days to months after transplant), or chronic rejection (years after transplant)
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft vasculopathy
  - approximately 50% develop graft vasculopathy within 10 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
  - cutaneous neoplasms most common, followed by non-Hodgkin lymphoma and lung cancer
- medication side effects
  - immunosuppressives (e.g. prednisone, cyclosporine nephrotoxicity, tacrolimus) may have nephrotoxic effects
- cardiac denervation
  - as the donor heart is completely denervated, it does not receive parasympathetic vagal stimulation or intrinsic postganglionic sympathetic stimulation so it will not respond to anticholinergics like atropine
- RV dysfunction
  - RV dysfunction with TR, particularly in patients with preoperative pulmonary HTN, due to myocardial dysfunction caused by long ischemic time and/or reperfusion injury
  - requires aggressive management for treatment using agents that dilate the pulmonary vasculature or, rarely, RVAD support



Effects of Donor Pre-Treatment with Dopamine on Survival after Heart Transplantation: A Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicentre Trial
J Am Coll Cardiol 2010;58:1768-1777
Treatment of brain-dead donors with dopamine of 4 µg/kg/min will not harm cardiac allografts but appears to improve the clinical course of the heart allograft recipient.



Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure
NEJM 2001;345:1435-1443
Increased survival of 23% vs. 8% with LVAD vs. medical management of HF after 2 yr.
Heartmate VAD has a biologic surface and, therefore, does not require long-term anticoagulation but confers a higher risk of infection.



Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness following Left Ventricular Assist Device Implantation
Can J Cardiol 2012;28:137-140
Patients with a continuous flow LVAD (NYHA class I-III) who are stable 2 mo post-LVAD implantation qualify for private driving (only) and are disqualified from commercial driving.



Canadian Cardiovascular Society/ Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care
Can J Cardiol 2020;36:335-56
Selection Criteria: Cardiac transplantation is recommended for consideration in HF patients ≤70 yr old. For all patients being considered, an assessment of frailty with a validated tool is recommended. Caution is recommended for patients with BMI >35. LVAD implantation is recommended for eligible patients with pulmonary hypertension on right heart catheterization. Finally, cardiac transplantation is not recommended for patients who show repeated nonadherence to medications, alcohol or illicit drug use, mental illness, and/or cognitive concerns that will render patients unlikely to adhere to post-transplantation regimens.

Ventricular Assist Devices

- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD); typical circuit is comprised of a pump, an outflow graft, and a driveline to connect to an external power source and controller (see *Figure 48*)
- indications:
  - bridge to transplantation, bridge to decision (for transplant), or long-term permanent therapy ("destination therapy")
  - postoperative mechanical support when unable to separate from CPB despite inotropic and IABP support
    - IABP is a catheter-based device inserted into the femoral artery and advanced to the descending aorta that decreases afterload, thus myocardial O_2 demand and increases blood flow to coronary arteries
    - inflation of the balloon occurs during diastole to increase ascending aorta and coronary artery perfusion pressure; deflation occurs at systole to reduce intra-aortic pressure thus reducing afterload
  - cardiogenic shock

Extracorporeal Membrane Oxygenation

- circuit includes: centrifugal pump, membrane oxygenator, venous and arterial cannulas (see *Figure 47*)
- venoatrial (VA) ECMO is treatment for cardiogenic shock due to broad availability, technical simplicity, and rapid deployment
- outcomes for ECMO poor with 35% survival
- indications: postcardiotomy shock, allograft failure, fulminant myocarditis, decompensated HF
- extracorporeal life support through ECMO use is an effective method of resuscitation in moribund patients

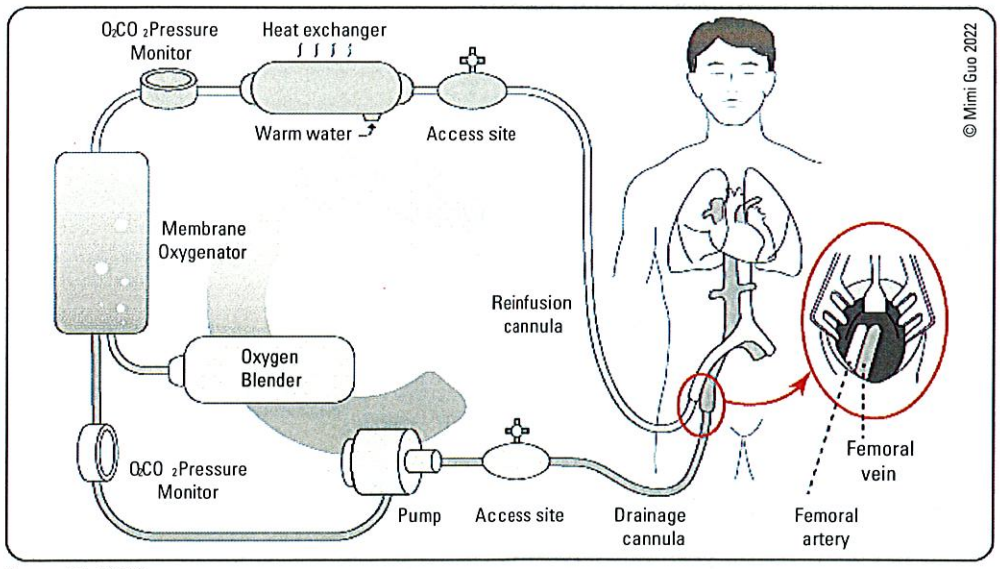


Figure 47. ECMO

Cardiac Tumours

Incidence

- cardiac tumours are more commonly derived from metastases than primary tumours
  - primary cardiac tumours have an estimated incidence of 1-30 in 100000 people per year
  - metastatic involvement of the heart is much more common and is present in 10-20% of autopsies of patients who die from cancer

Diagnosis

- TTE, TEE, MRI, PET and/or CT scan can be used to detect cardiac tumours
  - transvenous and open biopsy offer definitive diagnosis when required
- once detected, CT or PET scans screen for distant metastasis while cardiac MRI helps determine suitability for surgery
  - coronary angiography determines presence of concomitant CAD and neoplastic involvement of coronary vasculature

Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device
NEJM 2009;361:2241-51

Purpose: Assess quality of life in patients with advanced HF treated with implanted pulsatile-flow LVAD or new continuous-flow devices.

Methods: Patients with advanced medically-refractory HF were randomized (in a 2:1 ratio) to implantation of a continuous-flow LVAD or a pulsatile-flow LVAD. Quality-of-life tests and 6-min walk test data were collected at baseline, 1 month, 3 mo, 6 mo, then every 6 mo until study completion. The primary endpoint was a composite of 2-yr survival free of disabling stroke (Rankin score >3), or device reoperation for replacement.

Results: 86% of patients with the continuous-flow device and 76% of patients with the pulsatile-flow device were discharged from the hospital with the device in-place. The primary endpoint was achieved in 46% of patients implanted with the continuous-flow device, compared to 11% with the pulsatile-flow device (hazard ratio 0.38; 95% CI 0.27 to 0.54; P<0.001). The Kaplan-Meier estimates of survival revealed significantly better outcomes for patients with the continuous-flow devices compared with the pulsatile-flow device (RR 0.54; 95% CI 0.34 to 0.86; P=0.008).

Conclusions: Implantation of a continuous-flow device, compared to a pulsatile-flow device improved stroke-free survival and quality of life in patients with advanced medically-refractory HF.

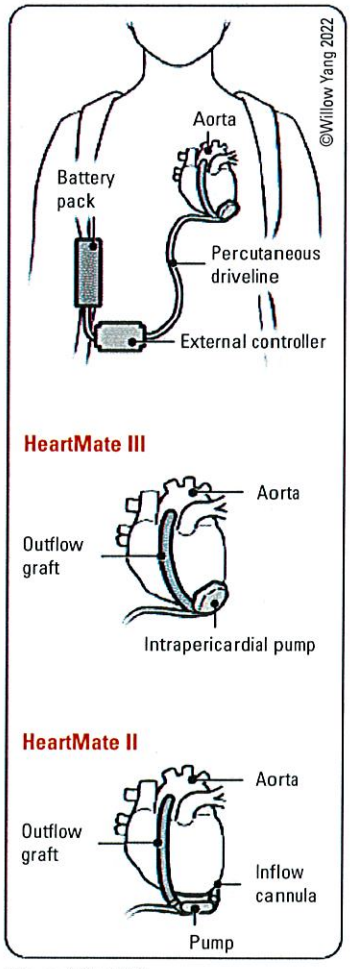


Figure 48. LVAD

Physiological Consequences of Cardiac Tumours

- systemic or pulmonic embolization
- symptoms of HF due to obstruction of circulation
- regurgitation due to interference with heart valves
- myocardial invasion causing impaired left ventricular function, arrhythmias, heart block, or pericardial effusion
- constitutional or systemic symptoms

Subtypes of Cardiac Tumours by Location

- right atrial tumours
  - may obstruct blood flow and present with symptoms similar to those of TS and right HF
  - fragments from right atrial tumours may cause pulmonary emboli
  - tumours affecting the AV node can cause heart block
  - myxomas are one of the most common
- right ventricular tumours
  - can induce right-sided HF by interfering with filling or outflow from the RV
  - may obstruct blood flow or beget TR and, as a result, simulate mitral valve disease and produce HF or secondary pulmonary HTN
- left atrial tumours
  - may release tumour fragments or thrombi into the systemic circulation
  - myxomas are one of the most common
- left ventricular tumours
  - intramural left ventricular tumours may induce arrhythmias or conduction defects
  - intracavitary tumours can present with systemic embolization or outflow obstruction
  - may ultimately result in left ventricular failure
- valvular tumours
  - papillary fibroelastomas are most common, equal incidence at AV and semilunar valves
  - asymptomatic until sentinel events such as distal embolization and coronary ostial obstruction
  - resection and repair of the valvular tissue is preferred over valve replacement
- pericardial tumours
  - includes lipomas and metastatic tumours
  - external compression of the heart as a result of both mass effect and propensity to generate pericardial effusions

Subtypes of Cardiac Tumours by Histopathology

- benign tumours
  - roughly 75% of cardiac tumours are benign
  - myxomas make up the majority of benign cardiac tumours and they most commonly arise in the LA
  - in patients over age 16, the three most common primary tumours are myxomas (50%), lipomatous tumours (21%), and papillary fibroelastomas (16%)
  - in patients under age 16, the four most common tumours are rhabdomyomas (55%), teratomas (16%), fibromas (10%), and myxomas (10%)
  - myxomas should be surgically resected to minimize the risk of cardiovascular complications, including embolization
- primary malignant cardiac tumours
  - sarcomas are the most common form of primary malignant cardiac tumours (75%)
  - these tumours progress rapidly and can infiltrate the myocardium, obstruct circulation, and release metastatic cells
  - prognosis dictated by anatomic location as opposed to histopathology
  - right-sided tumours are more invasive and metastasize earlier than left-sided ones
  - although the recommended treatment strategy is surgical resection when possible, these tumours are likely to recur
  - a combination of chemotherapy and surgical resection for primary cardiac sarcomas prolongs survival as compared with either surgery or chemotherapy alone
- metastatic involvement of the heart
  - metastatic cancer cells may reach the heart through hematogenous spread, direct invasion, or tumour growth through the venae cavae into the RA
  - incidence is highest in external layers of heart and reduced toward luminal layers, reflecting seeding through the coronary arteries and direct extension of adjacent thoracic tumours
  - when a cancer patient develops cardiovascular symptoms, cardiac or pericardial metastases should be suspected
  - although most metastases are asymptomatic, the most common symptom is pericardial effusion with or without tamponade

ALGrawany

Valvular Heart Disease

- see the 2020 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Management of Patients with Valvular Heart disease and the 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guidelines for the Management of Patients with Valvular Heart disease for details

Infective Endocarditis

- see Infectious Diseases, ID15
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  - only for patients with:
    - prosthetic valve material
    - past history of IE
    - cyanotic CHD
    - cardiac transplant recipients who develop valvulopathy
  - only for the following procedures:
    - dental
    - respiratory tract
    - procedures on infected skin/skin structures/MSK structures
    - not GI/GU procedures specifically

Rheumatic Fever

- see Pediatrics, P65

Prognosis

- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

Valve Repair and Valve Replacement

- indication for valve surgery depends on the severity of the pathology; typically recommended when medical management has failed to adequately clear the infection or improve symptoms
- surgical valve repair (rarely done): surgical valvuloplasty (commissurotomy, annuloplasty), tissue patch
- surgical valve replacement: typically for aortic and mitral valves
- surgical decision between mechanical vs. bioprosthetic prosthesis for patients 50-70 y/o remains uncertain as valve techniques evolve

Choice of Valve Prosthesis

Table 17. Mechanical Valve vs. Bioprosthetic Valve vs. Pulmonary Autograft-Ross Procedure

Type of Valve	Mechanical Valve	Bioprosthetic Valve	Pulmonary Autograft in Aortic Position (Ross Procedure*)
Valve Durability	Good durability	Limited long-term durability (mitral<aortic)	Only aortic valve replacement that restores life expectancy to the age- and sex-matched general population
Aortic Root	Less preferred in small aortic root sizes	Good flow in small aortic root sizes	Closest flow profile to native aortic roots
Risk of Thromboembolism	Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin	Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves	Low risk of thromboembolism
Anticoagulation Requirements	Target INR - aortic valves: 2.0-3.0 (mean 2.5); mitral valves: 2.5-3.5 (mean 3.0)	Some recommendation for limited anticoagulation for mitral valves	No anticoagulation required, enables higher activity and straightforward pregnancies
Risk of Hemorrhage	Increased risk of hemorrhage: 1-2%/yr	Decreased risk of hemorrhage	Low risk of hemorrhage
Patient Age	<50 yr for aortic valves and <65 for mitral valves	>65 yr for both aortic and mitral valves	Classically in children and young adults <50 yr

*should only be performed in high volume centers with extensive experience in aortic root procedures and the Ross operation



Twenty-Year Outcome After Mitral Repair Versus Replacement for Severe Degenerative Mitral Regurgitation: Analysis of a Large, Prospective, Multicenter, International Registry
Circulation 2017;135:410-22
Purpose: Analyze very-long term outcomes after MV repair and replacement for degenerative MR with a flail leaflet.
Methods: Employing the Mitral Regurgitation International Database, outcomes after MV repair and replacement were analyzed by propensity score matching and by inverse probability-of-treatment weighting.
Results: Operative mortality was lower after MV repair than replacement in the propensity-matched population (0.2% vs. 4.4%; P<0.001) and 20-yr survival was better after MV repair than replacement in the same population (41% vs. 24%; P<0.001). MV repair was also associated with a reduced rate of valvular complications.
Conclusions: MV repair was associated with lower operative mortality, better 20-yr survival and lower complication rates than MV replacement, in patients with degenerative mitral regurgitation with a flail leaflet.

Prosthetic Valve Management

Management and Follow-Up

- follow-up: dependent on valve type, residual heart disease, and clinical factors
  - TTE after prosthetic valve implantation to assess hemodynamics and ventricular function
    - if/when clinical symptoms or signs of prosthetic valve dysfunction arise, repeat TTE; additional investigations may be warranted if high clinical suspicion is present
    - TTE at 5 yr, 10 yr, and then annually thereafter is reasonable in otherwise asymptomatic patients with a surgically implanted bioprosthetic valve (if transcatheter implantation was used, annual TTE following the procedure is reasonable)
  - optimal dental care and endocarditis prophylaxis are required
- antithrombotic therapy: risk of bleeding must be considered and balanced whenever using/increasing any antithrombotic therapy
  - for patients with a mechanical valve, use anticoagulation with a vitamin K antagonist and INR monitoring
  - for patients with a bioprosthetic TAVI, bioprosthetic SAVR, or mitral valve replacement, short term other antithrombotic oral anticoagulation or antiplatelet therapies may be indicated

Prosthetic Valve-Related Complications

- prosthetic valve dysfunction
  - no known medical therapies to prevent bioprosthetic or mechanical valve degeneration
  - etiology: tissue degeneration, pannus formation, IE, thrombosis
  - presentation: prosthetic vascular stenosis or regurgitation
  - investigations and treatment: depend on the type/severity of pathology, as well as patient characteristics (see below)
- thromboembolic events
  - ensure to assess anticoagulation adequacy, time spent in therapeutic range; rule out infective endocarditis; screen for new-onset AF; consider other sources of a potentially underlying hypercoagulable state
  - patients with a mechanical aortic/mitral valve that were in therapeutic INR range on a vitamin K antagonist at the time of event: consider increasing INR goal or adding low-dose daily aspirin
  - patients with a bioprosthetic aortic/mitral valve that were on antiplatelet therapy at time of event: consider switching to vitamin K antagonist anticoagulation
- valve thrombosis
  - mechanical valve thrombosis (generally a subacute-acute event):
    - often associated with inadequate anticoagulation; leads to rapid valve dysfunction
      - recurrent thrombosis can be associated with pannus ingrowth
    - symptoms/signs/presentation: rapid onset of symptoms, acute pulmonary edema, stenotic murmur, muffled closing clicks
    - investigations: urgent multimodal imaging (TTE, TEE, fluoroscopy and/or multidetector CT imaging)
    - treatment: if thrombosed valve is left-sided and symptoms of valve obstruction are present, treat urgently with either fibrinolytic therapy or emergency surgery
  - bioprosthetic valve thrombosis
    - most common in first 3 mo post-implantation; bioprosthetic valves are less thrombogenic than mechanical valves
    - investigations: TTE or TEE or 4D CT imaging in suspected patients
    - treatment: if suspected or confirmed, treatment with a vitamin K antagonist is reasonable (assuming hemodynamically stable and no contraindications)
- graft dysfunction after Ross operation
  - etiology: autograft dilatation and RVOT conduit stenosis and/or regurgitation
    - autograft within LVOT requires reintervention more often than pulmonary homograft within RVOT
  - presentation: aortic regurgitation, pulmonary stenosis, pulmonary regurgitation, aortic root aneurysm
  - investigations: echocardiography, MRI if aneurysmal root
  - treatment: when done in expert centers reintervention results in low mortality
    - autograft dilatation: reoperation (autograft is spareable in majority of cases and survival advantage is still preserved)
    - RVOT graft dysfunction: transcatheter pulmonary valve replacement or surgical pulmonary valve replacement (transcatheter is preferred)



Ross Operation

- En bloc removal of a patient's native pulmonary root with valve (autograft) and transposition of the autograft into the aortic position to a replace a diseased aortic valve that cannot be spared
- The RVOT is then reconstructed with a cadaveric pulmonary homograft
- With proper technique, mitigation of risk factors for early graft failure, and strict postoperative blood pressure control, the pulmonary autograft adapts to the hemodynamics of the LVOT and left heart with low rates of reintervention
- Despite being more complex than isolated aortic valve replacement, morbidity and mortality are comparable to AVR with bioprosthesis or mechanical valves when done in experienced centres



Mechanical or Biological Prostheses for Aortic-Valve and Mitral-Valve Replacement
NEJM 2017;377:1847-57
Purpose: To elucidate differences in mechanical vs. biological prostheses in aortic- and mitral-valve replacements.
Methods: Patients who underwent primary aortic-valve or mitral-valve replacement in California in the period from 1996-2013 were analyzed. Outcomes included long-term mortality and rates of re-operation, stroke, and bleeding.
Results: In aortic-valve replacement, biologic prosthesis was associated with higher 15-yr mortality than mechanical prosthesis among patients aged 45-54 yr (30.6% vs. 26.4%), but not among patients aged 55-64 yr. In mitral-valve replacement, biologic prosthesis was associated with higher mortality than mechanical prosthesis among patients aged 40-49 yr (44% vs. 21%), and among those aged 50-69 yr (50.0% vs. 45.3%).
Conclusion: The long term mortality benefit from mechanical versus biologic prosthesis persisted until 70 yr among mitral-valve replacement patients, and until 55 yr among aortic-valve replacement patients.



Ross Procedure Compared with Bioprosthetic Aortic Valve Replacement
J Am Coll Cardiol;2022;79(10):993–1005
Purpose: The study aimed to compare long-term outcomes in patients undergoing the Ross procedure versus those receiving bioprosthetic aortic valve replacements (AVR).
Methods: Consecutive patients aged 16-60 who underwent a Ross procedure (n=108) or surgical bioprosthetic AVR (n=108). Propensity score matching accounted for baseline differences. The primary outcome was all-cause mortality. The secondary outcomes included, valve reintervention, deterioration, endocarditis, thromboembolic events, and/or pacemaker implantation.
Results: The Ross procedure demonstrated a lower all-cause mortality (HR: 0.35; 95% CI: 0.14-0.90; P = 0.028) compared to bioprosthetic AVR. When considering death as a competing risk, the Ross procedure was associated with decreased rates of reintervention (HR: 0.21; 95% CI: 0.10-0.41; P <0.001), valve deterioration (HR: 0.25; 95% CI: 0.14-0.45; P <0.001), thromboembolic events (HR: 0.15; 95% CI: 0.05-0.50; P = 0.002), and permanent pacemaker implantation (HR: 0.22; 95% CI: 0.07-0.64; P = 0.006).
Conclusion: In comparison to bioprosthetic AVR, the Ross procedure exhibited better superior long-term survival and a lower occurrence of adverse valve-related events.

Summary of Valvular Disease

General Principles for Evaluating Valvular Heart Disease

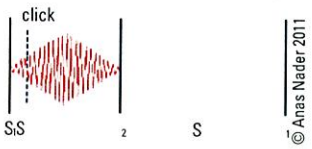
- initial evaluation
  - history and physical: symptom severity, valve disease, comorbidities, HF presence and severity
  - TTE (standard initial investigation): chamber size/function, valve morphology, severity of valvular heart disease, impacts to pulmonary/systemic circulations
  - ECG: rhythm, LVH, LV function
- further testing if indicated/needed
  - CXR: particularly useful for symptomatic patient; assesses for aortic and pericardial calcification, intrinsic pulmonary disease, heart size and congestion of the pulmonary vessels
  - TEE: assessment of mitral and prosthetic valve
  - CMR: LV volume/function, aortic disease, severity of valvular disease
  - PET CT: identification of infection/inflammation
  - stress testing: exercise capacity
  - catheterization: exercise- and drug-related hemodynamic responses, severity of valvular disease, pressures within the heart and pulmonary circulation
- future risk stratification
  - biomarkers: surrogate measure for myocardial damage and filling pressures
  - TTE strain: myocardial function
  - CMR: fibrosis
  - stress testing
  - procedural risk: The Society of Thoracic Surgeons (STS) and TAVI scores
  - frailty score
- preprocedural testing
  - dental exam: rule out sources of infection
  - invasive coronary angiogram or CT coronary angiogram
  - CT peripheral and cardiac (for transcatheter procedures)

Stages of Valvular Heart Disease

- stage A: at-risk (asymptomatic)
- stage B: progressive (mild-moderate severity; asymptomatic)
- stage C: asymptomatic, severe
  - C1: compensated LV or RV
  - C2: decompensated LV or RV
- stage D: symptomatic severe

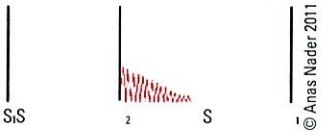
Table 18. Valvular Heart Disease

Aortic Stenosis



Etiology
Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease
Definition/Stages
Stage A: asymptomatic; congenital abnormality, bicuspid or sclerotic valve; aortic Vmax <2 m/s
Stage B: asymptomatic; can be mild AS (Vmax 2.0-2.9 m/s or mean pressure gradient <20 mm Hg) or moderate AS (Vmax 3.0-3.9 m/s or mean pressure gradient 20-39 mm Hg)
Stage C: asymptomatic; can be severe AS (Vmax ≥4 m/s or mean pressure gradient ≥40 mm Hg) or very severe AS (Vmax ≥5 m/s or mean pressure gradient ≥60 mm Hg) ± LV dysfunction
Stage D: symptomatic; can be severe AS or very severe AS; criteria also exist for low-flow, low-gradient AS with reduced LVEF and for low-gradient AS with either normal LVEF or paradoxical low-flow severe AS
Pathophysiology
Outflow obstruction → increased EDP → concentric LVH → LV failure → CHF, subendocardial ischemia
Symptoms
Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema, exertional dyspnea, decreased exercise tolerance, HF symptoms, presyncope, syncope
Physical Exam
Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI
Auscultation: crescendo-decrescendo SEM radiating to right clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S4, soft S2 with paradoxical splitting, S3 (late)
Investigations
ECG: LVH and strain, LBBB, LAE, AFib
CXR: post-stenotic aortic root dilatation, calcified valve, LVH, LAE, CHF
echo: etiology, valve area, valve morphology, hemodynamics, LV size, systolic function, prognosis, timing of intervention
Other: low-dose dobutamine stress testing, CT imaging/aortic valve calcium score, and exercise testing (contraindicated if symptomatic)
Treatment
Calcific AS: statin based on standard risk score for atherosclerotic prevention
Stages A-C: treat HTN
Asymptomatic: serial echos (repeated based on severity), avoid exertion
Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS
Procedural intervention considered in stage D, stage C, and other specific situations
Procedural Options
SAVR: if <65 yr old and >20 yr life expectancy, or if TAVR contraindication
- Conduct prior to pregnancy (if AS significant)
TAVR: if >80 yr old, if <10 yr life expectancy, or if high/prohibitive surgical risk
If patient between 65-80 yr old, decision between SAVR or TAVR is catered to specific patient
Percutaneous aortic balloon dilation: bridge to AVR in critical patients

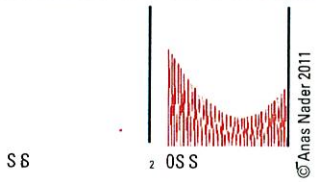
Aortic Regurgitation



Definition
Leakage of blood across the aortic valve into the LV (i.e. aortic insufficiency). May be primary or secondary AR
Etiology
Supravalvular: aortic root disease (Marfan syndrome, atherosclerosis and dissecting aneurysm, connective tissue disease)
Valvular: congenital (bicuspid aortic valve, large VSD), IE
Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve
Pathophysiology
Volume overload → LV dilatation → increased SV, high sBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)
Symptoms
Usually only becomes symptomatic late in disease when HF symptoms, SOBOE, dyspnea, orthopnea, PND, syncope, and/or angina develop as a result of LV failure
Physical Exam
Waterhammer pulse, bisferiens pulse, femoral-brachial sBP >20 mmHg (Hill's test: wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex
Auscultation: early decrescendo diastolic murmur at LLSB (cusp pathology) or RLSB (aortic root pathology); best heard sitting, leaning forward, on full expiration; soft S1, absent S2, present S3 (late)
Investigations
ECG: LVH, LAE
CXR: LVH, LAE, aortic root dilatation
echo/TTE: etiology/severity, quantify AR, leaflet or aortic root anomalies, LV size, systolic function, prognosis, timing of intervention
TEE, CMR, or cardiac catheterization if ≥ moderate AR, suboptimal/inconsistent TTE: systolic function, heart volumes, aortic size, AR severity
Cardiac catheterization lab (Cath lab): if >40 yr and surgical candidate – to assess for ischemic heart disease
Exercise testing: hypotension with exercise
Treatment
Asymptomatic: serial echos, afterload reduction (e.g. ACEI, nifedipine, hydralazine)
Symptomatic: avoid exertion, treat CHF
Surgery if: symptomatic severe AR; chronic, severe AR with LVEF ≤55%; severe AR and otherwise undergoing cardiac surgery; other specific situations
Surgical Options
Valve replacement
Valve repair
Bentall procedure: replacement of aortic root and valve

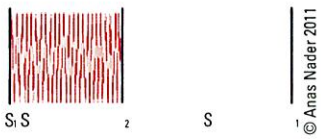
Table 18. Valvular Heart Disease

Mitral Stenosis



Etiology
rheumatic disease (most common), non-rheumatic calcification, congenital
Definition
Severe MS: mitral valve area (MVA) <1.5cm², diastolic pressure half-time ≥150 ms
Pathophysiology
MS → fixed CO and LAE → increased LA pressure → PVR and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)
Symptoms
SOBOE, orthopnea, fatigue, decreased exercise tolerance, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)
Physical Exam
AFib, left parasternal lift, palpable diastolic thrill at apex; if AFib, no "a" wave on JVP; if sinus, prominent "a" wave may be found on JVP
Auscultation: mid-diastolic rumble at apex; best heard with bell in left lateral decubitus position following exertion; loud S1, OS following loud P2 (heard best during expiration), long diastolic murmur, and short A2-OS interval correlate with worse MS
Investigations
ECG: NSR/AFib, LAE (P mitrale), RVH, RAD
CXR: LAE, CHF, mitral valve calcification
echo/TTE: diagnosis/severity, hemodynamics, valvular lesions, valve anatomy/morphology, LA thrombus if percutaneous mitral balloon commissurotomy being considered
Exercise testing: rheumatic MS and resting echo inconsistent with symptoms
Cath lab: if concurrent CAD and patient >40 yr (male) or >50 yr (female)
Treatment
Avoid exertion, fever (increased LA pressure); treat AFib and CHF; increase diastolic filling time (β-blockers, digitalis)
Vitamin K antagonist anticoagulation: in rheumatic MS if AF, previous embolism, or LA thrombus
Heart rate control (for some patients)
Intervention if: symptomatic, severe MS
Invasive Options
Percutaneous mitral balloon commissurotomy (PMBC): symptomatic, severe rheumatic MS with acceptable morphology, < moderate MR, and no LA thrombus (may be reasonable in other specific situations)
Mitral valve surgery (repair, commissurotomy, or replacement): symptomatic, severe rheumatic MS with contraindication/limited access for PMBC, previous failure of PMBC, or otherwise undergoing cardiac surgery (note: restenosis in 50% of patients in 8 yr after open mitral commissurotomy)
Nonrheumatic, calcific MS: if severe MS and severe symptoms, valve intervention can be contemplated pending discussion with patient about high procedural risk

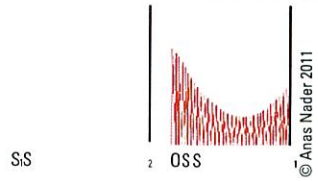
Mitral Regurgitation



Etiology
MVP, congenital cleft leaflets, LV dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan's syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease, leaflet perforation
Definition
Leakage of blood across the mitral valve from the LV into the LA; can be primary or secondary. Can use Carpentier's classification
Pathophysiology
Reduced CO → increased LV and LA pressure → LV and LA dilatation → and pulmonary HTN
Symptoms
Dyspnea, PND, orthopnea, palpitations, peripheral edema, decreased exercise tolerance, SOBOE
Physical Exam
Displaced hyperdynamic apex, left parasternal lift, apical thrill
Auscultation: holosystolic murmur at apex radiating to axilla ± mid-diastolic rumble, loud S2 (if pulmonary HTN), S3
Acute MR: sudden acute and hemodynamic instability (possibility during/post MI)
Investigations
ECG: LAE, left atrial delay (bifid P waves), ± LVH
CXR: LVH, LAE, pulmonary venous HTN
echo/TTE: etiology and severity of MR, LV/RV function, leaflets, pulmonary artery pressure, vegetations/abscesses, papillary muscle/chordal rupture, LA size, mitral valve apparatus, extent of remodelling
TEE: can be helpful with acute MR or if considering transcatheter interventions; also used when TTE findings are insufficient/inconsistent; assess for MR severity/mechanism and LV function
Swan-Ganz Catheter: prominent LA "v" wave
Other: CMR, exercise testing, stress nuclear/PET, stress echo. and serum biomarkers/novel measurement of LV function
Treatment
Acute MR: vasodilator therapy (use limited by systemic hypotension); intra-aortic balloon counter pulsation or percutaneous circulatory assist device may be employed
Asymptomatic: serial echos
Guideline-directed management and therapy for patients with severe MR and LV systolic dysfunction or HFrEF (e.g. ACEi, ARBs, beta blockers, aldosterone antagonists, ARNIs, biventricular pacing)
Intervention if: acute MR with CHF, papillary muscle rupture; severe MR with symptoms or LV systolic dysfunction; AFib; increasing LV size/presence of LV dilatation; pulmonary hypertension; decreasing exercise tolerance; can be reasonable in other situations if low mortality risk (<1%) and high probability of successful/durable repair (>95%) or if otherwise undergoing CABG
Procedural Options
Mitral valve surgery (preferably repair) is indicated and lifesaving in acute, severe, symptomatic, primary MR
Valve repair (preferred over replacement if degenerative disease is the etiology): >75% of patients with MR and myxomatous MVP – annuloplasty rings, leaflet repair, chordae transfers/shortening/replacement
Valve replacement if: failure of repair, heavily calcified annulus
Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation
Transcatheter edge-to-edge repair (TEER): reasonable in patients with severe, symptomatic primary MR with high/prohibitive surgical risk or in severe, symptomatic secondary MR if associated with LV dysfunction

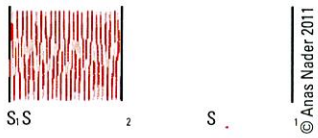
Table 18. Valvular Heart Disease

Tricuspid Stenosis



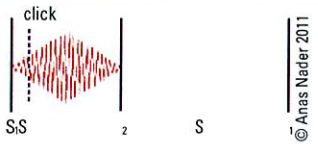
Etiology
Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS (in rheumatic heart disease), autoimmune disorders, atrial myxomas, blunt trauma, metastases, congenital, drug-associated valvulopathy
Definition
Tricuspid orifice narrowing; blood flow from the RA into the RV is obstructed
Pathophysiology
Increased RA pressure → right HF → CO decreased and fixed on exertion
Symptoms
Peripheral edema, fatigue, palpitations
Physical Exam
Prominent "a" waves in JVP, positive abdominojugular reflux, Kussmaul's sign, diastolic rumble 4th left intercostal space
Investigations
ECG: RAE
CXR: dilatation of RA without pulmonary artery enlargement
echo: diagnostic
Cardiac catheterization: large RA "a" wave (12-20 mm Hg); diastolic, mean pressure gradient of 4-8 mm Hg (Increased RA pressure with a slow decrease in early diastole + diastolic pressure gradient is classic for TS)
CMR: RV size/function
Treatment
Preload reduction (diuretics) for severe, symptomatic TS (caution: may exacerbate low output)
Treat underlying etiology
Slow HR
Surgery: usually performed at time of other cardiac surgery (e.g. mitral valve surgery for rheumatic MS)
Surgical Options
Valvotomy using 1-3 balloons
Valve surgery: repair or replacement (open or transcatheter options for replacement)
Usually tricuspid surgery favoured over percutaneous balloon tricuspid commissurotomy or valvuloplasty

Tricuspid Regurgitation



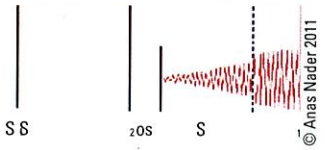
Etiology
RV dilatation, IE (particularly due to IV drug use), rheumatic disease, iatrogenic (device leads, endomyocardial biopsy), congenital (Ebstein's anomaly), pulmonary HTN, RV overload, DCM, annular dilation, leaflet tethering, RA dilatation, ischemic heart diseases, other (trauma, carcinoid, drugs, irradiation)
Definition
Leakage of blood across the tricuspid valve (i.e. tricuspid insufficiency); can be primary or secondary
Pathophysiology
RV dilatation → TR (and further RV dilatation)→ right HF
Symptoms
Peripheral edema, fatigue, palpitations, SOBOE, ascites
Physical Exam
elevated JVP, "cv" waves in JVP, positive abdominojugular reflux, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift,
Investigations
ECG: RAE, RVH, AFib
CXR: RAE, RV enlargement
echo/TTE: diagnostic – assess for etiology/severity of TR, IVC and right heart size, RV systolic function, left-sided disease and pulmonary artery systolic pressure
Invasive measurements (to address inconsistencies): cardiac index, right-sided diastolic pressure, pulmonary artery pressures, pulmonary vascular resistance, ventriculography
Treatment
Preload reduction (diuretics): reasonable if right-sided HF related to severe TR
Therapies to treat HF etiology reasonable if right-sided HF related to severe secondary TR
Surgery if: severe TR (stages C and D) and undergoing cardiac surgery for a left-sided valve; can be reasonable in other specific situations.
Surgical Options
Annuloplasty (i.e. repair; rarely replacement)

Pulmonary Stenosis



Etiology
Usually congenital, rheumatic disease (rare), carcinoid syndrome
Definition
Stiffening/narrowing of the pulmonic valve; blood flow into the pulmonary artery from the RV is obstructed
Pathophysiology
Increased RV pressure → RVH → right HF
Symptoms
Chest pain, syncope, fatigue, peripheral edema
Physical Exam
Systolic murmur at 2nd left intercostal space accentuated by inspiration; pulmonary ejection click; right-sided S4
Investigations
ECG: RVH
CXR: prominent pulmonary arteries, enlarged RV
echo: diagnostic
Treatment
Balloon valvuloplasty if severe symptoms
Surgical Options
Percutaneous or open balloon valvuloplasty

Pulmonary Regurgitation



Etiology
Pulmonary HTN, IE, rheumatic disease, tetralogy of Fallot (post-repair), defective valvular coaptation, annular dilatation, fibrinoid deposits
Definition
Insufficient closure of the pulmonic valve during diastole; reversal of flow into the RV
Pathophysiology
Increased RV volume → increased wall tension → RVH → right HF
Symptoms
Chest pain, syncope, fatigue, peripheral edema
Physical Exam
Early diastolic murmur at LLSB; Graham Steell (diastolic) murmur at 2nd and 3rd left intercostal space (increasing with inspiration)
Investigations
ECG: RVH
CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV
echo: diagnostic
Treatment
Rarely requires treatment; valve replacement (rarely done)
Surgical Options
Pulmonary valve replacement

Table 18. Valvular Heart Disease

Mitral Valve Prolapse



Etiology
Myxomatous degeneration of chordae; thick, bulky leaflets that crowd orifice; associated with connective tissue disorders; pectus excavatum; straight back syndrome, other MSK abnormalities; <3% of population

Definition
Valve leaflet(s) prolapse into the LA; common cause of MR. (i.e. click-murmur syndrome, Barlow's syndrome, billowing mitral valve leaflets, or floppy valve syndrome)

Pathophysiology
Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms. Generally benign; however, presentation may be with sudden cardiac death, infective endocarditis, or cerebrovascular accident

Symptoms
Can be asymptomatic. May have prolonged, stabbing chest pain or atypical chest discomfort; dyspnea; anxiety/panic attacks; palpitations; fatigue; presyncope, SOBOE, exercise intolerance; low blood pressure; syncope; orthostasis; mood changes; syncope

Physical Exam
Auscultation: mid-systolic click (diagnostic - due to billowing of mitral leaflet into LA and tensing of redundant valve tissue); followed by a mid to late systolic murmur at apex (murmur accentuated by Valsalva and diminished when patient squatting)

Investigations
ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy
echo: diagnostic – systolic displacement of mitral valve leaflets above mitral annulus into LA; assess mitral valve leaflet thickness
Cardiac catheterization/left ventriculography: if inconsistent clinical and echo findings; sometimes picks up MVP incidentally

Treatment
Asymptomatic: often no treatment; reassurance. If MR associated, follow-up annually; if not, follow-up q3-5 yr
Sinus rhythm and high-risk MVP: aspirin may be considered
Systemic embolism, recurrent TIAs despite aspirin, ischemic stroke, or AFib: anticoagulation
Symptomatic: β-blockers and avoidance of stimulants (e.g. caffeine) of significant palpitations; anticoagulation if AFib

Surgical Options
Mitral valve surgery (repair favoured over placement): if symptomatic and significant MR; may be reasonable if asymptomatic with MR and systolic HF
Transcatheter mitral valve repair considered if high/prohibitive surgical risk

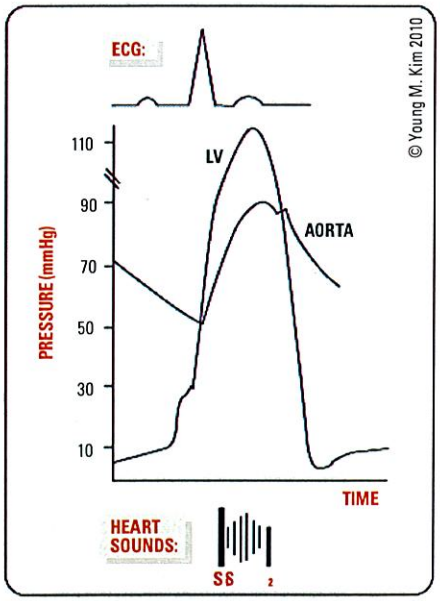


Figure 49. Hemodynamics of aortic stenosis
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the LV and the aorta, as well as a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure, hence diminishing S2

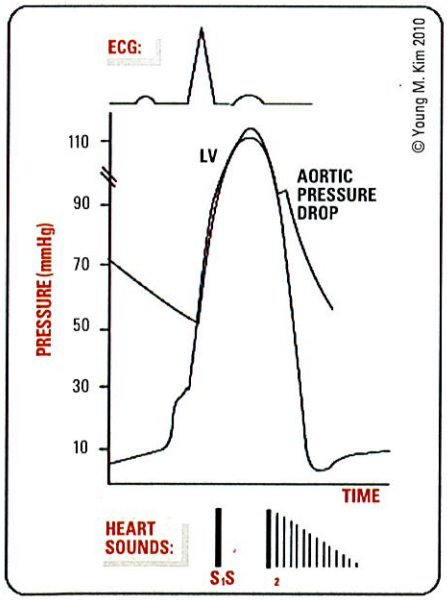


Figure 50. Hemodynamics of aortic regurgitation
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2). The presence of regurgitant blood from the aorta increases LV end diastolic volume

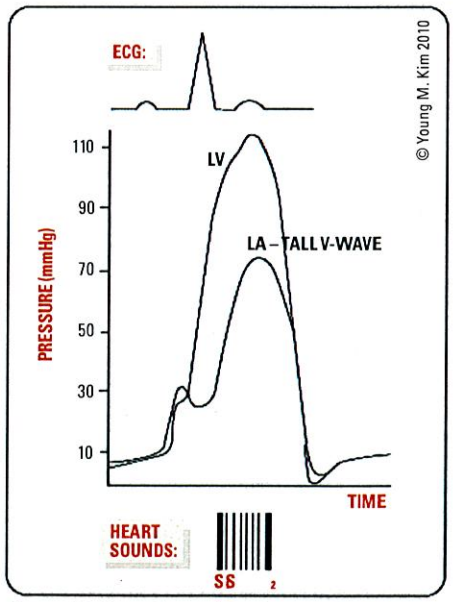


Figure 51. Hemodynamics of acute mitral regurgitation
During systolic contraction, blood regurgitates from the LV into the LA across the incompetent mitral valve resulting in a short but audible holosystolic murmur between S1 and S2. The portion of left ventricular end diastolic volume that regurgitates into the LA myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP). Severe, acute MR usually results in acute hemodynamic decompensation

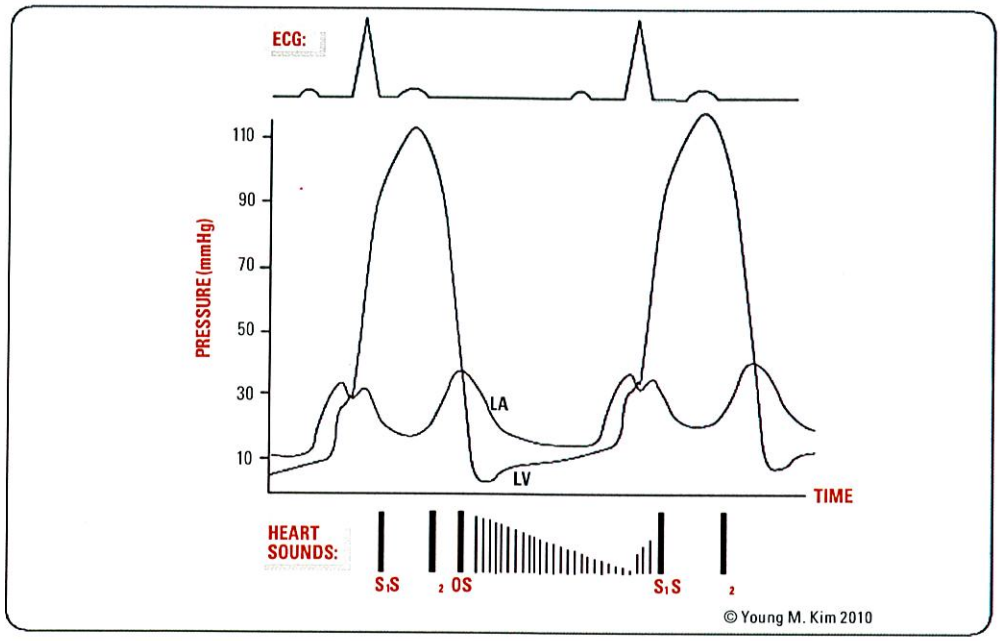


Figure 52. Hemodynamics of mitral stenosis
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to MS and there is a consequent generation of a pressure gradient across the LA and LV. In diastole, the stenotic mitral valve opens (which corresponds to the OS) and the passage of blood across the MS results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible

Transcatheter (TAVR) or Surgical (SAVR) Aortic-Valve Replacement in Intermediate-Risk Patients (PARTNER II Trial)
NEJM 2016;374:1609-1620
Purpose: To determine if TAVR and SAVR result in different survival rates among intermediate-risk patients with AS.
Methods: Patients with AS were randomized to either TAVR (N=1011) or to SAVR (n=1021). The primary endpoint was death from any cause or disabling stroke at 2 yr.
Results: The death rate from any cause or disabling stroke was similar in the TAVR and SAVR groups (P=0.001 for noninferiority). In the transfemoral-access cohort, TAVR resulted in a lower rate of death or disabling stroke than SAVR did (P=0.05). In the transthoracic-access cohort, similar outcomes were observed in the TAVR and SAVR groups. TAVR resulted in larger aortic valve areas and lower rates of AKI, severe bleeding, and new onset AFib. Fewer major vascular complications and less paravalvular AR were observed in patients who underwent SAVR.
Conclusion: In intermediate-risk patients with AS, TAVR and SAVR resulted in similar rates of all-cause mortality and disabling stroke.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on PARTNER III which details the outcomes of low-risk patients who underwent TAVR or surgical aortic-valve replacement.

Pericardial Disease

Acute Pericarditis

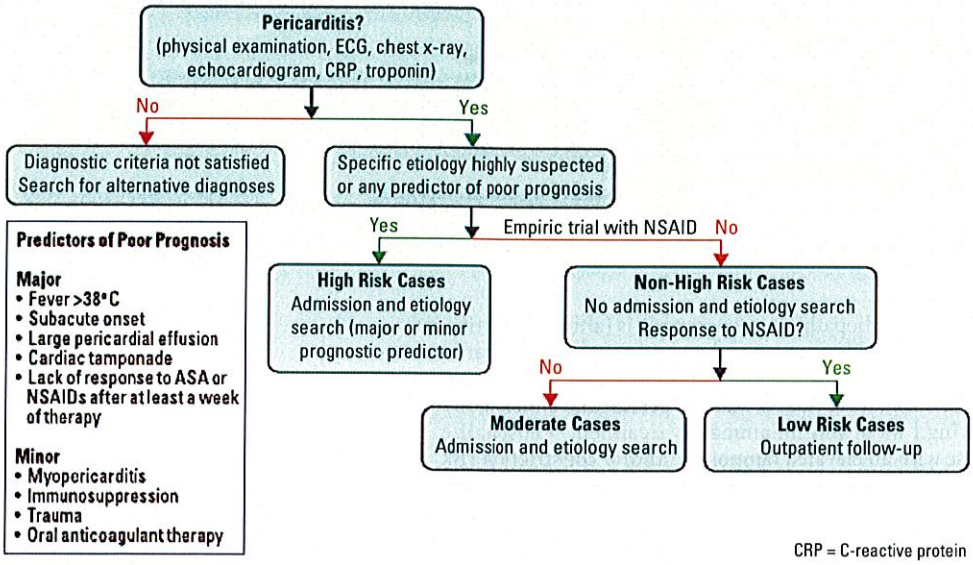
Definition

- syndrome involving the inflammation of the pericardium that may present with or without a pericardial effusion
- pericarditis can be divided into:
  - acute (<4-6 wk)
  - incessant (>4-6 wk with no remission)
  - recurrent (symptom-free remission period of 4-6 wk followed by new onset of pericarditis-associated signs and symptoms)
  - chronic (>3 mo)

Etiology of Pericarditis/Pericardial Effusion

- idiopathic is most common (presumed to be viral)
  - searching for and identifying the etiology is not required in all patients; in nations with low TB prevalence, the most common causes of pericarditis are generally benign
    - infectious only approximately 14%
  - viral: Coxsackie virus A, B (most common), echovirus, Parvovirus B19, Epstein-Barr virus, HIV
  - bacterial: *S. pneumoniae, S. aureus, B. burgdorferi, M. tuberculosis*
- fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other cardiac procedures (e.g pacemaker insertion or TAVR), or other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma, lymphoma
- collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (e.g. sarcoidosis), vaccination (e.g. smallpox)
- autoimmune diseases
- immune checkpoint-inhibitor-associated pericarditis (severe; requires immunosuppressive therapy)
- see *Figure 53, C62* for a proposed approach to triaging pericarditis

Anterior Leaflet Laceration to Prevent Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement (LAMPOON)
J Am Coll Cardiol. 2019 Jul 30;74(4):595
Background: Transcathether mitral valve replacement (TMVR) is routinely employed in patients with valvular disease who are unsuitable for open surgical interventions. The primary complication of this procedure is LVOT obstruction as a result of the anterior mitral leaflet impinging on the interventricular septum.
Purpose: To study intentional laceration of the anterior mitral valve leaflet (LAMPOON) alongside TMVR to prevent the complication of LVOT obstruction.
Methods: Between June 2017 and June 2018, 30 patients with severe MR/MS, high surgical risk, and prohibitive risk of LVOT obstruction, underwent TMVR with LAMPOON. The primary outcomes were technical success for TMVR and LAMPOON (successful laceration) procedures, LVOT gradient <30 mmHg, freedom from emergent re-intervention, and procedural mortality.
Results: The LAMPOON laceration was deemed successful in 100% of enrolled patients. 100% of patients survived immediately post-procedure, with 93% surviving 30-d after discharge. 90% of patients had an LVOT gradient <30 mmHg (optimal range) after TMVR, with 100% of patients showing LVOT gradient <50 mmHg (acceptable range). The procedural success rate was 73% from the remaining 22 subjects.
Conclusions: In the studied population, LAMPOON mitigates the risk of LVOT obstruction with TMVR. LAMPOON is technically feasible and serves to enable TMVR in patients otherwise deemed ineligible due to prohibitive risk of LVOT obstruction.



Proposed triage of acute pericaditis accordint to epidemiological background and predictors of poor prognosis at presentation. At least one predictor of poor prognosis is sufficient to identify a high risk case. Major criteria have been validated by multivariate analysis, minor criteria are based on expert opinion and literature review. Cases with moderate risk are defined as cases without negative prognostic predictors but incomplete or lacking response to non-steroidal anti-inflammatory drug (NSAID) therapy. Low risk cases include those without negative prognostic predictors and good response to anti-inflammatory therapy. Specific etiology is intended as non-ideopathic etiology

Figure 53. Proposed triage of pericarditis

Transcatheter Mitral-Valve Repair in Patients with Heart Failure
NEJM. 2018;379:2307-18
Background: Patients with symptomatic HF and secondary mitral regurgitation have a poor prognosis. Repairing the mitral valve with tanscatheter mitral valve repair (TMVR) may improve patient outcomes.
Purpose: The study Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) assesses if TMVR improves clinical outcomes for patients with HF and MR due to LV dysfunction.
Methods: 614 patients with symptomatic HF and secondary mitral regurgitation with maximal medical therapy were randomized to TMVR with medical therapy, or medical therapy alone. The primary endpoint was hospitalization for HF within 24 mo.
Results: The primary endpoint was 35.8% per patient-year in the intervention group and 67.9% per patient-year in the control group (hazard ratio 0.53; 95% CI 0.40 to 0.70; P<0.001). Death from any cause occurred at 29.1% in the intervention group and 46.1% in the control group (hazard ratio 0.62; 95% CI 0.46 to 0.82; P<0.001).
Conclusions: TMVR in patients with symptomatic HF and secondary MR despite maximal medical therapy had a lower rate of hospitalization for HF as well as all cause mortality compared to medical therapy alone.

Clinical Presentation, Investigations, and Diagnosis

- 2 of the following 4 needed for diagnosis
  1. chest pain
     - sharp, rapid onset (may be dull or throbbing)
     - pain commonly radiates to the trapezius ridge
     - pleuritic; pain related to inspiration, coughing, and potentially hiccoughs
     - improves with sitting up/leaning forward
  2. pericardial friction rub
     - with patient leaning forward or on elbows and knees, friction rub heard on left sternal border
     - classically triphasic; may be mono- or biphasic
     - varies in intensity over time; repeated examinations necessary
     - highly specific finding
  3. ECG changes (only about 60% of patients have sequential changes)
     - stage 1: PR depression and generalized ST elevation (a generally specific finding but up to 40% have nondiagnostic and atypical changes)
     - stage 2: stage 1 findings reversed; J points on baseline prior to flattening of T waves
     - stage 3: inversion of T-waves
     - stage 4: all changes normalized
     - changes noted on ECG can be localized or diffuse; PR depression may be the only sign
  4. pericardial effusion (new or worsening)
- other physical exam findings: ± malaise, ± sinus tachycardia, ± low-grade fever, ± non-cardiac findings if the acute pericarditis is related with a systemic condition (e.g. rash, arthritis, weight loss, night sweats)
- other investigations may aid in diagnosis/monitoring
  - biomarkers/inflammatory markers
    - cardiac-specific troponin I or T elevation (≥30% of patients) –evidence of myocardial involvement (could be myopericarditis or perimyocarditis). Imaging modalities such as echo or CMR may also provide evidence of myocardial involvement
    - elevated CRP, ESR, and/or WBC count found in majority of patients, but not sensitive or specific (elevated high-sensitivity CRP can predict recurrence risk)
  - imaging
    - CXR
      - usually normal heart size (effusion >300 mL needed to increase cardiothoracic index)
      - patients with a new/unexplained increase in heart size should be worked up for acute pericarditis (especially when lung fields are clear)
      - may demonstrate evidence of pleuropericardial involvement in the setting of pleuropulmonary disease
      - cause of pericarditis can sometimes be identified

- echo: often the only necessary modality for imaging (TEE > TTE) → normal in 40%
  - applications include:
    - identifying pericarditis-associated complications (e.g. cardiac tamponade, constrictive pericarditis) or components of myocarditis (e.g. ventricular dysfunction)
    - monitoring pericardial effusion and efficacy of therapy
    - providing real-time evaluation during pericardial drainage
  - CMR, CT may also have applications in the setting of pericarditis; assess for inflammation of pericardium
- differential diagnosis includes: Takotsubo syndrome, MI, myocarditis

Prognosis
- based on etiology (e.g. overall good prognosis = idiopathic/viral pericarditis (although significant recurrence risk), pericarditis with myocardial involvement; purulent and neoplastic pericarditis have a reported mortality rate between 20-30%)
  - negative prognostic factors: subacute onset, fever ≥38°C, >20mm pericardial effusion on echo, tamponade, lack of response following 1 wk of anti-inflammatory treatment → hospitalize patients with these factors and those with an elevated tamponade and/or constriction risk
    - minor negative prognostic factors: oral anticoagulation, trauma, immunosuppression

Treatment
- treat the underlying disease
- anti-inflammatory agents remain the mainstay for treatment (e.g. NSAIDs/ASA)
  - ketorolac may be employed in patients with severe pain or patients unable to take oral medication; use should be limited to 5 d
- colchicine may reduce symptom persistence and recurrent rates
- corticosteroid use is controversial but may be indicated in patients with incomplete response, failure of other anti-inflammatory medications, and/or other indicated situations (e.g. autoimmune disease-associated or immune checkpoint inhibitor-associated pericarditis)
- purulent pericarditis (rare but life-threatening): pericardial drainage and antimicrobial therapy catered to the culprit etiologic agent and/or local fibrinolytic therapy
- tuberculous pericarditis: multidrug regimen for several months (corticosteroids and pericardiectomy sometimes considered)
- pericarditis in the setting of viremia (particularly in immunocompromised patients): antiviral treatment
  - physical activity restriction until symptom resolution

Complications
- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Definition
- fluid accumulation in the pericardial sac (note: the pericardial sac normally hosts 10-50 mL of lubricating pericardial fluid). The composition of the fluid can include exudate, transudate, blood, and rarely air/gas

Etiology and Classification
- effusion is found incidentally on x-ray or echo for a significant proportion of patients
  - for these patients in developed countries, etiologies include:
    - idiopathic (up to 50%)
    - cancer (10-25%)
    - infections (15-30%)
    - iatrogenic causes (15-20%)
    - connective tissue diseases (5-15%)
  - in developing countries, TB is the predominant cause (>60%)
- for pericardial effusion with pericarditis, the prevalence of malignant/infectious etiologies is 15-50%
- transudative causes
  - increased systemic venous pressure or hydrostatic pressure: CHF, pulmonary HTN
  - decreased plasma oncotic pressure: cirrhosis, nephrotic syndrome, hypoalbuminemia/ hypoproteinemia
- exudative causes (serosanguinous or bloody)
  - pathologic process → inflammation → possible increased production of pericardial fluid
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- can be classified according to onset, distribution, hemodynamic impact, composition, and size
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

ALGrawany

Signs and Symptoms

- rate of development of pericardial effusion determines clinical presentation
- may be asymptomatic or similar to acute pericarditis
- classic symptoms: dyspnea on exertion (progressing to orthopnea), chest pain, and/or fullness
- symptoms related to local compression of extracardiac structures may include: nausea, dysphagia, hoarseness, hiccoughs; may cause esophageal/recurrent laryngeal nerve/trachea-bronchial/phrenic nerve irritation
- non-specific symptoms related to compression of related structures or reduced blood pressure and secondary sinus tachycardia: cough, weakness, fatigue, anorexia, palpitations, fever (may be associated with pericarditis)
- physical exam findings:
  - JVP increased with dominant "x" descent
  - arterial pulse normal-to-decreased volume; decreased pulse pressure
  - auscultation: distant heart sounds ± rub
  - Ewart's sign
  - often normal in patients without compromise to hemodynamic status; if tamponade present, findings can include fatigue, dyspnea, elevated JVP, neck vein distension, edema, pulsus paradoxus, muffled heart sounds (in moderate-large effusions). Rarely friction rubs heard (usually appreciated with concomitant pericarditis)



Ewart's Sign
Egophony, bronchial breathing, and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung

Investigations

- ECG: sinus tachycardia, low voltage (should raise concern for effusion with tamponade when present with sinus tachycardia; however, not specific for pericardial effusion), flat T waves, electrical alternans (highly specific for pericardial effusion (generally with tamponade), but not a sensitive enough sign to exclude effusion/tamponade)
  - be cautious in diagnosing STEMI in a patient with pericarditis and an effusion as antiplatelets may precipitate hemorrhagic effusion
- CXR: ± cardiomegaly with clear lung fields, ± rounded cardiac contour
- emergency room: bedside U/S with subxiphoid view showing fluid in pericardial sac
- echo/TTE (procedure of choice): fluid in pericardial sac; assess effusion size and hemodynamic effects, and assist in needle placement in pericardiocentesis
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, and investigating neoplastic involvement
- CT/CMR: compared with echo, provide greater field of view → enable loculated effusion detection, identification of masses or thickening associated with the pericardium, assessment for chest abnormalities (however, echo still preferred due to availability/portability/low cost)
- biomarkers: assessment of inflammation markers (e.g. CRP) recommended

Treatment (see *Figure 54, C65*)

- triage: based on size, hemodynamic effects (particularly assess for tamponade), inflammatory markers, concomitant pathologies → high risk patients should be admitted
- treat underlying etiology (60% of effusions associated with known disease)
- if inflammatory signs are present, or if associated with pericarditis, treat as if pericarditis; if elevated markers of inflammation, can try NSAIDs/colchicine/low-dose corticosteroids; if associated with systemic inflammation, Aspirin™/NSAIDs/colchicine recommended
- pericardiocentesis or cardiac surgery if: cardiac tamponade, symptomatic moderate-large effusion and unresponsive to medical therapy, or unknown bacterial/neoplastic etiology suspected
  - prolonged drainage using pericardiocentesis should also be considered if symptomatic effusion without evidence of inflammation or unresponsive to anti-inflammatory agents
  - if no inflammation and large, isolated effusion, pericardiocentesis alone may be required (no evidence for medical therapy), but recurrences are common
  - consider pericardiectomy or pericardial window (subxiphoid or video assisted thoracoscopic) if: re-accumulation of fluid, loculated effusion, biopsy required
- follow-up/frequent observation if no evidence/suspicion of:
  - tamponade
  - bacterial/neoplastic etiology
  - elevated inflammatory markers
  - associated pathology
  - large effusion (>20 mm)
    - Note: follow-up based on symptoms, effusion size and evolution, inflammatory markers, etc.

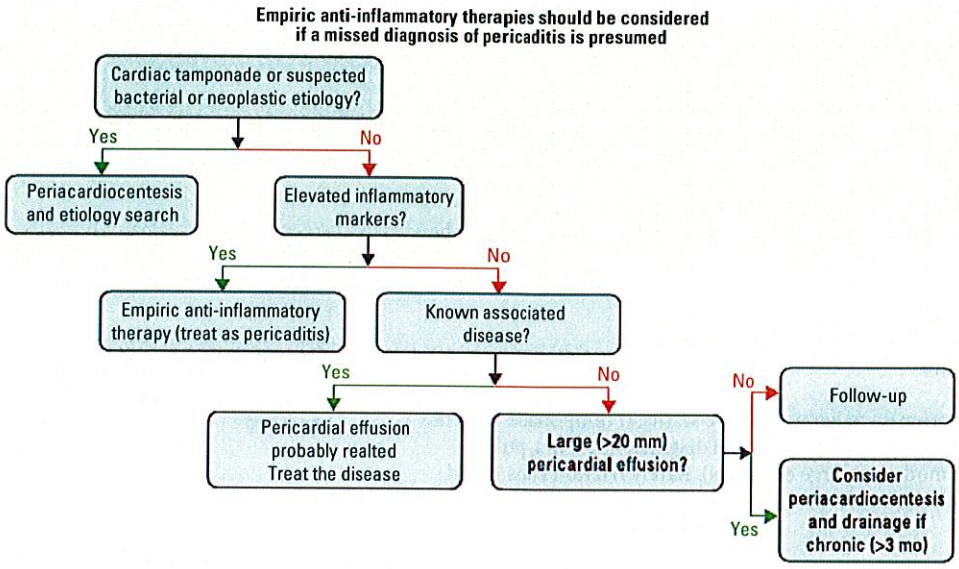


Figure 54. Triage/management algorithm for pericardial effusion

Cardiac Tamponade

Definition

- accumulation of fluid, pus, blood, clots or gas in the pericardium leading to life-threatening, slow or rapid compression of the heart

Etiology

- can be caused by inflammation, trauma, rupture of the heart or aortic dissection
- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- common causes: pericarditis, TB, iatrogenic, trauma, neoplasm/malignancy
- uncommon causes: collagen vascular diseases (e.g. SLE, rheumatoid arthritis, scleroderma), radiation, post-MI, uremia, aortic dissection, bacterial infection, pneumopericardium

Classic Quartet of Tamponade

- Hypotension
- Increased JVP
- Tachycardia
- Pulsus paradoxus

Beck's Triad

- Hypotension
- Increased JVP
- Muffled heart sounds

Pathophysiology

- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

Signs and Symptoms

- tachycardia, hypotension, increased JVP
- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in sBP >10 mmHg during quiet breathing)
- JVP "x" descent only, blunted "y" descent
- hepatic congestion/peripheral edema
- severity of signs/symptoms depend on rate of accumulation, volume of pericardial contents, pericardial distensibility, cardiac filling pressures, and chamber compliance

Investigations

- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- CXR: enlarged cardiac silhouette; slow-accumulating effusions
- CT/CMR: less available; usually only necessary if Doppler echo is infeasible
- echo (diagnostic modality of choice): pericardial effusion (size, location, hemodynamic impact), swinging of the heart, compression of cardiac chambers (RA and RV) in diastole, etc. → echo also used for the purpose of guiding pericardiocentesis
- cardiac catheterization (rare)

Treatment

- urgent drainage: needle pericardiocentesis recommended (with echo or fluoroscopic guidance); surgery (i.e. pericardiotomy) is an alternative drainage approach (e.g. with purulent pericarditis or in an urgent situation involving bleeding into the pericardium)
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO) as well as mechanical ventilation
- IV fluid may increase CO
- treat underlying cause

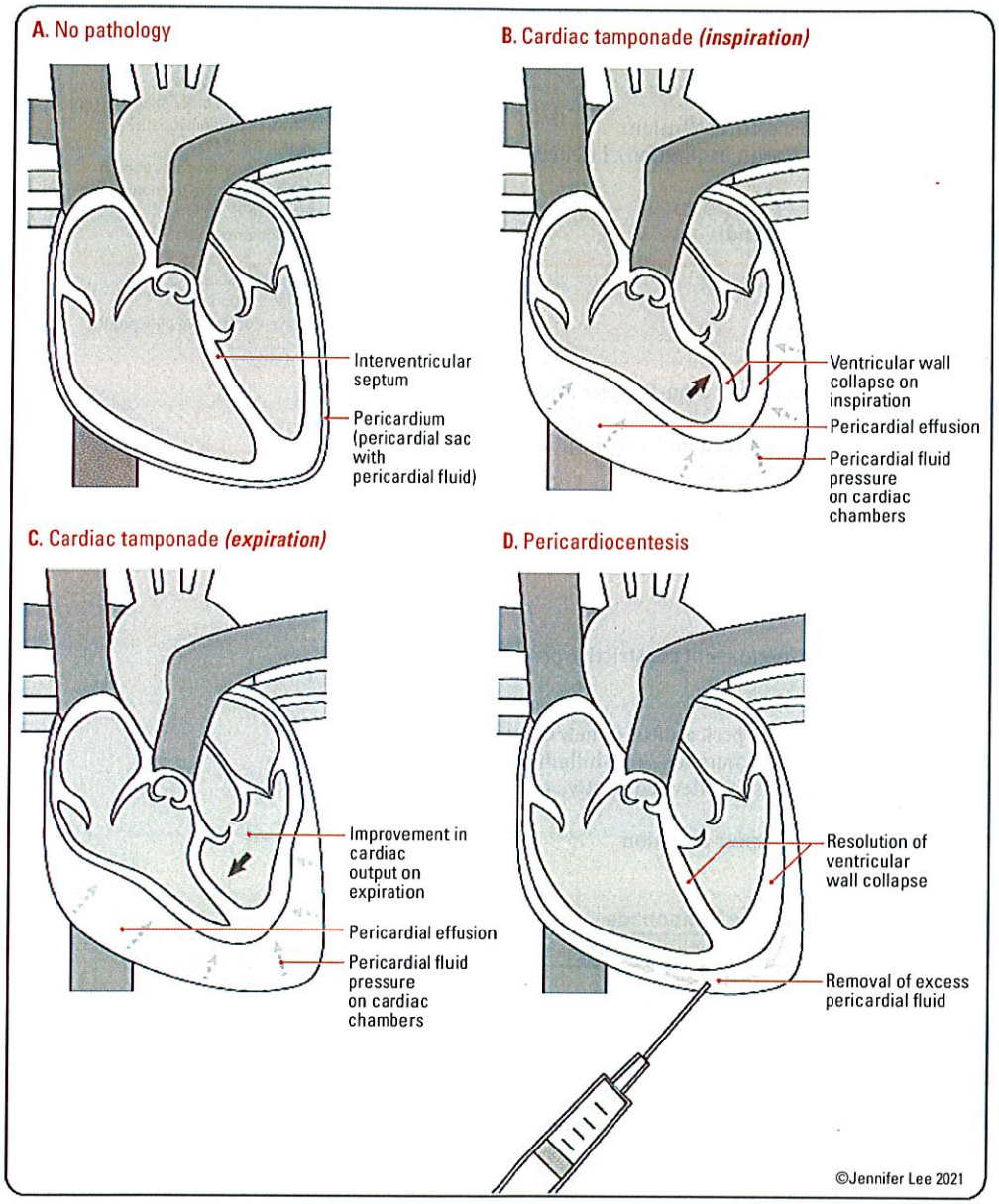


Figure 55. Cardiac tamponade pathophysiology

Constrictive Pericarditis

Definition

- loss of pericardial elasticity caused by granulation tissue formation; leads to restricted ventricular filling

Etiology

- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, bacterial pericarditis/purulent pericarditis, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease
- any pericardial disease process can cause constrictive pericarditis; risk of progression to constrictive pericarditis is based on the etiology of the pericardial disease

Pathophysiology

- rigid, fibrous pericardium impairs ventricular filling during diastole → decreased venous return to the heart → rise in systemic venous pressure → signs and symptoms of right-sided HF (classically with preserved ventricular function and otherwise no myocardial disease)
  - in advanced cases, there can be systolic dysfunction if myocardial fibrosis or atrophy present

Signs and Symptoms

- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  - venous congestion, ascites, hepatosplenomegaly, edema, pleural effusions
- increased JVP, Kussmaul's sign (paradoxical increase in JVP with inspiration), Friedreich's sign (prominent "y" descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see *Table 19* for differentiation from cardiac tamponade

Investigations

- ECG: non-specific findings low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/CMR: pericardial thickening, calcification ± characteristic echo-Doppler findings (Note: CMR is discouraged if patient is hemodynamically impaired)
- cardiac catheterization: indicated if other, non-invasive imaging modalities are insufficient to make diagnosis; assess for equalization of end-diastolic chamber pressures
- diagnosis: right HF symptoms + diastolic filling impairment caused by constriction (documented on ≥1 imaging modality including echo, CT, CMR, and/or catheterization)
- note: in up to 20% of patients, constriction can occur even with normal thickness of the pericardium (pericardiectomy equally efficacious in these patients)

Treatment

- surgery (pericardiectomy): mainstay treatment for chronic, permanent constrictive pericarditis
- medical therapy: can be used in 3 situations
  1. for specific pathologies/etiologies (e.g. TB)
  2. for transient constriction that is temporarily caused by pericarditis, or new constriction diagnosis with evidence of inflammation of the pericardium (use anti-inflammatories)
  3. supportive when high/prohibitive surgical risk (goal is to relieve congestive symptoms with diuretics, salt restriction)
- prognosis best with idiopathic or infectious cause and worst in post-radiation
- death may result from HF

Table 19. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

Characteristic	Constrictive Pericarditis	Cardiac Tamponade
JVP	"y" > "x"	"x" > "y"
Kussmaul's sign	Present	Absent
Pulsus paradoxus	Uncommon	Always
Pericardial knock	Present	Absent
Hypotension	Variable	Severe



DDx Pulsus Paradoxus

- Most etiologies of RV failure except restrictive cardiomyopathy (e.g. acute RV MI)
- Constrictive pericarditis (rarely)
- Severe obstructive pulmonary disease (e.g. asthma)
- Pneumothorax
- PE
- Cardiogenic shock
- Cardiac tamponade
- Effusive-Constrictive pericarditis

Extracorporeal Circulation

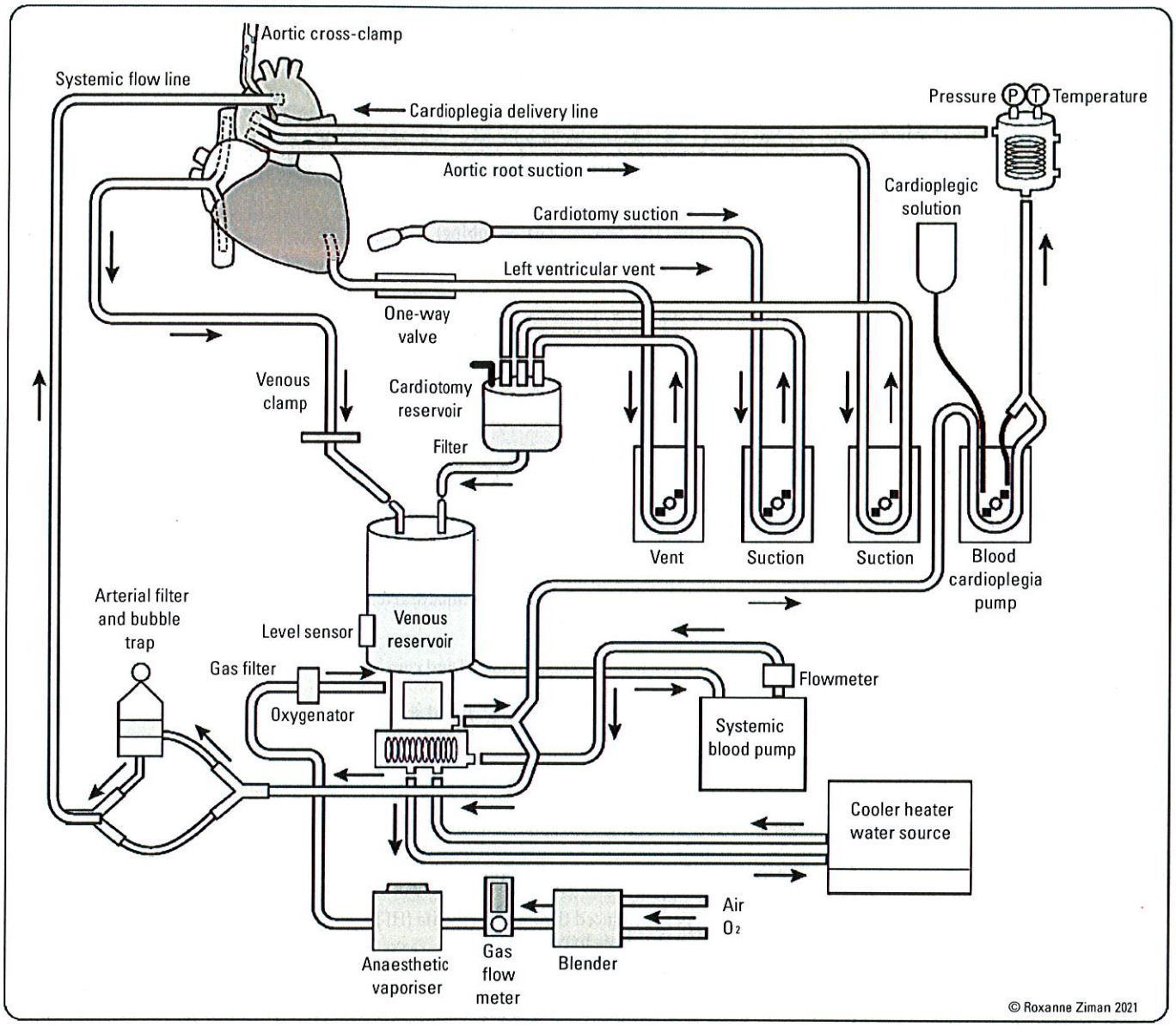


Figure 56. Cardiopulmonary bypass schematic
Modified from Cardiac Surgery in the Adult, second edition, Robert A.E Dion, p. 729, Copyright (2020), with permission from Elsevier

Cardiopulmonary Bypass

Overview

- CPB is commonly used in cardiac and thoracic aortic surgeries to obtain a still, bloodless surgical field by circumventing the heart and lungs while supplying blood to the systemic circulation
- essential functions of CPB: oxygenation, ventilation, circulation, temperature control

Components

- the standard components of a CPB circuit:
  - arterial cannula (aortic, femoral, or axillary) and line (3/8" heparin-coated tubing)
  - oxygenator (membrane oxygenator, defoamer, and heat exchanger)
  - pump (peristaltic/roller or centrifugal)
  - venous cannula (RA, SVC and IVC, or femoral) and line (1/2" heparin-coated tubing)
  - venous reservoir (rigid high capacitance reservoir or closed soft reservoir)

Mechanics

- venous blood is drained into venous reservoir. The blood is oxygenated, and CO_2 is eliminated, heated, or cooled (if applicable) and returned to the systemic circulation via the arterial cannula
  - heparin is first administered so that pump suckers can be turned on when the patient's ACT is >400 s and CPB initiated when ACT is >480 s
    - ACT is measured every 30 min while on CPB and additional heparin boluses are administered to maintain ACT >480 s
    - anticoagulation is reversed following separation of CPB by administering protamine which neutralizes heparin
  - the rate of blood draining into the venous reservoir is determined by the: CVP, height differential between venous cannula and venous reservoir, luminal radius of venous cannula and tubing, presence of air within the tubing
  - arterial cannulation is typically performed at the distal ascending aorta, distal to the aortic cross clamp, with alternative sites for cannulation including the aortic arch, innominate artery, subclavian artery, axillary artery, femoral artery, and LV apex
  - optimal flow rate is calculated to achieve a cardiac index of 2.4 L/min/m^2
  - patient parameters measured during CPB: ECG, BP, CVP, SaO_2, $ETCO_2$, peripheral and core temperature, urine output, ABG
  - CPB pump parameters measured during CPB: blood flow rate, roller pump/centrifugal speed, gas flow, pump blood temperature, heat exchanger water temperature, arterial line pressure, arterial and venous line O2 saturations, delivered O_2 concentration

Complications

- reaction to non-endothelialized foreign surfaces: systemic inflammatory response, hemolysis, coagulopathy
- vessel injury from cannulation: aortic dissection and embolization of aortic debris (e.g. porcelain aorta)
- heparin-related: heparin-associated thrombocytopenia, heparin-induced thrombocytopenia (HIT)
- systemic embolization: cerebrovascular accident, renal and splanchnic hypoperfusion
  - includes biologic and nonbiologic microemboli as well as air/gas/bubble emboli
  - cardiotomy reservoir must be filtered to reduce risk of microemboli

Cardiac and Neurological Protection during Cardiopulmonary Bypass

Myocardial Protection Techniques

- myocardial protection reduces myocardial ischemia during CPB by reducing myocardial oxygen consumption and maintaining oxygenated myocardial perfusion
- methods of myocardial protection to reduce oxygen demands include: unloading the heart (CPB), stopping the heart (cardioplegic diastolic arrest), cooling the heart (core hypothermia, cold saline external washing, hypothermic cardioplegia solutions)
- cardioplegia (given continuously or intermittently) induces diastolic arrest by altering myocytes' resting potential and ionic gradients via concentrated K+ solutions
  - crystalloid cardioplegia
    - extracellular solutions (high sodium) (e.g. St. Thomas' solution, del Nido solution) increase extracellular K+ concentration to prevent cardiomyocyte repolarization
    - intracellular solutions (low sodium) lower extracellular Na+ concentration thereby blocking depolarization
  - blood cardioplegia: autologous cold blood combined with tailored crystalloid solutions in various ratios
    - blood typically comprises majority of overall solution (e.g. 8:1, 4:1, 2:1)



Special Consideration of Blood Conservation for Jehovah's Witness Patients

- Preoperatively:
  - Administer erythropoietin
  - Stop all anticoagulant and antiplatelet medications for 7 d, if possible
- Intraoperatively:
  - Continuous cell salvage circuit
  - Meticulous hemostasis
  - OPCAB
  - Pharmacological adjuncts (tranexamic acid or aprotinin)
- Postoperatively:
  - Low threshold for resternotomy due to bleeding

Cerebral Protection

- cerebral protection techniques are required when CPB cannot supply the head vessels, such as during surgery on the aortic arch
- methods of cerebral protection to reduce oxygen demands include: hypothermia (most important) and anterograde/retrograde cerebral perfusion

Deep Hypothermic Circulatory Arrest

- deep hypothermic circulatory arrest reduces cerebral metabolism and oxygen consumption to the point that CPB can be discontinued
  - (30-40 min safe circulatory arrest at 20°C; 45-60 min safe circulatory arrest at 16°C)
    - concurrent ACP enables circulatory arrest at higher temperatures than DHCA alone
  - EEG monitoring occurs throughout to confirm adequate cerebral protection
  - mannitol (reduces cerebral edema) and steroids (decrease cerebral inflammation) are used adjunctively
  - complications related to deep hypothermic circulatory arrest include: coagulopathy and platelet dysfunction, systemic inflammatory response, neurological injury secondary to ischemia in watershed areas (neurologic dysfunction may be persistent or transient depending on etiology)

Common Medications

Table 20. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Contraindications	Side Effects
ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)					
	enalapril, perindopril, ramipril, lisinopril	Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis	HTN, CAD, CHF, post-MI, DM	Bilateral renal artery stenosis, pregnancy, caution in decreased GFR	**Dry cough (10%), hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema**
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)					
	candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	Block AT II receptors, causing similar effects as ACEI	Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated	Same as ACEI	Similar to ACEI, but less likely to cause dry cough
ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)					
	sacubitril/valsartan	Sacubitril inhibits neprilysin which leads to vasodilation and natriuresis Valsartan (ARB) - see above	HFrEF	Angioedema, pregnancy	Angioedema, hyperkalemia, hypotension, renal insufficiency
β-BLOCKERS					
β1 antagonists β1/β2 antagonists α1/β1/β2 antagonists β1 antagonists with intrinsic sympathomimetic activity	atenolol, metoprolol, bisoprolol, propranolol, labetalol, carvedilol, acebutolol	Block β-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand; also slow conduction through the AV node	HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension Caution in asthma, claudication, Raynaud's phenomenon, and decompensated CHF	Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud's phenomenon, and claudication
CALCIUM CHANNEL BLOCKERS					
Benzothiazepines Phenylalkylamines (non-dihydropyridines)	diltiazem, verapamil	Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate	HTN, CAD, SVT, AFib, diastolic dysfunction	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, CHF	Hypotension, bradycardia, edema
Dihydropyridines	amlodipine, nifedipine, felodipine	Block smooth muscle calcium channels causing peripheral vasodilation	HTN, CAD	Severe AS and liver failure	Hypotension, edema, flushing, headache, light-headedness
SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS					
	canagliflozin dapagliflozin empagliflozin ertugliflozin	Proposed mechanisms include: osmotic diuresis and natriuresis reducing preload; vasodilation leading to reduced afterload; myocardial metabolic stabilization	Dapagliflozin trial (DAPA-HF) indicates potential use in HFrEF with DM/non-DM, with multiple other SGLT2 inhibitors trials underway. Although dapagliflozin has received guideline recommendations in Canada, US and EU for use in HFrEF, no SGLT2 inhibitors have formal approval for HFrEF without DM by Health Canada HFpEF (see EMPEROR-Preserved trial)	Severe CKD (dapagliflozin contraindicated in patients with eGFR <30 mL/min/1.73m2), T1DM, history of DKA, advise holding during sick days	Yeast infections, Urinary tract infections, hypoglycemic episodes, diabetic ketoacidosis, decreased bone mineral density

Table 20. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Contraindications	Side Effects
DIURETICS					
Thiazides	hydrochlorothiazide, chlorthalidone, metolazone	Reduce Na^+ reabsorption in the distal convoluted tubule (DCT)	HTN (drugs of choice for uncomplicated HTN)	Sulfa allergy, pregnancy	Hypotension, hypokalemia, polyuria
Loop diuretics	furosemide (Lasix®)	Blocks Na^+/K^+-ATPase in thick ascending limb of the loop of Henle	CHF, pulmonary or peripheral edema	Hypovolemia, hypokalemia	Hypovolemia, hypokalemic metabolic alkalosis
Mineralocorticoid receptor antagonists	spironolactone eplenerone	Antagonize aldosterone receptors	HTN, CHF, hypokalemia	Renal insufficiency, hyperkalemia, pregnancy	Edema, hyperkalemia, gynecomastia
INOTROPES					
	digoxin (Lanoxin®)	Inhibit Na^+/K^+-ATPase, leading to increased intracellular Na^+ and Ca^{2+} concentration, and increased myocardial contractility Also slows conduction through the AV node	CHF, AFib	2nd or 3rd degree AV block, hypokalemia	AV block, junctional tachycardia, bidirectional VT, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V
ANTICOAGULANTS					
Coumarins	warfarin (Coumadin®)	Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X	AFib, LV dysfunction, prosthetic valves, venous thrombosis	Recent surgery or bleeding, bleeding diathesis, pregnancy	Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis
Heparins	Unfractionated heparin LMWHs: dalteparin, enoxaparin, tinzaparin	Antithrombin III agonist, leading to decreased clotting factor activity	Acute MI/ACS; (when immediate anticoagulant effect needed), PE, venous thrombosis	Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)	Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)
Direct thrombin inhibitors	dabigatran	Competitive, direct thrombin inhibitor, thrombin enables fibrinogen conversion to fibrin during the coagulation cascade	AFib, venous thrombosis, PE	Severe renal impairment, recent surgery, active bleeding Idarucizumab: FDA approved agent for reversal of dabigatran for bleeding	Bleeding, GI upset
Direct factor Xa inhibitors	rivaroxaban apixaban edoxaban	Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways	AFib, venous thrombosis, PE	Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation Andexanet alfa FDA approved agent for reversal of apixaban and rivaroxaban for bleeding	Bleeding, elevated liver enzymes
ANTIPLATELETS					
Salicylates	ASA (Aspirin®)	Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation	CAD, acute MI, post-MI, post-PCI, CABG	Active bleeding or PUD	Bleeding, GI upset, GI ulceration, impaired renal perfusion
Thienopyridines	clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®)	P2Y12 antagonist (block platelet ADP receptors	Acute MI, post-MI, post-PCI, CABG	Active bleeding or PUD	Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)
Nucleoside analogues	ticagrelor (Brillinta®)	P2Y12 antagonist (but different binding site than thienopyridines)			
Glycoprotein IIb/IIIa inhibitors	eptifibatide, tirofiban, abciximab	Block binding of fibrinogen to Gp IIb/IIIa	Acute MI, particularly if PCI is planned	Recent surgery or bleeding, bleeding diathesis	Bleeding
THROMBOLYTICS					
	alteplase, reteplase, tenecteplase, streptokinase	Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin	Acute STEMI	See *Table 10, C34*	Bleeding
NITRATES					
	nitroglycerin	Relax vascular smooth muscle, producing venous and arteriolar dilation	CAD, MI, CHF (isosorbide dinitrate plus hydralazine)	Concurrent use of cyclic guanosine monophosphate phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure	Headache, dizziness, weakness, postural hypotension

Table 20. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Contraindications	Side Effects
LIPID LOWERING AGENTS					
Statins	atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®)	Inhibit hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, an enzyme which catalyzes the rate-limiting step in cholesterol synthesis	Dyslipidemia (1° prevention of CAD), CAD, post-MI (2° prevention of CV events)	Liver or muscle disease	Myalgia, rhabdomyolysis, abdominal pain
Cholesterol absorption inhibitor	ezetimibe (Ezetrol®)	Inhibits gut absorption of cholesterol	Decreases low-density lipoprotein but does not reduce mortality	Liver or renal impairment	Myalgia, rhabdomyolysis, abdominal pain
PCSK9 inhibitor	evolocumab alirocumab	Monoclonal antibody that inhibits PCSK9's inhibitory action on the recycling of LDL receptors, thereby increasing the number of LDL receptors on the surface of liver cells	Hypercholesterolemia	Hypersensitivity reaction to drug	Mild reactions to site of injection, nasopharyngitis
Miscellaneous	fibrates, bile acid sequestrates, nicotinic acid		Primarily in familial hypercholesterolemia		GI side effects common

Antiarrhythmics

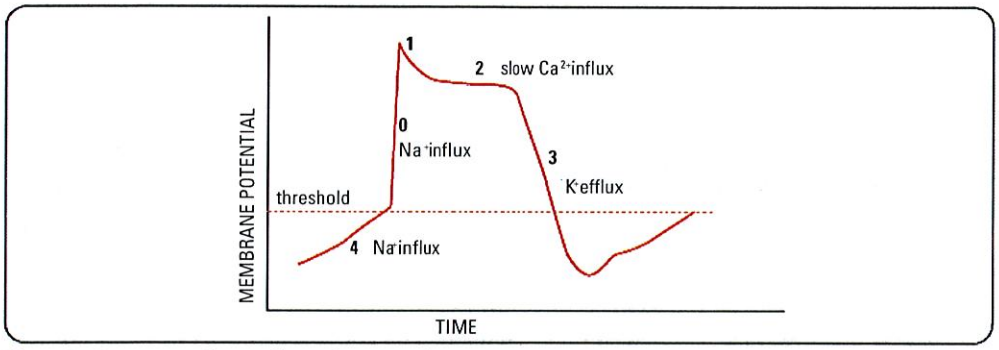


Figure 57. Representative cardiac action potential

Table 21. Antiarrhythmic* Drugs (Vaughan-Williams Classification)

Class	Agent	Indications	Side Effects	Mechanism of Action
Ia	quinidine procainamide disopyramide	SVT, VT	Torsades de Pointes (all Ia), diarrhea Lupus-like syndrome Anticholinergic effects	Moderate Na^+ channel blockade Slows phase 0 upstroke Prolongs repolarization, slowing conduction
Ib	lidocaine mexiletine	VT	Confusion, stupor, seizures GI upset, tremor	Mild Na^+ channel blockade Shortens phase 3 repolarization
Ic	propafenone flecainide encainide	SVT, VT AFib	Exacerbation of VT (all Ic) Negative inotropy (all Ic) Bradycardia and heart block (all Ic)	Upstroke
II	propranolol metoprolol, etc.	SVT, AFib	Bronchospasm, negative inotropy, bradycardia, AV block, impotence, fatigue	β-blocker Decreases phase 4 depolarization
III	amiodarone** sotalol	SVT, VT AFib SVT, VT	Amiodarone: photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR Amiodarone and sotalol: Torsades de Pointes, bradycardia, heart block, β-blocker side effects	Blocks K^+ channel Prolongs phase 3 repolarization, which prolongs refractory period
IV	verapamil diltiazem	SVT AFib	Bradycardia, AV block Hypotension	CCB Slows phase 4 spontaneous depolarization, slowing AV node conduction

*All antiarrhythmics have potential to be proarrhythmic
**Amiodarone has class I, II, III, and IV properties

Table 22. Actions of α and β Adrenergic Receptors

	α RECEPTORS		β RECEPTORS	
Target System	α1	α2	β1	β2
Cardiovascular	Constriction of vascular smooth muscle Constriction of skin, skeletal muscle, and splanchnic vessels Increase myocardial contractility Decrease HR	Same as α1 Peripherally act to modulate vessel tone Vasoconstrict and dilate; oppose α1 vasoconstrictor activity	Increased myocardial contractility Accelerate SA node conduction Accelerate ectopic pacemakers	Decreased vascular smooth muscle tone
Respiratory				Bronchodilation
Dermal	Pilomotor smooth muscle contraction Apocrine constriction			
Ocular	Radial muscle contraction		Ciliary muscle relaxation	
Gastrointestinal	Inhibition of myenteric plexus Anal sphincter contraction			
Genitourinary	Pregnant uterine contraction Penile and seminal vesicle ejaculation Urinary bladder contraction	Smooth muscle wall relaxation	Stimulation of renal renin release	Bladder wall relaxation Uterine relaxation
Metabolic	Stimulate liver gluconeogenesis and glycogenolysis at the liver	Same as α1 Fat cell lipolysis	Fat cell lipolysis Glycogenolysis	Gluconeogenesis Fat cell lipolysis

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

Table 23. Commonly Used Drugs that Act on α and β Adrenergic Receptors

	α RECEPTORS			β RECEPTORS		
Mechanism of Action	α1	α1 and α2	α2	β1	β1 and β2	β2
Agonist	Phenylephrine Methoxamine	Epinephrine Norepinephrine	Clonidine Methyldopa	Norepinephrine Dobutamine	Isoproterenol Epinephrine	Albuterol Terbutaline
Antagonist	Prazosin Phenoxybenzamine	Phentolamine	Yohimbine Mirtazapine	Metoprolol Acebutolol Alprenolol Atenolol Esmolol	Propranolol Timolol Nadolol Pindolol Carvedilol	Butoxamine

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

ALGrawany

Landmark Cardiac Trials

Trial Name	Reference	Clinical Trial Details
ASCVD/ISCHEMIC HEART DISEASE (Primary Prevention)		
HOPE (ACEi)	NEJM 2000;342:145-153	**Title**: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients Purpose: To investigate the impact of ramipril, an angiotensin-converting-enzyme inhibitor, on high-risk patients without left ventricular dysfunction or heart failure and their susceptibility to cardiovascular events. **Methods**: In a five-year study, 9,297 high-risk patients without HF were randomly assigned to receive ramipril or placebo. The primary outcome measured MI, stroke, or cardiovascular death. Vitamin E effects were analyzed separately. **Results**: In the trial, 651 out of 4,646 patients (14.0%) receiving ramipril reached the primary endpoint, compared to 826 out of 4,630 patients (17.8%) on placebo. Ramipril treatment resulted in reductions in cardiovascular death (6.1% vs. 8.1%), MI (9.9% vs. 12.3%), stroke (3.4% vs. 4.9%), overall mortality (10.4% vs. 12.2%), revascularization procedures (16.3% vs. 18.8%), cardiac arrest (0.8% vs. 1.3%), heart failure (9.1% vs. 11.6%), and diabetes-related complications (6.4% vs. 7.6%). **Conclusions**: Ramipril effectively lowers mortality, MI, and stroke rates in high-risk patients without preexisting low ejection fraction or HF.
DAPT(Antiplatelet)	NEJM 2014;371:2155-66	**Title**: Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents Purpose: Study the effects of dual antiplatelet therapy beyond 1 yr, to prevent thrombotic complications after drug-eluting stents. **Methods**: After 12 mo treatment with clopidogrel or prasugrel, patients were randomized to continuing this therapy or receiving placebo. The primary endpoints were stent thrombosis and major adverse CV events from 12-30 mo. **Results**: Continued treatment reduced the rates of stent thrombosis (0.4% vs. 1.4%; 95% CI 0.17 to 0.48; P<0.001), and major CV and cerebrovascular events (4.3% vs. 5.9%; 95% CI 0.59 to 0.85; P<0.001). The rate of moderate-severe bleeding was increased in the continued treatment group (2.5% vs. 1.65%; P=0.001). **Conclusions**: Dual antiplatelet therapy beyond 1 yr confers additional benefit.
ARRIVE (ASA)	Lancet 2018;392:1036-46	**Title**: Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE): A Randomised, Double-blind, Placebo-controlled Trial Purpose: Assess efficacy and safety of ASA versus placebo in patients with moderate risk of a first CV event. **Methods**: Patients with moderate CV risk were randomized to receive ECASA or placebo tablets, once daily. The primary endpoint was a composite of time to CV death, MI, UA, stroke, or TIA. **Results**: The primary endpoint occurred in 4.29% of ASA-treated patients versus 4.48% of placebo-treated patients (hazard ratio 0.96; 95% CI 0.81 to 1.13; P=0.6). The overall incidence of adverse events was similar between groups (82.01% in ASA group versus 81.72% in placebo group). **Conclusions**: Among patients at moderate risk of CHD, the use of ASA was not beneficial. ASA was not associated with a reduction in adverse CV events.
European Coronary Surgery Study (CABG vs medical therapy)	NEJM 1988;319:332-37	**Title**: Twelve-Year Follow-up of Survival in the Randomized European Coronary Surgery Study Purpose: Evaluate survival rates in men with good LVEF after CABG or medical therapy. **Methods**: 767 men were randomized to early CABG or medical therapy. **Results**: At the projected 5-yr follow-up period, there was a significantly higher survival rate in the surgical group than in the medical treatment group (92.4% vs. 83.1%, P=0.0001). **Conclusions**: CABG resulted in higher survival than medical therapy at 5-yr follow-up but not at 12-yr follow-up.
ASCOT-LLA (Statin)	Lancet 2003;361:1149-58	**Title**: Prevention of Coronary and Stroke Events with Atorvastatin in Hypertensive Patients who have Average or Lower-than-Average Cholesterol Concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-lla): A Multicentre Randomised Controlled Trial Purpose: Assess benefits of cholesterol lowering in primary prevention of CHD in hypertensive patients. **Methods**: Hypertensive patients aged 40-79 were randomized to atorvastatin 10 mg or placebo. The primary endpoint was non-fatal MI and fatal CHD after 5-yr follow-up. **Results**: 100 primary events occurred in the atorvastatin group compared to 154 events in the placebo group at a median follow-up of 3.3 yr (hazard ratio 0.64; 95% CI 0.50 to 0.83; P=0.0005). Fatal and non-fatal stroke, total CV events and total coronary events were also lowered in the atorvastatin group. **Conclusions**: In hypertensive patients with risk factors for CHD and average cholesterol levels. atorvastatin reduced non-fatal MI, fatal CHD, fatal/non-fatal stroke, coronary events but not all-cause mortality.
JUPITER	NEJM 2008;359:2195-207	**Title**: Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein Purpose: Evaluate the effects of statin treatment on CV events in patients with elevated CRP without hyperlipidemia . **Methods**: 17802 apparently healthy patients with LDL levels <130 mg/dL and CRP levels >2.0 mg were randomized to rosuvastatin 20 mg daily or placebo. The primary endpoint was a composite of MI, stroke, revascularization, hospitalization for UA, or CV death. **Results**: The rates of the primary endpoint were 0.77 and 1.36 per 100 person-years in the statin and placebo groups respectively (hazard ratio 0.56; 95% CI 0.46 to 0.69; P<0.00001). The rosuvastatin group did not have a significant increase in myopathy or cancer, but a higher rate of diabetes. **Conclusions**: With low to normal LDL and elevated high CRP, treatment with rosuvastatin significantly reduced major CV events.
ASCVD/ISCHEMIC HEART DISEASE (Secondary Prevention)		
EUROPA (ACEi)	Lancet 2003;362:782-88	**Title**: Efficacy of Perindopril in Reduction of Cardiovascular Events Among Patients with Stable Coronary Artery Disease: Randomised, Double-blind, Placebo-controlled, Multicentre Trial (The EUROPA Study) Purpose: Assess whether ACEI reduced CV risk in a low-risk population with stable coronary disease. **Methods**: After a run-in of 4 wk, in which all patients received perindopril, 12218 patients were randomized to perindopril 8 mg OD or matching placebo. The primary endpoint was CV death, MI, or cardiac arrest **Results**: 8% of perindopril patients experienced a primary endpoint, compared with 10% of placebo patients. These benefits were consistent in all subgroups and secondary endpoints. **Conclusions**: With stable CAD and no CHF, perindopril reduced CV death, MI, and total mortality.
COMPASS (Anticoagulant ± ASA)	NEJM 2017; 377:1319-1330	**Title**: Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease Purpose: Assess the efficacy of rivaroxaban in combination with ASA compared to ASA alone for secondary cardiovascular prevention **Methods**: 27, 394 patients with stable atherosclerosis were randomly assigned to receive rivaroxaban with ASA or ASA alone in a double-blind trial. Primary outcomes were CV death, stroke or MI. **Results**: Primary outcomes occurred 4.1% in rivaroxaban and ASA-treated group compared to 5.4% with ASA alone (hazard ratio 0.76; 95% CI, 0.66 to 0.86; p<0.001). More major bleeding occurred in the rivaroxaban and ASA-treated group compared to ASA alone (3.1% vs 1.9% hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). **Conclusions**: Rivaroxaban with ASA had better cardiovascular outcomes than ASA alone but resulted in more major bleeding.
CURE (Anticoagulant and ASA)	NEJM 2001;345:494-502	**Title**: Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation Purpose: Evaluate efficacy and safety of clopidogrel with ASA in patients with ACS without ST-elevation. **Methods**: 12562 patients who presented within 24 h of symptom onset were randomized to clopidogrel or placebo in addition to ASA for 3-12 mo. The primary endpoint was a composite of CV mortality, non-fatal MI, or stroke. **Results**: The primary endpoint occurred in 9.3% of clopidogrel patients and 11.4% of patients in the placebo group (RR 0.80; 95% CI 0.72 to 0.90; P<0.001). There were significantly more patients with bleeding in the clopidogrel group than the placebo group (3.7% vs. 2.7%; RR 1.38; P=0.001). **Conclusions**: Clopidogrel plus ASA reduced death from CV causes, non-fatal MI, or stroke but increased bleeding complications.
OASIS-5 (Anticoagulant and LMWH)	NEJM 2006;354:1464-76	**Title**: Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes Purpose: Assess whether fondaparinux would reduce bleeding risk while retaining the anti-ischemic benefits of enoxaparin. **Methods**: 20078 patients were randomized to receive either fondaparinux 2.5 mg daily, or enoxaparin 1 mg/kg twice daily. The primary outcomes were death, MI, refractory ischemia at 9 d, or bleeding. **Results**: The primary outcome rates were similar between the two groups (hazard ratio 1.01; 95% CI 0.90 to 1.13). The rate of 9-d major bleeding was lower in the fondaparinux group than the enoxaparin group (2.2% vs. 4.1%; hazard ratio 0.52; P<0.001). **Conclusions**: Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 d, and MI at 30 and 180 d.

Trial Name	Reference	Clinical Trial Details
ISCHEMIA (Angiography and revascularization vs. medical therapy)	NEJM 2020; 382:1395-1407	**Title**: Initial Invasive or Conservative Strategy for Stable Coronary Disease Purpose: Compare outcomes from invasive intervention and medical therapy vs medical therapy alone in patients with stable coronary disease and moderate or severe ischemia. **Methods**: 5179 patients with moderate or severe ischemia were randomly assigned to invasive therapy (angiography and revascularization) with medical therapy or medical therapy, with angiography if medical therapy failed. Primary outcome was death from CV causes, MI or hospitalization due to unstable angina, HF or resuscitated cardiac arrest. Secondary outcome was death due to CV causes or MI. **Results**: The rate of primary endpoint at 6 mo was 5.3% for the invasive strategy and 3.4% for the conservative strategy (95% CI, 0.8-3.0) and at 5 years 16.4% and 18.2%, respectively (95% CI -4.7 to 1.0). There were 145 and 144 death, respectively (hazard ratio, 1.05; 95% CI, 0.83 to 1.32). **Conclusions**: There was no evidence that initial invasive therapy compared to conservative therapy reduced the risk of ischemic CV events or death in patients with stable coronary artery disease and moderate or severe ischemia.
CAPRIE (Antiplatelet vs ASA)	Lancet 1996;348:1329-39	**Title**: A Randomised, Blinded, Trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) Purpose: Assess the relative efficacy of clopidogrel and ASA in reducing risk of clinical thrombotic events. **Methods**: Patients with atherosclerotic vascular disease were randomized to clopidogrel 75 mg once daily or ASA 325 mg once daily. Primary endpoints were a composite of ischemic stroke, MI, or vascular death. **Results**: Patients treated with clopidogrel had a 5.32% annual risk of stroke, MI or death, compared with 5.83% of ASA patients (p=0.043). There were no major differences in terms of safety. **Conclusions**: In atherosclerotic vascular disease, clopidogrel reduced the rates of stroke, MI, or vascular death compared to ASA.
COLCOT (Antiinflammatory)	NEJM 2019;381:2497-505	**Title**: Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction Purpose: Assess the efficacy and safety of low-dose colchicine after MI. **Methods**: Patients were randomized to receive 0.5 mg colchicine once daily or placebo. The primary endpoint was a composite of CV death, resuscitated cardiac arrest, MI, stroke, or UA leading to revascularization. **Results**: The primary endpoint occurred in 5.5% of colchicine-treated patients and 7.1% in the placebo group (hazard ratio 0.77; 95% CI 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 for CV death, 0.83 for resuscitated cardiac arrest, 0.91 for MI, 0.26 for stroke, and 0.50 for UA. **Conclusions**: In patients with recent MI, colchicine lowered the risk of subsequent CV events as compared to placebo.
PEGASUS-TIMI 54 (Antiplatelet)	NEJM 2015;372:1791-800	**Title**: Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction Purpose: Investigate the safety and efficacy of ticagrelor after an ACS. **Methods**: 21162 patients who had a prior MI were randomized to ticagrelor 90 mg BID, or placebo. The primary endpoints were a composite of CV death, MI, or stroke. The primary safety endpoint was thrombolysis in MI and major bleeding. **Results**: Kaplan-Meier event rates showed that ticagrelor reduced event rates at 3 yr, at 7.77% for the treatment group and 9.04% in the placebo group (hazard ratio 0.85; 95% CI 0.75 to 0.96; P=0.008). Rates of major bleeding were higher with ticagrelor than with placebo (P<0.001). **Conclusions**: Ticagrelor on top of ASA reduces CV events in patients with a history of MI.
PLATO (Antiplatelet)	NEJM 2009;361:1045-57	**Title**: Ticagrelor vs. Clopidogrel in Patients with Acute Coronary Syndromes Purpose: Evaluate the efficacy of ticagrelor vs. clopidogrel in patients with an ACS. **Methods**: 18624 patients admitted to hospital with ACS, with or without ST-elevation, were randomized to ticagrelor (180 mg loading, 90 mg twice daily after) or clopidogrel (300-600 mg loading; 75 mg daily after). The primary endpoint was a composite of vascular death, MI, or strok. **Results**: The primary endpoint occurred in 9.8% of patients receiving ticagrelor, compared with 11.7% of patients receiving clopidogrel (hazard ratio 0.84; 95% CI 0.77 to 0.92; P<0.001). The rate of death was also reduced with ticagrelor (4.5% vs. 5.9%; P<0.001). There were no significant differences in the rates of major bleeding. **Conclusions**: In ACS patients with either STEMI or NSTEMI, regardless of reperfusion strategy, ticagrelor reduced mortality, MI, and stroke without increased bleeding compared to clopidogrel.
PLATO (Antiplatelet)	NEJM 2007;357:2001-15	**Title**: Prasugrel vs. Clopidogrel in Patients with Acute Coronary Syndromes Purpose: Compare clopidogrel and prasugrel in preventing thrombotic complications of ACS and PCI. **Methods**: 13608 patients with ACS and scheduled PCI were randomized to prasugrel (60 mg loading, 10 mg maintenance) or clopidogrel (300 mg loading, 75 mg maintenance). The primary endpoint was CV death, non-fatal MI, or non-fatal stroke. The safety endpoint was major bleeding. **Results**: The primary endpoint occurred in 12.1% of clopidogrel patients and 9.9% of prasugrel patients (hazard ratio 0.81; 95% CI 0.73 to 0.90; P<0.001). Major bleeding was observed in 2.4% of prasugrel patients and 1.8% of clopidogrel patients (hazard ratio 1.32; 95% CI 1.03 to 1.68; P=0.03.) **Conclusions**: In ACS patients scheduled for PCI, prasugrel reduced ischemic events but increased major bleeding compared to clopidogrel.
BHAT (β-Blocker)	JAMA 1982;247:1707-14	**Title**: A Randomized Trial of Propranolol in Patients with Acute Myocardial Infarction Purpose: Study the effects on mortality of administering propranolol hydrochloride in patients who experienced at least one M. **Methods**: 3387 patients were randomized to either propranolol or placebo for 21 d post-infarction. The primary outcome was all-cause mortality. **Results**: Total mortality during the average 25-mo follow-up was 7.2% in the propranolol group and 9.2% in the placebo group. **Conclusions**: In acute MI, propranolol reduced all-cause mortality, CV death, and sudden death from atherosclerotic heart disease.
COMMIT (β-Blocker)	Lancet 2005; 366:1622-1632	**Title**: Early Intravenous then Oral Metoprolol in 45,852 Patients with Acute Myocardial Infarction: randomised placebo-controlled trial Purpose: To evaluate the risks and benefits of incorporating early intravenous followed by oral metoprolol alongside standard therapies in a diverse group of patients. **Methods**: A study involving 45,852 patients admitted to hospitals within 24 h of suspected acute MI evaluated the effects of metoprolol versus placebo. Primary outcomes included a composite of cardiovascular death, reinfarction, or cardiac arrest, and death from any cause during the treatment period. **Results**: Allocation of metoprolol did not yield significant reductions in the co-primary outcomes. The occurrence of death, reinfarction, or cardiac arrest did not significantly differ between metoprolol (9.4%) and placebo (9.9%) groups (OR 0.96, 95% CI 0.90-1.01, p=0.1). However, metoprolol exhibited a lower risk of reinfarction (2.0% vs. 2.5%) and ventricular fibrillation (2.5% vs. 3.0%) per 1000 treated. Conversely, there was a higher incidence of cardiogenic shock (5.0% vs. 3.9%) (OR 1.30, 95% CI 1.19-1.41, p<0.00001). The overall impact varied over time, with an adverse effect in the early days and a beneficial effect thereafter. The net effect depended on patient stability, with a substantial hazard in haemodynamically unstable patients and moderate benefit in relatively stable patients (particularly after the initial days). **Conclusions**: Early β-blocker therapy in acute MI decreases reinfarction and ventricular fibrillation but increases cardiogenic shock risk, primarily within the first day.
ROOBY (CABG)	NEJM 2017;377:623-32	**Title**: Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass Purpose: Reporting of 5-yr outcomes in patients included in the Veterans Trial of on-pump vs. off-pump CABG. **Methods**: 2203 patients were randomly assigned to undergo either on-pump or off-pump CABG. The primary 5-yr outcomes were all-cause mortality and a composite of major CV events or non-fatal MI. **Results**: 5-yr mortality was 15.2% in the off-pump group, compared with 11.9% in the on-pump group (RR 1.28; 95% CI 1.03 to 1.58; P=0.02). The rate of major CV events in the off-pump group was 31.0% compared to 27.1% in the on-pump group (RR 1.14; 95% CI 1.00 to 1.30; P=0.046). **Conclusions**: Off-pump CABG led to lower rates of 5-yr survival and event-free survival when compared to on-pump CABG.
SYNTAX (CABG and PCI)	NEJM 2009;360:961-72	**Title**: Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease Purpose: Compare PCI and CABG for treating patients with previously untreated three-vessel or left main CAD. **Methods**: 1800 patients with three-vessel or left main coronary disease were randomized to CABG or PCI (1:1 ratio). The primary outcomes were a major adverse cardiac or cerebrovascular event. **Results**: Rates of primary outcomes at 12 mo were significantly higher in the PCI group (17.8% vs. 12.4%; P=0.002). At 12 mo, rates of death and MI were similar between groups and stroke was significantly more likely with CABG. **Conclusions**: CABG had a lower rate of major cardiac or cerebrovascular events, however the rate of stroke was increased with CABG whereas the rate of repeat revascularization was increased with PCI.

Trial Name	Reference	Clinical Trial Details
AMPLITUDE-O (GLP-1 Agonist)	NEJM 2021; 385: 896-907	**Title**: Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes Purpose: To understand the effect of an exendin-based GLP-1 receptor agonist, efpeglenatide, on cardiovascular and renal outcomes in patients with T2DM. **Methods**: Randomized, placebo-controlled trial across 28 countries in 344 sites. Participants were randomly allocated to receive either weekly subcutaneous injections of efpeglenatide or placebo. The primary focus was on the occurrence of the first major adverse cardiovascular event (MACE). **Results**: 4076 participants were enrolled. Among participants assigned to receive efpeglenatide, a composite renal outcome event, encompassing a decline in kidney function or the presence of macroalbuminuria, occurred in 353 individuals (13.0%). In contrast, among those assigned to receive placebo, 250 participants (18.4%) experienced the same outcome. Adverse effects such as diarrhea, constipation, nausea, vomiting, or bloating were more common with efpeglenatide compared to placebo. Conclusion: The administration of weekly subcutaneous injections of efpeglenatide resulted in a reduced risk of cardiovascular events compared to those who received a placebo.
HARMONY-OUTCOMES (GLP-1 Agonist)	Lancet 2018; 392: 1519-1529	**Title**: Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes): A Double-Blind, Randomized Placebo-Controlled Trial Purpose: To assess the safety and effectiveness of albiglutide in preventing cardiovascular death, myocardial infarction, or stroke. **Methods**: Double-blind, randomized, placebo-controlled trial in 28 countries with 610 sites. The primary outcome was the initial incidence of cardiovascular death, MI, or stroke, as assessed in the intention-to-treat population. **Results**: 4731 patients received albiglutide and 4732 patients received placebo. In the albiglutide group, the primary composite outcome was observed in 338 patients (7%) out of a total of 4731, with an incidence rate of 4.6 events per 100 person-years. In contrast, the placebo group had 428 patients (9%) out of 4732, with an incidence rate of 5.9 events per 100 person-years. Conclusion: Albiglutide demonstrated superiority over placebo in terms of major adverse cardiovascular events among patients diagnosed with both type 2 diabetes and cardiovascular disease.
LEADER (GLP-1 Agonist)	NEJM 2016;375:311-22	**Title**: Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes Purpose: To investigate the cardiovascular effects of liraglutide (GLP1 analogue) when added to standard care in patients with T2DM. **Methods**: 9340 patients with T2DM at high cardiovascular risk were randomly assigned to receive liraglutide or placebo. **Results**: The primary outcome (first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke) was observed in significantly less patients on liraglutide (13.0%) than placebo (14.9%) (hazard ratio, 0.87; 95% confidence interval, 0.78-0.97; P<0.001 for noninferiority; P=0.01 for superiority). Conclusion: In patients with T2DM, liraglutide reduced the rate of first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
PIONEER 6 (GLP-1 Agonist)	NEJM 2019; 381: 841-851	**Title**: Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes Purpose: To establish cardiovascular safety data for oral semaglutide. **Methods**: Event-driven, randomized, double-blind, placebo-controlled trial involving patients at high cardiovascular risk. **Results**: 3183 patients received either oral semaglutide or placebo through random assignment. Within the oral semaglutide group, 61 out of 1591 patients (3.8%) experienced major adverse cardiovascular events, while in the placebo group, 76 out of 1592 patients (4.8%) encountered such events. Conclusion: In patients with T2DM, cardiovascular risk profile of oral semaglutide was not inferior to that of the placebo.
REWIND (GLP-1 Agonist)	Lancet 2019;394:121-30	**Title**: Dulaglutide and Cardiovascular Outcomes in T2DM (REWIND): A Double-Blind, Randomized Placebo-Controlled Trial Purpose: To assess the effects of adding the GLP-1 receptor agonist dulaglutide to existing antihyperglycemic regimens on major cardiovascular events in patients with T2DM. **Methods**: 9901 patients with T2DM ≥50 years old with previous CVD or cardiovascular risk factors were randomly assigned to receive dulaglutide (1.5 mg weekly) or placebo. Primary composite outcome was first occurrence of non-fatal MI, non-fatal stroke, or death from cardiovascular causes. **Results**: Over a median follow-up of 5.4 years, patients treated with dulaglutide had a lower rate of the primary composite outcome compared to those on placebo (12.0% vs. 13.4%). However, there was no significant difference in all-cause mortality between the two groups. Conclusion: In middle-aged and older adults with T2DM with previous CVD or cardiovascular risk factors, dulaglutide could be considered for managing glycemic control.
SUSTAIN-6 (GLP-1 Agonist)	NEJM 2016; 375: 1834-1844	**Title**: Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes Purpose: To evaluate whether semaglutide is noninferior to placebo in terms of cardiovascular safety in patients diagnosed with type 2 diabetes. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. **Methods**: Randomized, double-blind, placebo-controlled, parallel-group trial in 20 countries at 230 sites. The primary outcome was the initial instance of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. **Results**: The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group. Conclusion: In high-risk type 2 diabetes patients, semaglutide showed significantly lower rates of cardiovascular death, myocardial infarction, or stroke compared to placebo.
COMPLETE (PCI)	NEJM 2019;381:1411-21	**Title**: Complete Revascularization with Multivessel PCI for Myocardial Infarction Purpose: To assess whether PCI of nonculprit lesions reduced rates of CV death or MI in STEMI patients. **Methods**: Patients with STEMI and successful PCI of culprit lesions were randomized to complete revascularization with PCI or no further revascularization. The primary outcome was a composite of CV death or MI. **Results**: At 3 yr, the primary outcome occurred in 7.8% of patients in the complete-revascularization group, compared with 10.5% in the culprit-lesion PCI only group (hazard ratio 0.74; 95% CI 0.60 to 0.91; P=0.004). The benefit was observed regardless of the intended timing of nonculprit lesion PCI. **Conclusions**: In patients with STEMI and multivessel CAD, complete revascularization by PCI further reduced the risk of CV death or MI as compared to culprit-lesion-only PCI.
COURAGE (PCI)	NEJM 2007;356:1503-16	**Title**: Optimal Medical Therapy with or without PCI for Stable Coronary Disease Purpose: Compare initial strategy of PCI plus intensive pharmacological therapy and lifestyle intervention against optimal medical therapy alone, in patients with stable coronary disease. **Methods**: 2287 patients with myocardial ischemia and significant CAD were randomized to PCI with optimal medical therapy, or optimal medical therapy alone. The primary outcome was all-cause mortality and non-fatal MI. **Results**: There were 211 primary events in the PCI group and 202 in the optimal medical therapy group (hazard ratio for PCI, 1.05; 95% CI 0.87 to 1.27; P=0.62). There were no significant differences between groups in the composite of death, MI, stroke, or hospitalizations for ACS. **Conclusions**: Compared with optimal medical therapy alone, PCI plus medical therapy did not reduce all-cause mortality and non-fatal MI, and it did not reduce the incidence of major CV events.
EXCEL (PCI)	NEJM 2019;381:1820-30	**Title**: Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease Purpose: Assess long-term outcomes after PCI with contemporary drug-eluting stents, as compared with CABG, in patients with left main CAD. **Methods**: 1905 patients with left main CAD of low/intermediate anatomical complexity were randomized to PCI or CABG. The primary outcome was a composite of death, stroke or MI. **Results**: At 5 yr, the primary outcome occurred in 22.0% of PCI patients and 19.2% of CABG patients (2.8% difference; 95% CI -0.9 to 6.5; P=0.13). Rates of CV death and MI were not significantly different between groups. All cerebrovascular events were less frequent after PCI than CABG (3.3% vs. 5.2%; 95% CI -3.8 to 0). **Conclusions**: Among patients with left main CAD, there was no significant difference between PCI and CABG in terms of the composite outcome of death, stroke, or MI at 5 yr.
MASS II (PCI, CABG, and medical therapy)	Circulation 2010;122:949-57	**Title**: Ten-Year Follow-Up Survival of the Medicine, Angioplasty, or Surgery Study (MASS II) Purpose: Compare 10-yr follow-up of PCI, CABG, and medical treatment in patients with multivessel coronary disease, UA, and preserved ventricular function. **Methods**: 611 patients were randomized to CABG, PCI, or medical treatment. The primary endpoints were overall mortality, Q-wave MI, or refractory angina requiring revascularization. **Results**: 10-yr survival was 74.9% with CABG, 75.1% with PCI, and 13.3% with medical treatment (P=0.089). 10-yr rates of MI were 10.3% with CABG, 13.3% with PCI, and 20.7% with medical treatment (P<0.010). 10-yr freedom from angina was 64% with CABG, 59% with PCI, and 43% with medical treatment (P<0.001). **Conclusions**: Compared to medical therapy, CABG resulted in greater relief of angina symptoms and lower rates of subsequent MI, additional revascularization, and cardiac death. Compared to PCI, CABG resulted in decreased need for further revascularization, a lower incidence of MI, and lower risk of combined events.

Trial Name	Reference	Clinical Trial Details
PRAMI (PCI)	NEJM 2013; 369:1115-1123	**Title**: Randomized Trial of Preventive Angioplasty in Myocardial Infarction Purpose: To determine whether incorporating preventive PCI into infarct artery treatment would decrease the overall occurrence of cardiac-related deaths, nonfatal MI, or persistent angina. **Methods**: 465 acute STEMI patients receiving infarct-artery PCI were randomized to preventive PCI or none. The primary endpoint was a composite of cardiac death, MI, or refractory angina. **Results**: The trial on preventive PCI was terminated early in January 2013 due to conclusive **results**. During a 23-month follow-up, patients receiving preventive PCI had significantly lower rates of the primary outcome compared to those without preventive PCI. **Conclusions**: Preventive PCI in non-infarct coronary arteries reduced adverse cardiovascular events compared to PCI limited to the infarct artéry.
ODYSSEY OUTCOMES (PCSK9)	NEJM 2018;379:2097-107	**Title**: Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome Purpose: Determine whether alirocumab would improve CV events after ACS in patients receiving high-intensity statin therap.y **Methods**: 18924 patients receiving high-intensity statins for ACS 1-12 prior were randomized to alirocumab SQ at 75 mg or placebo, every 2 wk. The primary endpoint was a composite of death from CHD, non-fatal MI, fatal or non-fatal stroke, or UA **Results**: The primary endpoint occurred in 9.5% of patients in the alirocumab group and in 11.1% of patients in the .placebo group (hazard ratio 0.85; 95% CI 0.78 to 0.93; P<0.001). The incidence of adverse events was similar in the two groups. **Conclusions**: Among patients with ACS in the preceding 1-12 mo, use of alirocumab significantly reduces all-cause mortality and MI.
ACME (PCTA)	NEJM 1992;326:10-16	**Title**: A Comparison of Angioplasty with Medical Therapy in the Treatment of Single-Vessel Coronary Artery Disease Purpose: Compare the effects of percutaneous transluminal coronary angioplasty (PTCA) on angina and exercise tolerance in patients with stable single-vessel disease **Methods**: Patients with exercise-induced myocardial ischemia and epicardial artery stenosis were randomized to PTCA or medical therapy, and repeat exercise testing performed at 6 mo. **Results**: PTCA was successful in 80% of patients, reducing mean % stenosis from 76% to 36%. At 6 mo, 64% PTCA patients were angina-free, compared with 46% of medically treated patients. PTCA-treated patients had longer exercise durations (2.1 vs. 0.5 min, P<0.0001) than medically treated patients. **Conclusions**: PTCA offers earlier and better relief of angina than medical therapy in patients with single-vessel disease.
BARI 2D (Revascularization vs medical therapy)	NEJM 2009;360:2503-15	**Title**: A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease Purpose: Determine optimal treatment for patients with T2DM and stable ischemic heart disease. **Methods**: Patients with T2DM and heart disease were randomized to prompt revascularization with intensive medical therapy, or intensive medical therapy alone. Primary endpoints were mortality, MI, or stroke. **Results**: 5-yr survival did not differ significantly between groups (88.3% in revascularization group vs. 87.8% in the medical therapy group; P=0.97). In the PCI group, there were no significant differences in primary endpoints, while in the CABG group, rates of CV events were significantly lower with revascularization than medical therapy (22.4% vs. 30.5%; P=0.01). **Conclusions**: There was no significant difference in the rates of death and major CV events between prompt revascularization and medical therapy.
CANVAS (SGLT2 Inhibitors)	NEJM 2017;377:644-57	**Title**: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes Purpose: To assess the effects of canagliflozin on cardiovascular, renal, and safety outcomes in patients with T2DM. **Methods**: 10142 patients with T2DM at high cardiovascular risk were randomly assigned to receive canagliflozin or placebo. Primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. **Results**: In comparison to placebo, canagliflozin showed significantly lower rates of the primary outcome (26.9 vs. 31.5 participants per 1000 patient-years). However, canagliflozin was associated with a higher risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years). Conclusion: Canagliflozin lowered the risk of cardiovascular events but increased the risk of amputation in patients with T2DM at high cardiovascular risk.
DECLARE-TIMI 58 (SGLT2 Inhibitors)	NEJM 2019;380:347-57	**Title**: Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes Purpose: To assess the safety and efficacy of the SGLT2i dapagliflozin in patients with T2DM who had or were at risk for ASCVD. **Methods**: 17160 patients were randomly assigned to receive 10 mg dapagliflozin daily or placebo. Primary composite safety outcome was MACE (major adverse cardiovascular events), defined by cardiovascular death, MI, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. **Results**: In terms of safety, dapagliflozin was found to be noninferior to placebo. In terms of efficacy, dapagliflozin was associated with a lower rate of cardiovascular death or hospitalization for heart failure compared to placebo. However, it did not significantly reduce rates of major adverse cardiovascular events (MACE). Conclusion: Dapagliflozin was noninferior to placebo with respect to MACE but was associated with lower rates of cardiovascular death or hospitalization for heart failure in patients with T2DM who had or were at risk for ASCVD.
EMPA-REG OUTCOME (SGLT2 Inhibitors)	NEJM 2015;373:2117-28	**Title**: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Purpose: To investigate the effects of empagliflozin on cardiovascular morbidity and mortality in patients with T2DM at high cardiovascular risk. **Methods**: 7020 patients were randomly assigned to receive empagliflozin (10 mg or 25 mg) or placebo daily. **Results**: Risk of hospitalization from heart failure, death from any cause, or cardiovascular causes was significantly lower in the pooled empagliflozin group as compared to placebo. There were no significant differences in the rates of MI or stroke. There were increased rates of genital infection with empagliflozin. Conclusion: Empagliflozin reduced rates of death from any cause and death from CVD in patients with T2DM at high risk for cardiovascular events.
IMPROVE-IT (Selective cholesterol absorption inhibitor and statin)	NEJM 2015;372:2387-97	**Title**: Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes Purpose: Assess the effects of adding ezetimibe to statin therapy in reducing the rate of CV events. **Methods**: 18144 patients who were hospitalized with ACS were randomized to combination (simvastatin 40 mg plus ezetimibe 10 mg), simvastatin 40 mg alone, or placebo. Primary endpoint was a composite of CV death, non-fatal MI, UA, or non-fatal stroke. **Results**: The Kaplan-Meier event rates for the primary endpoint were 32.7% in the combination group and 34.7% in the statin monotherapy group (P<0.001). Rates of pre-specified muscle, gallbladder, and hepatic adverse effects were similar. **Conclusions**: Ezetimibe added to statin reduces mortality in ACS patients.
CARE (Statin)	NEJM 1996;335:1001-09	**Title**: The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels Purpose: Determine the effects of cholesterol-lowering in patients with coronary disease and average cholesterol levels. **Methods**: Patients with MI who had plasma cholesterol levels <240 mg were administered either 40 mg pravastatin or placebo. The primary endpoint was a fatal coronary event or fatal MI. **Results**: The primary endpoint occurred in 10.2% of the pravastatin-treated patients and 13.2% of placebo-treated patients (95% CI 9% to 36%; P=0.003). There were no significant differences in overall mortality or mortality from nonvascular causes. Pravastatin lowered the rate of coronary events more among men than women. **Conclusions**: Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol.
PROVE IT – TIMI 22 (Statin)	NEJM 2004;350:1495-504	**Title**: Intensive vs. Moderate Lipid Lowering with Statins after Acute Coronary Syndromes Purpose: Determine the optimal LDL-C level in patients undergoing statin therapy for reduction in risk of CV events. **Methods**: 4162 patients hospitalized with ACS in the preceding 10 d were assigned to pravastatin 40 mg daily or atorvastatin 80 mg daily. The primary end point was a composite of all-cause mortality MI, UA, revascularization, and stroke. **Results**: Event rates were 26.3% in the pravastatin group and 22.4% in the atorvastatin group (P=0.005; 95% CI 5 to 26%). The study established the superiority of the more intensive regimen. **Conclusions**: In patients hospitalized for ACS, high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin.
TNT (Statin)	NEJM 2005;352:1425-35	**Title**: Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease Purpose: Assess the efficacy and safety of LDL-lowering below 100 mg/dL in patients with stable CHD. **Methods**: 10001 patients with stable CHD and LDL <130 mg/dL were randomized to double blind therapy of atorvastatin 10 mg or 80 mg daily. The primary endpoint was the occurrence of a first major CV event. **Results**: A primary endpoint occurred in 8.7% of patients treated with atorvastatin 80 mg, as compared with 10.9% in patients receiving atorvastatin 10 mg. There was no difference in overall mortality between groups. **Conclusions**: Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d.

Trial Name	Reference	Clinical Trial Details
TRANSCATHETER AORTIC VALVE REPLACEMENT		
PARTNER II	NEJM 2016;374:1609-20	**Title**: Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients Purpose: Evaluate survival rates between TAVR and surgical aortic valve replacement, in intermediate risk patients. **Methods**: 2032 intermediate risk patients were randomized to TAVR or surgical replacement. The primary endpoint was all-cause mortality or disabling stroke at 2 yr. **Results**: The rates of primary outcomes were similar between TAVR and surgical replacement groups (P=0.001). At 2 yr, the Kaplan-Meier event rates were 19.3% in the TAVR group and 21.1% in the surgical group (hazard ratio 0.89; 95% CI 0.73 to 1.09; P=0.25). Surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation. **Conclusions**: In intermediate-risk patients with AS, TAVR and SAVR resulted in similar rates of all-cause mortality and disabling stroke.
PARTNER III	NEJM 2019;380:1695-705	**Title**: Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients Purpose: Compare major outcomes in low-risk patients between TAVR and surgical aortic-valve replacement. **Methods**: 1000 patients with severe aortic stenosis and low surgical risk were randomized to TAVR or surgical aortic valve replacement. The primary endpoint was a composite of death, stroke, or rehospitalization at 1 yr. **Results**: The Kaplan-Meier event rates were significantly lower in the TAVR group than the surgery group (8.5% vs. 15.1%; 95% CI -10.8 to -2.5; P<0.001). At 30 d, TAVR resulted in lower stroke rates and new-onset atrial fibrillation. There were no significant differences in major vascular complications, new pacemaker insertion, or paravalvular regurgitation. **Conclusions**: Among low-surgical risk patients with severe AS, the rate of the composite of death, stroke, or rehospitalization was significantly lower with TAVR compared to surgical aortic-valve replacement.
HEART FAILURE		
COAPT	NEJM 2018;379:2307-18	**Title**: Transcatheter Mitral-Valve Repair in Patients with Heart Failure Purpose: Assess improvement in outcomes in patients with MR due to LV dysfunction, from transcatheter mitral valve repair. **Methods**: Patients with HF and secondary mitral regurgitation were randomized to transcatheter mitral-valve repair plus medical therapy, or to medical therapy alone. The primary endpoint was hospitalization for HF at 24 mo. **Results**: The primary endpoint was 35.8% in the intervention group, compared to 67.9% in the control group (hazard ratio 0.53; 95% CI 0.40 to 0.70; P<0.001). Death from any cause occurred at 29.1% in the intervention group compared with 46.1% in the control group (hazard ratio 0.62; 95% CI 0.46 to 0.82; P<0.001). **Conclusions**: Among patients with HF and secondary MR who remained symptomatic despite medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for HF and lower mortality than medical therapy alone.
CHARM	Lancet 2003;362:759-66	**Title**: Effects of Candesartan on Mortality and Morbidity in Patients with Chronic Heart Failure: The Charm-Overall Programme Purpose: Determine whether ACEI use could reduce mortality and morbidity in patients with CHF. **Methods**: Patients with LVEF <40% not receiving ACEIs were randomized to candesartan or placebo. The primary outcome was all-cause mortality, CV death, or hospital admission for CHF. **Results**: Mortality was 23% in the candesartan group and 25% in the placebo group (hazard ratio 0.91; 95% CI 0.83 to 1.00; P=0.055), with fewer CV deaths (18% vs. .20%; P=0.012). **Conclusions**: Candesartan reduced overall mortality, CV death, and CHF hospitalizations.
CIBIS II	Lancet 1999;353:9-13	**Title**: The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial Purpose: Investigate the efficacy of bisoprolol in decreasing all-cause mortality in CHF. **Methods**: 2647 patients with LVEF <35% receiving standard therapy were randomized to bisoprolol or placebo. The primary outcome was all-cause mortality. **Results**: All-cause mortality was significantly lower with bisoprolol than placebo (11.8% vs. 17.3%, hazard ratio 0.66; 95% CI 0.54 to 0.81; P<0.0001). Treatment effects were independent of etiology or severity of HF/ **Conclusions**: Bisoprolol reduced all-cause mortality, CV death, all-cause hospitalization, and CHF hospitalization/
COMET	Lancet 2003;362:7-13	**Title**: Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients with Chronic Heart Failure in the Carvedilol or Metoprolol European Trial (Comet): Randomised Controlled Trial Purpose: Compare outcomes of chronic HFrEF patients on carvedilol or metoprolol. **Methods**: 1511 patients with CHF were randomized to carvedilol 25 mg twice daily, and 1518 randomized to metoprolol 50 mg twice daily. The primary endpoints were all-cause mortality, and the composite of all-cause mortality or all-cause admissio.n **Results**: The all-cause mortality was 34% for carvedilol patients and 40% for metoprolol patients (hazard ratio 0.83; 95% CI 0.74 to 0.93; P=0.0017). Incidence of side effects and withdrawal did not differ significantly between groups. **Conclusions**: Carvedilol was associated with a reduction in all-cause mortality compared with metoprolol.
COPERNICUS	NEJM 2001;344:1651-58	**Title**: Effect of Carvedilol on Survival in Severe Chronic Heart Failure Purpose: Assess the effects of β-blockade on hospitalization and mortality in patients with severe HF. **Methods**: 2289 patients with HF symptoms at rest and an EF <25% were randomized to carvedilol or placebo. Primary endpoints were rates of hospitalization and mortality. **Results**: There was a 35% reduction in mortality risk in patients treated with carvedilol than placebo (95% CI 19% to 48%; P=0.0018). **Conclusions**: Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF.
DAPA-HF	NEJM 2019;381:1995-2008	**Title**: Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction Purpose: Assess the efficacy of the SGLT2 inhibitor dapagliflozin in patients with HFrEF, independent of T2DM status. **Methods**: 4744 patients with HF and EF <40% were randomized to receive dapagliflozin 10 mg once daily, or placebo, in addition to recommended therapy. The primary outcome was worsening HF or CV death. **Results**: The primary outcome occurred in 16.3% of dapagliflozin-treated patients and 21.2% of placebo patients (hazard ratio 0.74; 95% CI 0.65 to 0.85; P<0.001). A worsening of HF occurred at 10.0% in the dapagliflozin group and 13.7% in the placebo group (hazard ratio 0.70; 95% CI 0.59 to 0.83). Findings in patients with DM were comparable to those in patients without DM. **Conclusions**: In patients with HFrEF, the risk of worsening HF or death from CV causes was lower among those who received dapagliflozin than those who received placebo.
DELIVER	NEJM 2022;387:1089-1098	**Title**: Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction Purpose: Assess the efficacy of SGLT2 inhibitor dapagliflozin in patients with HFpEF or mildly reduced EF, independent of T2DM status **Methods**: 6263 patients with HF and EF >40% were randomized to receive dapagliflozin 10 mg once daily, or placebo, in addition to recommended therapy. The primary outcome was worsening HF or CV death. **Results**: The primary outcome occurred in 16.4% of dapagliflozin-treated patients and 19.5% of placebo-treated patients (hazard ratio, 0.82; 95% CI 0.73 to 0.92; P<0.001). Worsening of HF occurred at 11.8% in the dapagliflozin group and 14.5% in the placebo group (hazard ratio 0.79; 95% CI 0.69 to 0.91). Findings in patients with EF >60% and EF <60% were comparable. Findings in patients with DM were comparable to those in patients without DM. **Conclusions**: In patients with HF and EF >40%, dapagliflozin reduced the risk of worsening HF or CV death.
EMPEROR-Preserved	NEJM 2021;385:1451-1461	**Title**: Empagliflozin in Heart Failure with a Preserved Ejection Fraction Purpose: Assess the efficacy of the SGLT2 inhibitor empagliflozin in patients with HFmrEF and HFpEF, irrespective of diabetes status. **Methods**: 5988 patients with symptomatic HF and an EF >40% were randomized to receive empagliflozin 10 mg once daily, or placebo, in addition to usual therapy. The primary outcome was a composite of CV mortality or hospitalization for HF. **Results**: Empagliflozin was associated with a lower risk of CV mortality or hospitalization for HF (13.8% vs.17.1%; HR 0.79; 95% CI 0.69 to 0.90; P<0.001), which was mainly related to fewer HF hospitalization events in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. **Conclusions**: In patients with HFmrEF and HFpEF, empagliflozin was associated with a lower risk of the CV mortality or hospitalization for HF, and this effect was primarily driven by fewer HF hospitalizations.
EMPEROR-Reduced	NEJM 2020;383:1413-1424	**Title**: Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure Purpose: Assess the efficacy of the SGLT2 inhibitor empagliflozin in patients with HFrEF, irrespective of diabetes status. **Methods**: 3730 patients with symptomatic HF and an EF <40% were randomized to receive empagliflozin 10 mg once daily, or placebo, in addition to usual therapy. The primary outcome was a composite of CV mortality or hospitalization for worsening HF. **Results**: Empagliflozin was associated with a lower risk of CV mortality or hospitalization for HF (19.4% vs. 24.7%; HR 0.75; 95% CI 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of diabetes status. **Conclusions**: In patients with HFrEF, empagliflozin was associated with a lower risk of CV mortality or hospitalization for HF, independent of diabetes status.

Trial Name	Reference	Clinical Trial Details
I-PRESERVE	NEJM 2008;359:2456-67	**Title**: Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction Purpose: Study the effects of irbesartan in patients with HF and EF >45%. **Methods**: 4128 patients with HF and EF >45% were randomized to irbesartan 300 mg daily, or matching placebo. The primary outcome was a composite of all-cause mortality or CV hospitalization. **Results**: The primary outcome occurred in 742 patients in the irbesartan group and 763 placebo patients (hazard ratio 0.95; 95% CI 0.86 to 1.05; P=0.35). Overall, rates of death were 52.6 and 52.3 per 1000-patient-yr, respectively. **Conclusions**: In patients with CHF and normal LVEF, treatment with ARB (irbesartan) did not improve mortality or CV morbidity compared to placebo.
PARADIGM-HF	NEJM 2014;371:993-1004	**Title**: Angiotensin–Neprilysin Inhibition vs. Enalapril in Heart Failure Purpose: Compare survival in HFrEF patients treated with enalapril or an angiotensin-neprilysin inhibitor. **Methods**: 8442 patients with HF and EF <40% were randomized to LCZ696 200 mg twice daily, or enalapril 10 mg twice daily. The primary endpoint was a composite of CV death and HF hospitalization. **Results**: The primary outcome occurred in 21.8% of LCZ696-treated patients and 26.5% of enalapril patients (hazard ratio 0.80; 95% CI 0.73 to 0.87; P<0.001). 13.3% and 16.5% of patients treated with LCZ696 and enalapril, respectively, died of CV causes (hazard ratio 0.80; 95% CI 0.71 to 0.89; P<0.001.) **Conclusions**: Novel drug (LCZ696) containing valsartan and a neprilysin inhibitor (prevents degradation of natriuretic peptides) reduces hospitalization and mortality.
PRESERVED-HF	Nature 2021; 27: 1954-1960	**Title**: The SGLT2 iInhibitor Dapagliflozin in Heart Failure with Preserved Ejection Fraction: A Multicenter Randomized Trial Purpose: To determine if treatment with SGLT2 inhibitor dapagliflozin will improve symptoms, physical limitations, and exercise function in patients with and without T2DM **Methods**: Randomized, multicentre trial. 324 patients were randomized to receive dapagliflozin or placebo. **Results**: The impact of dapagliflozin on multiple endpoints, including Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS), 6-minute walk test (6MWT), KCCQ Overall Summary Score (KCCQ-OS), weight, natriuretic peptides, glycated hemoglobin, and blood pressure, was assessed in a trial with 324 randomized patients. **Results**: Dapagliflozin demonstrated improvements in KCCQ-CS, physical limitations scores, 6MWT, KCCQ-OS, proportion of participants with meaningful improvements in KCCQ-OS, and weight reduction. No significant differences were observed in other secondary endpoints. Adverse events were comparable between dapagliflozin and placebo groups. **Conclusions**: After 12 wk of treatment with dapagliflozin, there was a significant improvement reported by patients in symptoms, physical limitations, and exercise function.
RALES	NEJM 1999;341:709-17	**Title**: The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure Purpose: Assess the efficacy of spironolactone on morbidity and mortality in patients with severe HF. **Methods**: 1663 patients with severe HF and LVEF <35% who were being treated with ACEI, loop diuretic and digoxin, were randomized to spironolactone 25 mg daily or placebo. The primary endpoint was all-cause mortality. **Results**: There was a mortality rate of 46% in the placebo group, compared to 35% in the spironolactone group (RR 0.70; 95% CI 0.60 to 0.82; P<0.001). The frequency of hospitalization for worsening HF was 35% less in the intervention group (RR 0.651 95% CI 0.54 to 0.77, P<0.001). **Conclusions**: In severe CHF (class III/IV) and LVEF <35%, spironolactone reduced all-cause mortality, sudden death, and death due to progression of HF.
SCD-HeFT	NEJM 2005;352:225-37	**Title**: Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure Purpose: Study prognosis differences in CHF patients treated with amiodarone or ICD. **Methods**: 2521 patients with CHF and LVEF <35% were randomized to conventional therapy plus placebo, conventional therapy plus amiodarone, or conventional therapy plus shock-only single-lead ICD. The primary endpoint was death from any cause. **Results**: Mortality rates were 29% in placebo patients, 28% in the amiodarone group, and 22% in the ICD group (hazard ratio 1.06; 97.5% CI 0.86 to 1.30; P=0.53). ICD was associated with a decreased risk of death of 23% compared to placebo (hazard ratio 0.77; 97.5% CI 0.62 to 0.96; P=0.007). **Results** did not vary based on ischemic or nonischemic causes of CHF. **Conclusions**: In mild-to-moderate CHF, shock-only ICD significantly reduces risk of death; amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF.
TRACE	NEJM 1995;333:1670-76	**Title**: A Clinical Trial of the Angiotensin-Converting–Enzyme Inhibitor Trandolapril in Patients with Left Ventricular Dysfunction after Myocardial Infarction Purpose: Determine whether the mortality benefit of ACEI post-MI extends to all patients, or only selected patients. **Methods**: On d 3-7 post-MI, 1749 patients were randomized to receive oral trandolapril or placebo. The primary endpoint was all-cause mortality. **Results**: The mortality rate was 34.7% in the trandolapril group, compared with 42.3% in the placebo group (P=0.001; RR 0.78; 95% CI 0.67 to 0.91). Trandolapril reduced rates of sudden death (RR 0.75; 95% CI 0.59 to 0.98; P=0.03) and CV death (RR 0.75; 0.62 to 0.89; P=0.001). **Conclusions**: In patients with LV dysfunction post-MI, long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death.
ARRHYTHMIA		
AFFIRM	NEJM 2002;347:1825-33	**Title**: A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation Purpose: Compare rate and rhythm control in patients with AFib and high risk of stroke or death. **Methods**: 4060 patients with AFib were randomized to rhythm-control therapy with antiarrhythmic drugs, or rate-control therapy. **Results**: The mortality rate was 23.8% in rhythm-controlled patients and 21.3% in rate-controlled patients (hazard ratio 1.15; 95% CI 0.99 to 1.34; P=0.08). More patients were hospitalized in the rhythm-control group, with higher rates of adverse drug events. **Conclusions**: No significant difference in mortality rates between rate or rhythm control of AFib.
ARISTOTLE	NEJM 2011;365:981-92	**Title**: Apixaban vs. Warfarin in Patients with Atrial Fibrillation Purpose: Assess the efficacy of apixaban for stroke prevention in patients with AF, in comparison with warfarin. **Methods**: 18201 patients with AFib and one additional RF for stroke were randomized to apixaban 5 mg twice daily or warfarin. The primary outcome was stroke or systemic embolism. **Results**: The rate of primary outcome was 1.27% per year in the apixaban group and 1.60% per year in the warfarin group (hazard ratio 0.79; 95% CI 0.66 to 0.95; P<0.001). The rate of major bleeding was 2.13% per year with apixaban and 3.09% per year with warfarin (hazard ratio 0.69; 95% CI 0.69 to 0.80; P<0.001). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group and 0.47% per year in the warfarin group. **Conclusions**: AFib patients treated with apixaban had a lower incidence of stroke, major bleeding and mortality compared to warfarin.
AUGUSTUS	NEJM 2019;380:1509-24	**Title**: Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation Purpose: Elucidate benefits of antithrombotic regimens for patients with AFib and either ACS or previous PCI. **Methods**: Patients with AFib and a prior ACS or PCI were randomized to apixaban or a vitamin K antagonist, and to ASA or placebo for 6 mo. The primary outcome was major or clinically relevant non-major bleeding. **Results**: The primary outcome occurred in 10.5% of apixaban patients and 14.7% of vitamin K antagonist-patients (hazard ratio 0.69; 95% CI 1.59 to 2.25; P<0.001). Patients in the apixaban group had a lower incidence of death or hospitalization compared to the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio 0.83; 95% CI 0.74 to 0.93; P=0.002). **Conclusions**: In patients with AFib and recent ACS or PCI, apixaban reduced bleeding compared to regimens that included a vitamin K antagonist, ASA, or both.
COACT	JAMA Cardiol. 2020;5:1358-65	**Title**: Coronary Angiography after Cardiac Arrest without ST Segment Elevation: One-Year Outcomes of the COACT Randomized Clinical Trial Purpose: Compare 1-yr clinical outcomes of immediate angiography and PCI versus delayed angiography in resuscitated cardiac arrest patients without STEMI. **Methods**: 552 patients who had undergone cardiac arrest in the absence of STEMI were randomized to immediate coronary angiography, or angiography after recovery of neurological function. PCI was carried out as indicated by angiography, in keeping with the time allotments between groups. The primary endpoints were survival, MI, revascularization, hospitalization for HF, and the composite of death and MI, at 1 yr follow-up time. **Results**: Survival at 1-yr follow-up were 61.4% and 64.0% in the immediate angiography and delayed angiography groups, respectively (OR 0.90; 95% CI 0.63 to 1.28; P=0.51). Similar to 90-d outcomes, this represents a statistically insignificant difference. MI rates were 0.8% and 0.4% in the immediate and delayed groups, respectively (OR 1.96; 95% CI 0.18 to 21.8). The composite outcome of death, revascularization, or MI occurred at a rate of 42.9% and 40.6% in the immediate and delayed groups, respectively (OR 1.10; 95% CI 0.77 to 1.56). **Conclusions**: Similar to the previous 90-d follow-up, immediate angiography did not significantly improve 1-yr clinical outcomes compared to delayed angiography in resuscitated cardiac arrest patients without evidence of STEMI.

Trial Name	Reference	Clinical Trial Details
ENGAGE AF-TIMI48	NEJM 2013;369:2093-104	**Title**: Edoxaban vs. Warfarin in Patients with Atrial Fibrillation Purpose: Compare the long-term efficacy and safety of edoxaban and warfarin in AFib patients. **Methods**: 21105 patients with moderate-high risk AFib were randomized to two once-daily regimens of edoxaban or warfarin. The primary endpoint was stroke or systemic embolism. **Results**: The primary endpoint rate was 1.50% with warfarin and 1.18% in the edoxaban group (hazard ratio 0.79; 97.5% CI 0.63 to 0.99; P<0.001). The annualized rate of major bleeding was 3.43% with warfarin and 2.75% with high-dose edoxaban (hazard ratio 0.80; 95% CI 0.71 to 0.91; P<0.001). **Conclusions**: AFib patients treated with edoxaban had similar rates of stroke and lower rates of major bleeding compared to warfarin.
ETOH-AFib	NEJM 2020;382:20-28	**Title**: Alcohol Abstinence in Drinkers with Atrial Fibrillation Purpose: Study the effects of alcohol abstinence on secondary prevention of atrial fibrillation. **Methods**: Adults who consumed >10 standardized drinks/wk with AFib were randomized to abstinence or continuation of current practices. The two primary endpoints were freedom from AFib recurrence and total AFib burden. **Results**: After a 2-wk blanking period, AFib recurred in 53% of patients in the abstinence group and 73% of patients in the control group (hazard ratio 0.55; 95% CI 0.36 to 0.84; P=0.005). The AFib burden after 6 mo was lower in the abstinence group than the control group. **Conclusions**: Abstinence from alcohol reduced arrhythmia recurrences in regular drinkers with AFib.
RE-LY	NEJM 2009;361:1139-51	**Title**: Dabigatran vs. Warfarin in Patients with Atrial Fibrillation Purpose: Compare the reduction of stroke risk in AFib patients with warfarin versus dabigatran. **Methods**: 18113 patients with AFib and stroke risk were randomized to fixed doses of dabigatran (110 mg or 150 mg twice daily) or warfarin. The primary outcome was systemic embolism. **Results**: Rates of primary outcomes were 1.69% per year with warfarin, compared with 1.53% per year with 110 mg dabigatran (RR 0.91; 95% CI 0.74 to 1.11; P<0.001) and 1.11% per year with 150 mg dabigatran (RR 0.66; 95% CI 0.53 to 0.82; P<0.001). The rate of major bleeding was 3.36% in the warfarin group, compared to 2.71% in the dabigatran 110 mg group and 3.11% in the dabigatran 150 mg group. **Conclusions**: AFib patients treated with dabigatran had a lower incidence of stroke compared to warfarin, with similar rates of major bleeding.
ROCKET-AFib	NEJM 2011;365:883-91	**Title**: Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation Purpose: Compare rivaroxaban with warfarin in reducing stroke risk in AFib patients. **Methods**: 14264 patients with nonvalvular AFib were randomized to rivaroxaban 20 mg daily or dose-adjusted warfarin. The primary endpoint was stroke or systemic embolism. **Results**: The primary endpoint occurred in 1.7% of patients in the rivaroxaban group and 2.2% of patients on warfarin (hazard ratio 0.79; 95% CI 0.66 to 0.96; P<0.001). Major and non-major bleeding occurred in 14.9% of patients in the rivaroxaban group and 14.5% of warfarin patients (hazard ratio 1.03; 95% CI 0.96 to 1.11; P=0.44). **Conclusions**: In patients with AFib, rivaroxaban is non-inferior to warfarin for stroke prevention without an excess of major bleeding.
HYPERTENSION		
HYVET	NEJM 2008;358:1887-98	**Title**: Treatment of Hypertension in Patients 80 Years of Age or Older Purpose: Assess antihypertensive therapy for stroke risk reduction, in patients >80 yr with hypertension. **Methods**: 3845 patients with sBP >160 mmHg and >80 yr were randomized to indapamide SR 2.5 mg or placebo. Perindopril 2 mg or 4 mg was added if needed to achieve target BP 150/80 mmHg. The primary endpoint was fatal or non-fatal stroke. **Results**: Active treatment was associated with a 30% reduction in fatal or non-fatal stroke (95% CI -1 to 51; P=0.06), a 39% reduction in death from stroke (95% CI 1 to 62; P=0.05) and a 21% reduction in all-cause mortality (95% CI 4 to 35; P=0.02). **Conclusions**: In hypertensive patients >80 yr, treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke.
SPRINT	NEJM 2015;373:2103-16	**Title**: A Randomized Trial of Intensive vs. Standard Blood-Pressure Control Purpose: Determine appropriate targets for sBP to reduce CV morbidity and mortality among patients without DM. **Methods**: 9361 patients with an sBP 130 mmHg or greater and increased CV risk, without diabetes, were randomized to sBP target <120 mmHg or <140 mmHg. The primary outcome was a composite of MI, other ACS, stroke, HF, or CV death. **Results**: There was a significant reduction in the rates of primary outcome in the intensive group compared to the conservative group (1.65% vs. 2.19%; hazard ratio 0.75; 95% CI 0.64 to 0.89; P<0.001). All-cause mortality was significantly lowered in the intensive group (hazard ratio 0.73; 95% CI 0.60 to 0.90; P=0.003). **Conclusions**: In patients with high risk of CV events excluding DM, strict sBP control (<120 mmHg) is associated with fewer CV events and lower all-cause mortality.
VALUE	Lancet 2004;363:2022-31	**Title**: Outcomes in Hypertensive Patients at High Cardiovascular Risk Treated with Regimens Based on Valsartan or Amlodipine: The Value Randomised Trial Purpose: Determine whether valsartan would reduce cardiac morbidity more than amlodipine in hypertensive patients with high CV risk. **Methods**: 15245 patients with hypertension and high CV risk were randomized to valsartan or amlodipine. The primary endpoint was a composite of cardiac morbidity and mortality. **Results**: The primary composite endpoints occurred in 10.6% of patients in the valsartan group and 10.4% of patients in the amlodipine group (hazard ratio 1.04; 95% CI 0.94 to 1.15; P=0.49). **Conclusions**: The valsartan group had a higher incidence of MI than the amlodipine group.

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CP Clinical Pharmacology

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Acronyms

ACE	angiotensin converting enzyme	cGMP	cyclic guanosine monophosphate	INR	international normalized ratio	PK	pharmacokinetics
ACh	acetylcholine			MME	milligram morphine equivalents	SLC	solute carrier
ADE	adverse drug event	Cl	clearance rate	NDC	National Drug Code	SSRI	selective serotonin reuptake inhibitor
ADME	absorption, distribution, metabolism, and excretion	COMT	catechol-O-methyltransferase	NE	norepinephrine (NPN)		
		CSF	cerebrospinal fluid	NPO	nothing by mouth (nil per os)	TBW	total body water
ADR	adverse drug reaction	CYP	cytochrome P450 enzyme	NS	nervous system	TDM	therapeutic drug monitoring
ARB	angiotensin receptor blocker	DIN	drug identification number	$P_{o/w}$	partition coefficient of a drug	TI	therapeutic index
AUC	area under the concentration-time curve	FDA	Food and Drug Administration	PD	pharmacodynamics	Vd	volume of distribution
		GFR	glomerular filtration rate	PDE	phosphodiesterase		
BBB	blood-brain barrier	HH	Henderson-Hasselbalch	P-gp	P-glycoprotein		

General Principles

Drug Nomenclature

- **DIN or NDC:** Drug Identification Number assigned to each drug approved by Health Canada; National Drug Code assigned by FDA (US), equivalent to the DIN in Canada
- **DIN-HM:** identification number assigned to registered homeopathic products in Canada
- **NPN:** Natural Product Number; refers to natural health products (excluding homeopathic medicines) regulated by the Natural and Non-Prescription Health Products Directorate (NNHPD) within Health Canada
- **chemical name:** describes chemical structure; consistent in all countries via International Union of Pure and Applied Chemistry (IUPAC) (e.g. N-(4-hydroxyphenyl)acetamide = acetaminophen)
- **non-proprietary (generic) name:** approved name (requires approval from nomenclature committee), official name (listed in pharmacopeia), often referred to as the generic name; may contain an ending similar to drugs in its class (e.g. atorvastatin, pravastatin, simvastatin)
- **proprietary (trade) name:** the brand name or registered trademark (e.g. Lipitor®)

Phases of Clinical Drug Testing

- pre-clinical: assessments of the drug before it is given to humans (e.g. laboratory studies in cells, tissues, organs, or animals) to examine PK and PD properties and potential toxicities
- phase I: first administration of the drug to a small number of healthy volunteers, following preclinical studies; to explore PK and safety
- phase II: first administration of the drug to patients, small sample sizes; primarily to determine efficacy, safety, dose range, and PK
- phase III: comparative studies (new drug vs. placebo or standard of care) to establish safety and efficacy in a larger group of patients; generally involves double-blinded RCTs
- phase IV: post-marketing surveillance, wider distribution; to determine effectiveness (in contrast to efficacy), monitor long-term drug effects, and detect previously unappreciated ADRs

Drug Administration

- choice of route of administration depends on available formulations, local and systemic effects, desired time to onset and/or duration of action, adherence, and other patient characteristics

Table 1. Routes of Drug Administration

Route	Advantage	Potential Disadvantages
Oral (PO)	Convenient, easy to administer Large surface area for absorption Inexpensive relative to parenteral administration	Incomplete absorption Hepatic and/or intestinal first-pass effects Adverse GI effects Higher likelihood of drug-drug/drug-food interactions May be affected by dietary factors Requires an intact GI system Affected by GI motility
Buccal/Sublingual (SL)	Rapid onset of action No intestinal/hepatic first-pass effect	Must be lipid-soluble, non-irritating
Rectal (PR)	Smaller hepatic first-pass effect than with oral Use when NPO, vomiting, or unconscious	Inconvenient Irritation at site of application Erratic absorption Appropriate for limited number of drugs
Intravenous (IV)	No first-pass effect Provides rapid onset of action Easy to titrate dose	Little ability to undo inappropriate drug administration Risk of infection, bleeding, vascular injury, and extravasation More expensive Requires sterile conditions and trained professionals
Intramuscular (IM)	Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action (e.g. epinephrine for serious allergic reactions)	Pain/hematoma at site of injection Requires sterile conditions
Subcutaneous (SC)	Constant, even absorption Alternative to IV Easier administration (can be self-administered)	Pain at site of injection Generally smaller volumes than IM Possible tissue damage from multiple injections
Intrathecal	Directly into CSF Bypasses BBB and blood-CSF barrier	Risk of infection and CSF leak Requires sterile conditions and trained personnel Invasive procedure
Inhalation	Immediate action in lungs Rapid delivery to blood No hepatic first-pass effect and generally less presystemic clearance	Inhalation can cause irritant effects on airways such as stimulation of the cough reflex
Topical (skin, mucous membranes, eyes)	Easy to administer Localized (limited systemic absorption)	Effects are generally limited to site of application
Transdermal	Drug absorption through intact skin, easy to apply No intestinal/hepatic first-pass effect	Irritation at site of application Delayed onset of action
Others (Intraperitoneal, Intra-articular)	Local effect	Risk of infection and hemorrhage Requires sterile conditions and trained personnel

Pharmacokinetics

- "what the body does to the drug" – i.e. the fate of a drug in the body following administration
- **definition:** the time-course of drug absorption, distribution, metabolism, and excretion from the body following drug administration

Absorption

- **definition**: movement of the drug from the site of administration into bloodstream

Mechanisms of Drug Absorption

- most drug absorption involves passive diffusion
- other mechanisms include active transport, facilitated diffusion, and pinocytosis/phagocytosis

Factors Affecting the Rate and Extent of Drug Absorption

- **lipophilicity** ($P_{o/w}$)
- local blood flow at the site of administration (e.g. sublingual vessels facilitate rapid absorption of sublingually-administered medications)
- **molecular size** (e.g. drugs with large molecular weights (i.e. >1000 Da) are not as easily absorbed by passive diffusion as drugs with smaller molecular weights)
- **pH and drug ionization**
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus exist in ionized and non-ionized forms in the body
  - non-ionized (uncharged) forms cross cell membranes more readily by passive diffusion than ionized (charged) forms
  - the ratio of ionized to non-ionized forms is determined by body compartment pH and drug pKa (as per the Henderson-Hasselbalch equation)
- **total surface area for absorption** (e.g. small intestinal villi have a large surface area and are the primary site of absorption for most orally-administered drugs)
- **drug transporters** (e.g. P-glycoprotein (P-gp), Organic anion transporting polypeptides (OATPs))

Bioavailability (F)
- **definition**: proportion of dose that reaches systemic circulation in an unchanged state that is available to access the site of action
- lower F usually reflects limited drug absorption or significant presystemic clearance (e.g. first-pass effect, substrate for drug transporters)
- IV dose has 100% bioavailability (F=1)

First-Pass Effect
- **definition**: metabolism (i.e. biotransformation) of the drug prior to reaching systemic circulation, resulting in reduced F
- can occur with PO administration of a drug: GI tract (absorption with possible metabolism) → portal vein to liver (possible first-pass metabolism) → systemic circulation
- with rectal administration, approximately 50% of drug absorbed goes through the portal system

Drug Transporters
- there are many drug transporters that can affect the uptake or efflux of drugs from cells and organelles, and affect drug absorption, distribution, and excretion
- P-gp is a transport protein of clinical relevance as it is found in a wide variety of body tissues (including the small intestinal epithelium, proximal tubule, bile canaliculi, and BBB) where it acts as a multidrug efflux pump and provides a "natural defence mechanism" against drugs and xenobiotics
- P-gp opposes the absorption of and enhances the elimination of many P-gp substrates (e.g. digoxin, etoposide, paclitaxel, tacrolimus, cyclosporine, apixaban)
- some drugs (e.g. most macrolide antibiotics) inhibit P-gp, leading to increased serum concentrations of P-gp substrates; P-gp inducers (e.g. rifampin, St. John's wort) increase efflux activity, leading to decreased serum concentrations of P-gp substrates
- some tumours overexpress P-gp, leading to multidrug resistance to chemotherapeutic agents
- other members of the ATP Binding Cassette (ABC) superfamily and the Solute Carrier (SLC) superfamily of drug transporters also affect drug absorption; members of the SLC superfamily generally function as uptake drug transporters

Distribution

- **definition**: movement of drugs between different body compartments, including their sites of action
- major body fluid compartments include plasma, interstitial fluid, intracellular fluid, and transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments include fat, muscle, and brain

Factors Affecting the Rate and Extent of Drug Distribution
- physical and chemical properties of the drug (e.g. $P_{o/w}$, pKa, and molecular weight)
- pH of fluid
- binding to plasma proteins
- binding within compartments (i.e. depots such as heart muscle, bone, fat tissue)
- regional blood flow
- drug transporters

Plasma Protein Binding
- some drug molecules bind to plasma proteins in the blood and exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free (unbound): can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
- bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
- reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in increased concentration of free drug, which is often cleared with no harmful effects, although toxicity is possible

Volume of Distribution
- V_d: the apparent volume of fluid into which a drug distributes
- a calculated value (V_d) = amount of drug in body (i.e. dose administered) ÷ initial plasma drug concentration
- a theoretical value that does not correspond to an actual physiologic volume; V_d can greatly exceed TBW
  - Total Body Water (TBW) represents the maximal anatomical fluid volume thought to be accessible to a drug (~40 L for average adult)
- small V_d (e.g. <0.04 L/kg) generally corresponds to a drug that distributes in plasma and/or binds plasma proteins to a high degree
- large V_d corresponds to a drug that preferentially distributes into tissues (e.g. fat, muscle, etc.); since most of the drug is not located in blood, the measured drug concentration in blood is low; thus, when dividing the dose by the blood/plasma drug concentration, it "appears" to distribute in a large volume
- V_d of drugs that are highly bound to plasma proteins can be altered by liver and kidney disease due to changes in plasma protein binding

- V_d of drugs changes with age
- V_d of drugs may change in the geriatric population based on the drug $P_{o/w}$; as there is often a reduction in total body water and total muscle mass, but an increase in total body fat in older adults, resulting in an increase in the V_d of hydrophobic drugs

Depot

- a body compartment in which drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam, THC)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate dosed q3 mo; depot risperidone dosed q2 wk)

Barriers (Relative)

- anatomical body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- physiological barriers such as drug transporters (e.g. P-gp), often serve as a natural defence mechanism against drugs and xenobiotics
- need to consider dosing route and/or drug interactions for drug penetration across these barriers
- barriers are important in determining sites of action and side effect profiles of drugs (e.g. risk of CNS depression if drug crosses BBB, risk of harm to a fetus if drug crosses placenta)

Metabolism (Biotransformation)

- **definition:** chemical transformation of a drug in vivo
- sites of biotransformation include the liver (main), GI tract, lung, plasma, kidney, and most other tissues
- as a result of the process of biotransformation:
  - a prodrug (i.e. inactive drug) may be activated (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be changed to another active metabolite (e.g. diazepam to oxazepam and others)
  - a drug may be changed to a toxic metabolite (e.g. acetaminophen to NAPQI)
  - a drug may be inactivated, as with most drugs (e.g. acetaminophen to acetaminophen glucuronide)

Drug Metabolizing Pathways

- phase I reactions
  - oxidation, reduction, or hydrolysis reactions that introduce or unmask polar groups on a parent compound to slightly increase water solubility (e.g. hydroxylation, demethylation)
  - the change in $P_{o/w}$ is typically minimal compared to phase II, and often phase I places a polar "handle" on a hydrophobic drug to permit conjugation in phase II
  - often mediated by cytochrome P450 (CYP) enzymes found in the endoplasmic reticulum (primarily in hepatocytes, but in lots of other tissues)
  - products of the reaction can be excreted or undergo further phase II reactions
- phase II (conjugation) reactions
  - conjugation with large endogenous substrates that are often polar (e.g. glucuronic acid, glutathione, sulphate, acetyl groups, methyl groups, or amino acids)
  - often substantially increases water solubility and renal elimination
  - can result in biologically active metabolites (e.g. morphine glucuronide)
  - can occur independently of phase I reactions (e.g. morphine to morphine glucuronides)



Examples of CYP Substrates, Inhibitors, and Inducers
drug-interactions.medicine.iu.edu/MainTable.aspx

Factors Affecting Drug Biotransformation

- **genetic polymorphisms** of metabolizing enzymes
  - for some enzymes, individual genotypes may alter the rate of drug metabolism (e.g. poor, intermediate, extensive, or ultra-rapid metabolizers, with extensive being considered the "normal" or average condition)
  - may lead to toxicity (e.g. if poor metabolizer) or ineffectiveness (e.g. if ultra-rapid metabolizer) of a drug at a normal dose
  - tamoxifen, tramadol, and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas hypermorphic alleles impart "ultra-rapid metabolizer" phenotype)
  - warfarin is metabolized by CYP2C9 (loss-of-function alleles lead to higher drug concentrations, greater effect and lower dose requirements)
- **enzyme inhibition** may result from other chemical exposures including drugs and foods
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin (CYP3A4 inhibitor) can predispose patients to simvastatin (CYP3A4 substrate) toxicity)
  - grapefruit juice is a potent inhibitor of intestinal CYP3A4, resulting in markedly reduced first-pass metabolism and numerous drug interactions (e.g. saquinavir AUC increased 3-fold, simvastatin AUC increased 17-fold)

- **enzyme induction** may be due to the same or other medications
  - for example, certain medications enhance gene transcription to increase the activity of metabolizing enzymes
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of oral contraceptive pills) by inducing the CYP system
- **liver dysfunction** (e.g. hepatitis, alcoholic liver disease, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but it is not always clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug metabolism
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, but toddlers often have increased capacity, and doses should be adjusted accordingly
- **nutrition** may be involved, as insufficient protein and fatty acid intake decreases biotransformation, and vitamin/mineral deficiencies may also impact metabolizing enzymes
- **alcohol** has varying effects; while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1, increasing the risk of hepatocellular damage from acetaminophen by increasing the production of the toxic metabolite (NAPQI)
- **smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline, clozapine)

Excretion

- **definition**: removal of a drug from the body

Routes of Drug Excretion

- **kidney** (main organ of excretion)
  - renal drug clearance = (glomerular filtration + tubular secretion) − (tubular reabsorption)
  - renal function (assessed using serum creatinine) decreases with age (7.5 mL/min per decade) and is affected by many disease states (e.g. diabetes)
  - processes affecting renal excretion:
    1. glomerular filtration
       - a passive process, thus only the free drug fraction can be eliminated
       - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
    2. tubular secretion
       - a saturable transport process allowing both protein-bound and free drug fractions to be excreted
       - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, metformin)
       - drugs may block the secretion of other drugs if one or more share or inhibit the same drug transporter (e.g. probenecid can inhibit the excretion of penicillin via organic anion transporters)
    3. tubular reabsorption: some drugs can be actively or passively reabsorbed back into the systemic circulation, reducing their excretion
- **stool:** some drugs and metabolites are actively secreted into the bile or directly into the GI tract
  - enterohepatic recirculation occurs when drugs are reabsorbed from the intestine and returned to the liver to cycle between the intestine and liver, which can prolong the drug's duration in the body (e.g. some glucuronic acid conjugates that are excreted in bile may be hydrolyzed in the intestines by bacteria back to their original form and can be systemically reabsorbed)
- **lungs:** elimination of anesthetic gases and vapours by exhalation
- **other routes:** sweat, saliva, and breast milk are generally less significant routes, but saliva concentrations of some drugs parallel their plasma concentrations (e.g. rifampin) and drug excretion into breast milk is a concern for some drugs

Pharmacokinetic Considerations

- **definition**: the term "pharmacokinetics" is used to describe given aspects of drug disposition (i.e. the fate of drugs in the body) and encompasses absorption, distribution, metabolism, and excretion (ADME)
- absorption, distribution, and elimination can be graphically represented (e.g. a graph of concentration vs. time)

Time Course of Drug Action

- many kinetic parameters are measured after IV dosing because it avoids the complications of incomplete absorption, and distribution for most drugs is rapid
- when drug doses or concentrations are plotted vs. time, the dose or concentration plotted on the x-axis is often converted to a logarithmic scale (commonly $\log_{10}$) to allow for easier mathematical calculations
- the shape of the elimination phase of a concentration (or dose) or log-concentration (or log-dose) vs. time curve indicates whether the drug undergoes a first-order rate of elimination (visualized as a straight line on a log-dose or log concentration vs. time curve) or a zero-order rate of elimination (curvilinear on a log-dose or log-concentration vs. time curve)
- drugs such as warfarin can exhibit hysteresis (for a single drug concentration, there may be two different response levels)

Half-Life
- definition: time taken for the serum drug concentration to decrease by 50%; usually referred to as the elimination half-life
- applies only to drugs with first-order kinetics (i.e. most drugs), which require approximately four to five half-lives to reach steady-state with repeated dosing, or for complete drug elimination once dosing is stopped

Steady-State Drug Concentration
- drug concentration remains constant when the amount of drug entering the system is equivalent to the amount eliminated from the system
- determination of drug concentrations in therapeutic drug monitoring is of greatest utility when steady-state concentration has been reached
- special dosing situations
  - use a loading dose for drugs with a long half-life and/or when there is a clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin, some antibiotic settings)
  - use continuous infusion for drugs with a very short half-life and when there is a need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, unfractionated heparin, naloxone)

Clearance Rate
- quantitative measurement of the volume of body fluid from which a substance is removed per unit time
- Cl = rate of elimination of drug ÷ plasma drug concentration
- may be determined for a particular organ (e.g. liver or kidney), but if not specified, represents the total body clearance rate determined from the sum of individual clearance rates or by determining ke x Vd, where ke is the elimination rate constant equal to ln 2/half-life

Elimination Kinetics
- first-order kinetics (most common type)
  - constant proportion of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the Cl is less than would be predicted for a given concentration
  - shows linear relationship when plotted on a graph of concentration (log) vs. time (linear)
  - the concentration axis is converted to a log scale to allow for easier mathematical calculations
- non-linear or zero-order kinetics (less common, applies to a few drugs in the therapeutic range (e.g. alcohol, phenytoin, Aspirin®) and is more commonly associated with overdose)
  - constant amount of drug eliminated per unit time, regardless of concentration; the concept of half-life does not apply
  - saturation of various ADME processes creates non-linear kinetics, with first-order exhibited at lower concentrations and zero-order exhibited at higher concentrations after saturation
  - the complexity of dosing drugs with non-linear kinetics has resulted in the creation of drug-specific nomograms to aid clinicians in dosing, with these drugs often being the target of TDM (e.g. phenytoin, theophylline)

Loading and Maintenance Doses
- loading doses are used when an immediate effect is needed, with parenteral administration being the most common way of giving a large dose to "fill up" the volume of distribution for drugs that distribute extensively outside the vascular compartment
- maintenance doses can be given after a loading dose, but are most commonly initiated without a loading dose
  - steady-state levels are achieved after approximately four to five half-lives
  - can be given as either a continuous infusion (rare) or more commonly as intermittent oral doses

Pharmacodynamics
- study of "what the drug does to the body"
- **definition:** study of the effects of the drug on the body

Dose-Response Relationship
- graded dose-response relationship: relates dose to intensity of effect

Efficacy
- the relative ability of a drug to produce a maximal (biological/biochemical) response
- measured by E_{max} (the maximal response that a drug can elicit)

Potency

- measured by EC_{50} (the concentration of a drug needed to produce 50% of E_{max}); ED_{50} if dose is used (derived from graded dose-response curves)
- a drug that reaches its EC_{50} at a lower concentration is more potent (e.g. in Figure 1, drug A is more potent than drug B)

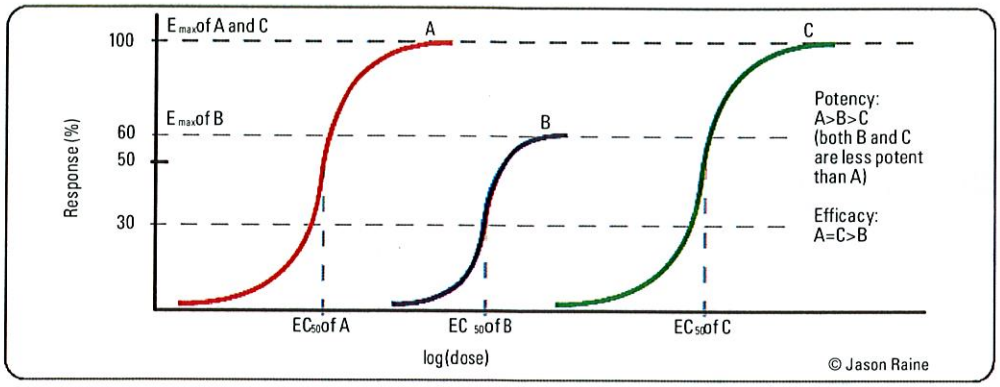


Figure 1. Log(dose)-response curve illustrating efficacy and potency

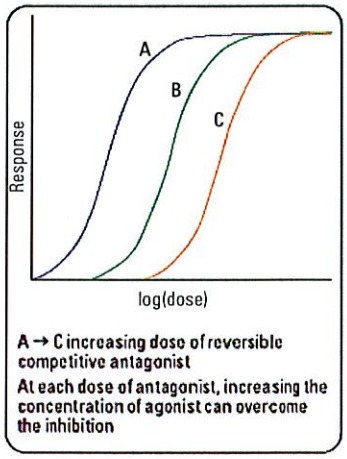


Figure 2. The log(dose)-response curve for reversible competitive antagonism

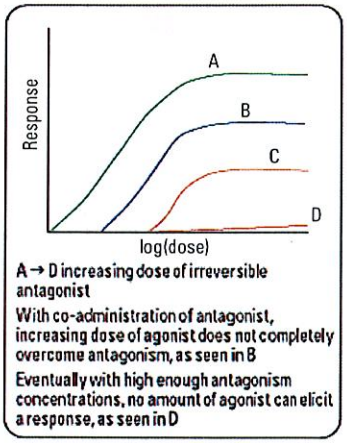


Figure 3. The log(dose)-response curve for irreversible antagonism

Effects of Drugs on Receptors

Agonists

- drugs that mimic the effects of the endogenous ligand and evoke a response when bound to the receptor
  - **affinity**: the ability and strength of the agonist to bind to the receptor (e.g. the β2-agonist salbutamol has greater affinity for β2-receptors than β1-receptors, thus it binds preferentially to β2-receptors)
  - **efficacy**: the ability to elicit a response via the receptor interaction (e.g. binding of salbutamol to β2-receptors results in smooth muscle relaxation)
    - drug efficacy is often determined under ideal conditions whereas drug effectiveness is a better measure of how the drug works in real-world situations
- full agonists: can elicit a maximal effect at a receptor (e.g. methadone or morphine on the μ opioid receptor system)
- partial agonists: can only elicit a partial effect, irrespective of the concentration at the receptor; also known as a ceiling effect (i.e. reduced efficacy compared to full agonists) (e.g. buprenorphine on the μ opioid receptor system)

Antagonists

- drugs that reduce the action of an agonist drug or of an endogenous ligand
- **chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for the removal of heavy metals, such as charcoal)
- **physiological/functional antagonism**: drugs that produce opposite physiological effects (e.g. insulin decreases blood glucose levels through its action at insulin receptors vs. glucagon raises blood glucose levels through its action at glucagon receptors)
- **pharmacological antagonism**: antagonist binds to the same site as the agonist or an alternative effector site and reduces the ability of the agonist to bind
  - **competitive antagonism**: antagonist binds directly to the active site on a given receptor, without activating it (i.e. zero efficacy) and prevents the agonist from binding to the active site
    - **reversible competitive antagonists**: bind non-covalently to the receptor, thus increasing concentrations of agonist may overcome the antagonist (e.g. naloxone is a competitive antagonist to morphine or heroin)
    - **irreversible competitive antagonists**: form a covalent bond with the receptor and cannot be displaced, thus irreversibly blocking other substrates from binding (e.g. phenoxybenzamine forms a covalent bond with adrenergic receptors preventing adrenaline and NE from binding)
  - **non-competitive antagonism**: antagonist (negative allosteric modulator) binds to an alternate site on the receptor which is distinct from the active site, producing allosteric effects that reduce the ability of the agonist to bind

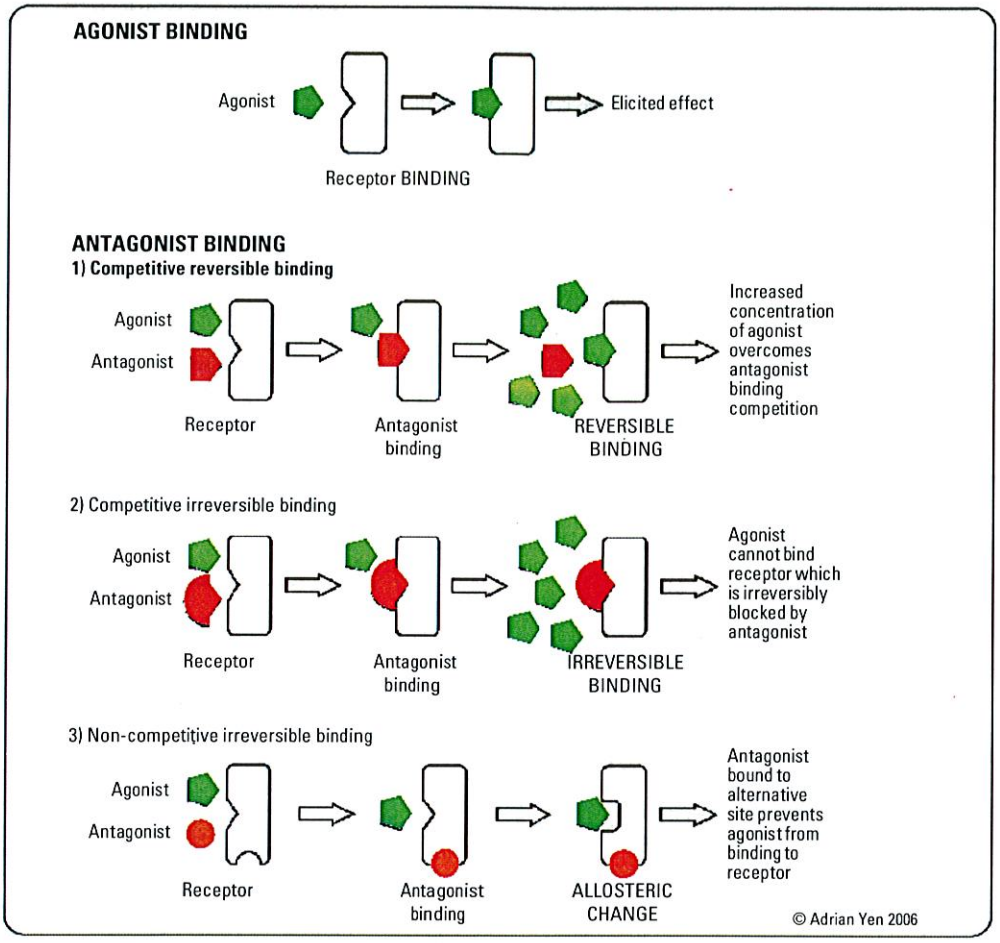


Figure 4. Mechanism of agonists and antagonists

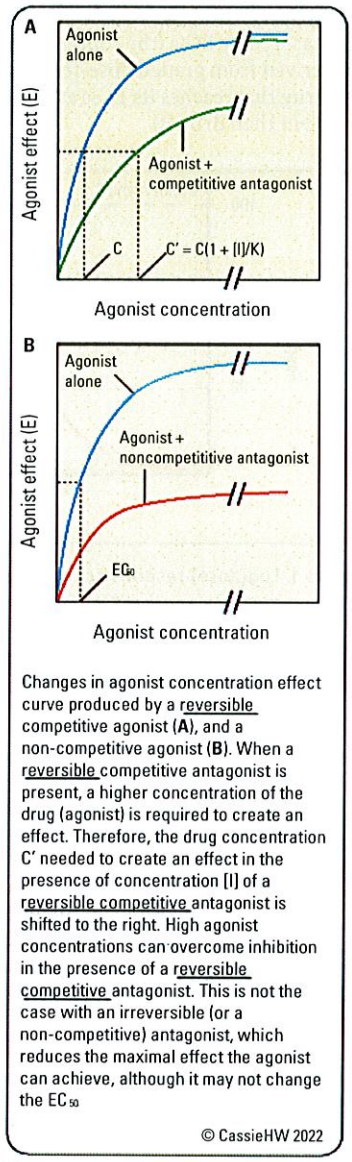


Figure 5. Agonist concentration

Effectiveness and Safety

Effectiveness

- ED_{50} (effective dose): the dose of a drug needed to elicit a therapeutic effect in 50% of a test population (derived from quantal dose-response curves)

Safety

- LD_{50} (lethal dose): the dose of a drug needed to cause death in 50% of a test population of subjects (usually derived from animal or cell data)
- TD_{50} (toxic dose): the dose of a drug needed to cause a harmful effect in 50% of a test population of subjects (usually derived from animal or cell data)

Therapeutic Indices

Therapeutic Index: TD_{50}/ED_{50} (LD_{50}/ED_{50} in animals)

- a measure of relative drug safety often used when comparing drugs to examine the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer the drug
- common drugs with a narrow therapeutic window or low TI that sometimes require TDM include digoxin, theophylline, warfarin, lithium, and cyclosporine
- factors that can change the TI include presence of interacting drugs, changes in drug ADME, and patient characteristics (e.g. age, pregnancy, and organ impairment)

Certain Safety Factor: TD_1/ED_{99}

- a comparison of the dose that is effective in at least 99% of the population and toxic in less than 1% of the population
- regulatory agencies often like to see a certain safety factor or margin of safety above 100

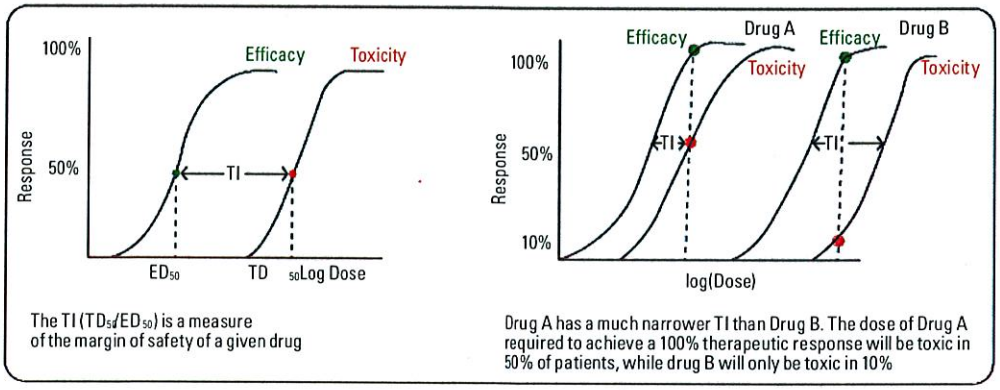


Figure 6. ED50, TD50, and the TI

Therapeutic Drug Monitoring

- **definition**: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance). Serum drug samples are usually taken when the drug has reached steady-state (i.e. after approximately 4-5 half-lives)
- TDM is often used for drugs that have low TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, and/or wide interpatient PK variability
- nomograms are often used for low TI drugs, particularly in the setting of patients with complex clinical factors such as renal insufficiency, hepatic failure, dialysis, and hypoalbuminemia
- examples of drugs that sometimes require TDM include:
  - vancomycin
  - aminoglycosides (gentamicin, tobramycin)
  - digoxin
  - phenytoin and other anticonvulsants
  - warfarin
  - lithium

Adverse Drug Reactions

- **definition**: ADEs are events that occur while a patient is on a drug at either appropriate or inappropriate dosage. A causal relationship is not required
- **definition**: ADRs are reactions to drugs that occur when a drug is used for the appropriate indication at normal therapeutic doses

Table 2. Characteristics of Type A-E Adverse Drug Reactions

Classification	Definition	Characteristics
A (Augmented)	Dose-related	Predictable extension of drug's pharmacologic effect (e.g. β-blockers causing bradycardia) >80% of all ADRs
B (Bizarre)	Not dose-related	Reactions unrelated to the known pharmacological actions of the drug, generally with a genetic basis E.g. drug hypersensitivity syndromes, immunologic reactions (e.g. penicillin hypersensitivity), and idiosyncratic reactions (e.g. malignant hyperthermia)
C (Chronic)	Dose- and time-related	Related to cumulative doses Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates, retinal toxicity from hydroxychloroquine)
D (Delayed)	Time-related	Occurs some time after use of drug (e.g. cardiovascular toxicity following doxorubicin therapy) May also be dose-related
E (End of use)	Withdrawal	Occurs after cessation of drug use (e.g. opioid withdrawal resulting from opioid dependence)



Tips to Reduce Drug-Related Adverse Events in the Elderly

- Be mindful of longstanding medications that have never been adjusted for patient age, renal function, or hepatic function
- Consider whether medications initiated during hospital admission are needed long-term (and whether the discharge dose is appropriate for maintenance)
- Avoid polypharmacy by decreasing the dose of or discontinuing medications that are causing side effects or are no longer indicated (i.e. deprescribing)
- Verify adherence to medications before automatically increasing the dose of subtherapeutic treatment
- When prescribing medications, preferentially use those with a high TI
- Review the patient's problem list and reconcile current medications to avoid duplication or inappropriate dosing/frequency



Antibiotic Allergies - What is the Risk of Cross-Reactivity?

- In clinical practice, cross-reactivity between drugs presents a problem for both patients and physicians
- In the case of penicillin allergy, cross-reactivity to cephalosporins is less than 2%. However, in patients who have a history of true anaphylactic reaction, cross-reactivity is closer to 40% depending on the side chain
- Cross-reactivity between penicillins and carbapenems is <1%
- The term "sulfa allergy" is often misused and has no formal definition. Current evidence suggests cross-reactivity between sulfonamide antibiotics (e.g. sulfamethoxazole-trimethoprim) and non-antibiotic sulfonamides, including loop diuretics (e.g. furosemide), thiazide diuretics (e.g. hydrochlorothiazide), protease inhibitors containing an arylamine group (e.g. darunavir), carbonic anhydrase inhibitors (e.g. acetazolamide), and sulfonylureas (e.g. glipizide)

Approach to Suspected Adverse Drug Reactions

- history and physical exam: signs and symptoms of reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, de-challenge (response when drug is removed), and re-challenge (response when drug is given again, if applicable)
  - medication history should include prescription, non-prescription and over-the-counter, natural health products/samples, supplements, creams, ear/eye drops, inhalers, and nasal sprays
  - dosage, frequency, route of administration, and duration of use should be recorded for each
- differentiate between drug therapy vs. disease pathophysiology
- treatment of serious adverse drug reactions: stop the drug, supportive care, and symptomatic relief. Specific interventions (e.g. steroids, immunosuppressants) used for some ADRs
- resources: check recent literature, Health Canada, and FDA; contact the pharmaceutical company; call Poison Control (1-800-268-9017) if overdose or poisoning suspected; check with MotherToBaby (https://mothertobaby.org/) in cases involving pregnant or breastfeeding women
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
  - Canadian Adverse Drug Reaction Monitoring Program available for online reporting
    - https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug/health-care-providers.html

Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements due to age, genetics, disease states, drug interactions, diet, environmental factors, etc.
- possible causes of individual variability in drug response include problems with:
  - intake: medication adherence
  - absorption: vomiting, diarrhea, or steatorrhea; first-pass effect increased due to enzyme induction or decreased due to enzyme inhibition or liver disease
  - pharmacokinetic or pharmacodynamic drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones in the GI lumen, impairing absorption)
  - distribution: very high or low percentage body fat, intact or disrupted BBB, patient is elderly or a neonate, or has liver dysfunction
  - biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism), kidney or liver dysfunction
  - PD: genetic variability in drug response (e.g. immune-mediated reactions), diseases that affect drug PD, drug tolerance or cross-tolerance

Drug Interactions

- concomitant medications (including natural health products, e.g. St. John's wort) or foods (e.g. grapefruit juice): one drug alters the effect of one or more other drugs by changing PK and/or PD
- PK interactions involve changes in drug concentration when a new drug is added
  - absorption: alterations in gastrointestinal pH, gastric mucosa and/or emptying, intestinal motility, and/or transporter function
  - distribution: alterations in blood flow, plasma protein binding, anatomical and/or functional barriers (e.g. drug transporters)
  - metabolism: alterations in drug metabolism
  - excretion: alterations in renal or hepatic excretion
- PD interactions are due to two or more drugs that exert similar effects (additive or synergistic) or opposing effects (antagonistic)



Examples of Clinically Relevant Drug Interactions

Interaction	Potential Effect	Mechanism of Interaction
Warfarin plus ciprofloxacin, clarithromycin, erythromycin, metronidazole, or trimethoprim-sulfamethoxazole	Increased effect of warfarin	Multiple proposed PK and PD mechanisms (including antibiotic interference with enteric flora-mediated Vitamin K2 production and alterations in drug metabolism)
Warfarin plus acetaminophen Note that this is not with typical use, but with more chronic and higher dose use	Acetaminophen (NAPQI) further increases INR	PD (reduction of Vitamin K-dependent clotting factors by NAPQI)
Oral contraceptive pills plus rifampin	Decreased effectiveness of oral contraception	PK (rifamycin induces CYP3A4, which increases hormone metabolism)
Sildenafil plus nitrates	Hypotension	PD (both PDE5 inhibitors and nitrates potentiate cGMP production)
SSRIs plus St. John's wort	Serotonin syndrome	PD (concomitant use of serotonergic medications)
SSRIs plus selegiline or non-selective MAOI	Serotonin syndrome	PD (all decrease metabolism of serotonin, so excess serotonin in synaptic cleft)
Some **HMG-CoA reductase inhibitors** plus niacin, gemfibrozil, erythromycin or itraconazole	Possible rhabdomyolysis	PK (various mechanisms based on drugs listed; CYP3A or OATP1B1, e.g. clarithromycin inhibits)
Sulfamethoxazole-trimethoprim and ACEIs/ARBs, or spironolactone	Increased risk of hyperkalemia	PD (reduced renal potassium excretion in the presence of trimethoprim resulting from decreased sodium reabsorption as a result of inhibition of sodium channels in the distal tubule)

Autonomic Pharmacology

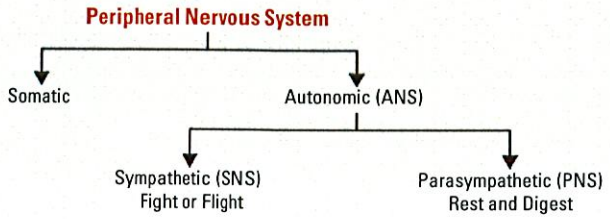


Figure 7. Subdivisions of the peripheral nervous system

- most organs are innervated by both sympathetic and parasympathetic nerves, which have opposing effects (see Neurology, N8)
- ACh and NE are the main neurotransmitters of the autonomic NS
- ACh binds to many cholinergic receptor subtypes, which include nicotinic and muscarinic receptors
- NE binds to adrenergic receptors, which principally include β1, β2, α1, and α2
- ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
- acetylcholinesterase inhibitors (pyridostigmine, donepezil, galantamine, and rivastigmine) can be used to increase ACh levels in conditions such as myasthenia gravis or Alzheimer's disease
- NE action is terminated by reuptake at the presynaptic membrane, diffusion from the synaptic cleft, and degradation by monoamine oxidase (MAO) and COMT

Parasympathetic Nervous System

- blood vessels, sweat glands, the spleen capsule, and adrenal medulla do NOT have parasympathetic innervation
- parasympathetic pre-ganglionic fibres originate in the lower brainstem from cranial nerves III, VII, IX, and X, and in the sacral spinal cord at levels S2-S4. For this reason, it is sometimes referred to as the "craniosacral" nervous system. They connect with post-ganglionic fibres via nicotinic receptors in ganglionic cells located near or within the target organ (e.g. ciliary ganglion)
- post-ganglionic fibres connect with effector tissues via:
  - M1 muscarinic receptors located in the CNS
  - M2 muscarinic receptors located in smooth muscle, cardiac muscle, and glandular epithelium

Sympathetic Nervous System

- sympathetic preganglionic fibres originate in the spinal cord at spinal levels T1-L2/L3
- preganglionic fibres connect with postganglionic fibres via nicotinic receptors located in one of two groups of ganglia:
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. prevertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- post-ganglionic fibres connect with effector tissues via:
  - β1 receptors in cardiac tissue
  - β2 receptors in smooth muscle of bronchi and GI tract
  - α1 receptors in vascular smooth muscle
  - α2 receptors in vascular smooth muscle
  - M3 muscarinic receptors located in sweat glands

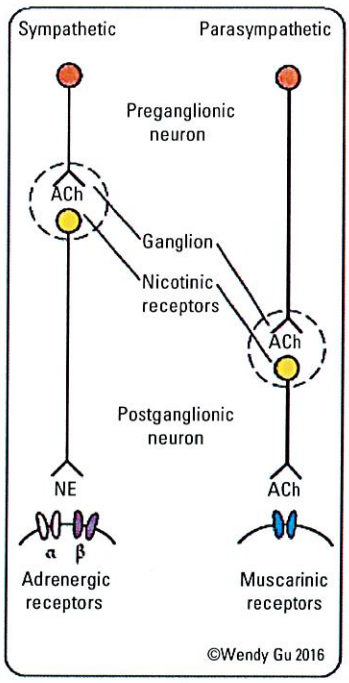


Figure 8. Autonomic nervous system efferent tracts

Table 3. Direct Effects of Autonomic Innervation on the Cardiorespiratory System

Organ	Sympathetic NS		Parasympathetic NS	
	Receptor	Action	Receptor	Action
Heart				
1. Sinoatrial	β1	Increased HR	M	Decreased conduction
2. Atrioventricular node	β1	Increased conduction	M	Decreased conduction
3. Atria	β1	Increased contractility	M	Decreased conduction
4. Ventricles	β1	Increased contractility	M	Decreased HR
Blood Vessels				
1. Skin, splanchnic	α1, β2	Constriction	M	Dilatation
2. Skeletal muscle	α	Constriction	M	Dilatation
3. Coronary	β2 (large muscles)	Dilatation	M	Dilatation
	α1, β2	Constriction	M	Dilatation
	β2	Dilatation	M	Dilatation
Lungs				
1. Bronchiolar smooth muscle	β2	Relaxation	M	Constriction
2. Bronchiolar glands	α1, β2	No stimulation	M	Stimulation

Opioid Therapy and Chronic Non-Cancer Pain

General Management Principles

- when first considering therapy for patients with chronic non-cancer pain, optimize non-opioid pharmacotherapy and non-pharmacologic therapy rather than starting a trial of opioids (strong recommendation)
- general approaches to opioid use include avoiding high doses, and when possible, a slow, collaborative approach when tapering
- for patients with chronic non-cancer pain beginning opioid therapy, restrict the prescribed dose to <90 MME/day, and ideally <50 MME/day, especially at starting dose
  - for patients with chronic non-cancer pain who are currently using 90 MME/day or more, encourage a slow, collaborative taper of opioids to the lowest effective dose, potentially discontinuing
- for patients with chronic non-cancer pain who are using opioids and experiencing serious challenges in tapering, a formal multidisciplinary program is suggested
- please refer to national opioid guidelines for a comprehensive approach to opioid use (https://www.cmaj.ca/content/189/18/E659#sec-11)



Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs. Increased Pain at Taper Completion?
Pain Med 2019;20:2179-2197
Purpose: Support or refute the hypothesis that opioid tapering in chronic pain patients (CPPs) improves pain or maintains the same pain level by taper completion but does not increase pain levels.
Methods: Structured systematic review searching relevant subject headings. 20 studies met inclusion/exclusion criteria and were of type III/IV level evidence. Characteristics were abstracted for numerical analysis.
Results: Total of 2109 CPPs tapered in all studies combined. 8% of the studies showed that by taper completion, pain had improved. In 15% of the studies, pain remained the same.
Conclusions: There is consistent type 3 and 4 evidence that opioid tapering in CPPs reduces or maintains the same pain levels. Studies were marginal in quality and further controlled studies needed.

Common Drug Endings

Table 4. Common Drug Endings

Ending	Category	Example
-afil	PDE-5 inhibitor	sildenafil
-ane	Inhaled general anesthetic	halothane
-azepam	Benzodiazepine	lorazepam
-azole*	Antifungal	ketoconazole
-caine	Local anesthetic	lidocaine
-mab	Monoclonal antibody	adalimumab
-nib	Small molecular inhibitor	imatinib
-olol	β-blocker	propranolol
-prazole	Proton pump inhibitor	omeprazole
-pril	ACE inhibitor	captopril
-sartan	ARB	candesartan
-statin	HMG-CoA inhibitor	atorvastatin
-terol	β2 agonist	albuterol
-tidine	H2 antagonist	cimetidine
-tropin	Pituitary hormone	somatotropin
-vir	Antiviral	acyclovir
-zosin	α1 antagonist	prazosin

Note: This table provides the most common drug endings for which there are only a few exceptions (e.g. methimazole, an antithyroid; stanozolol is an anabolic steroid) and is not exhaustive
*Unless ending is -prazole

Dangerous Abbreviations, Symbols, and Dose Designations

- the abbreviations, symbols, and dose designations in *Table 5* should never be used when communicating medication information as they are frequently misinterpreted and involved in harmful medication error

Table 5. Dangerous Abbreviations, Symbols, and Dose Designations

Abbreviation/Symbol/Dose Designation	Intended Meaning	Problem	Correction
U	unit	Mistaken for "0" (zero), "4" (four), or cc	Use "unit"
IU	international unit	Mistaken for "IV" (intravenous) or "10" (ten)	Use "unit"
Abbreviations for drug names		Misinterpreted because of similar abbreviations for multiple drugs; e.g., MS, MSO_4 (morphine sulphate), $MgSO_4$ (magnesium sulphate) may be confused for one another	Do not abbreviate drug names
QD QOD	Every day Every other day	QD and QOD have been mistaken for each other, or as 'qid'. The Q has also been misinterpreted as "2" (two)	Use "daily" and "every other day"
OD	Every day	Mistaken for "right eye" (OD = oculus dexter)	Use "daily"
OS, OD, OU	Left eye, right eye, both eyes	May be confused with one another	Use "left eye", "right eye" or "both eyes"
D/C	Discharge	Interpreted as "discontinue whatever medications follow" (typically discharge medications)	Use "discharge"
cc	cubic centimetre	Mistaken for "u" (units)	Use "mL" or "millilitre"
µg	microgram	Mistaken for "mg" (milligram) resulting in one thousand-fold overdose	Use "mcg"
@	at	Mistaken for "2" (two) or "5" (five)	Use "at"
> <	Greater than Less than	Mistaken for "7" (seven) or the letter "L". Confused with each other	Use "greater than"/"more than" or "less than"/"lower than"
Trailing zero	X.0 mg	Decimal point is overlooked resulting in 10-fold dose error	Never use a zero by itself after a decimal point. Use "X mg"
Lack of leading zero	.X mg	Decimal point is overlooked resulting in 10-fold dose error	Always use a zero before a decimal point. Use "0.X mg"

Adapted from Institute for Safe Medication Practices Canada (ISMP)'s List of Error-Prone Abbreviations, Symbols, and Dose Designations 2006

For more information on medical pharmacology, please refer to our textbook product
Pharmacology You See

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D Dermatology

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Acronyms

β-hCG	β-human chorionic gonadotropin
ACEI	angiotensin-converting enzyme inhibitor
AGEP	acute generalized exanthematous pustulosis
AD	atopic dermatitis
AK	actinic keratoses
ASO	anti-streptolysin O
BCC	basal cell carcinoma
BCG	bacillus Calmette-Guerin
BSA	body surface area
BUN	blood urea nitrogen
CMV	cytomegalovirus
CNS	central nervous system
Cr	creatinine
CXR	chest x-ray
DIHS	drug-induced hypersensitivity syndrome
DLE	discoid lupus erythematosus
DM	diabetes mellitus
DRESS	drug reaction with eosinophilia and systemic symptoms
DVT	deep vein thrombosis
EM	erythema multiforme
Er:YAG	erbium-doped yttrium aluminum garnet
ESR	erythrocyte sedimentation rate
Fe	iron
FTA-ABS	fluorescent treponemal antibody-absorption
GAS	group A β-hemolytic Streptococcus
GVHD	graft-versus-host disease
HHV	human herpes virus
HLA	human leukocyte antigen
HPA	hypothalamic-pituitary-adrenal
HPV	human papillomavirus
HRT	hormone replacement therapy
HSV	herpes simplex virus
HZV	herpes zoster virus
IBD	inflammatory bowel disease
IFN	interferon
IVIg	intravenous immunoglobulin
MAOI	monoamine oxidase inhibitor
MM	malignant melanoma
NB-UVB	narrow band ultraviolet B
Nd:YAG	neodymium-doped yttrium aluminum garnet
NMN	nevomelanocytic nevus
NMSC	nonmelanoma skin cancers
OCP	oral contraceptive pill
OTC	over-the-counter
PABA	para-aminobenzoic acid
PASI	psoriasis area and severity index
PDE-4	phosphodiesterase-4
PPD	purified protein derivative
PUVA	psoralens and UVA
RA	rheumatoid arthritis
SCC	squamous cell carcinoma
SJS	Stevens-Johnson syndrome
SPF	sun protection factor
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded skin syndrome
STI	sexually transmitted infection
TB	tuberculosis
TCS	topical corticosteroid
TEN	toxic epidermal necrolysis
TMP/SMX	trimethoprim-sulfamethoxazole
UC	ulcerative colitis
URTI	upper respiratory tract infection
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
UVC	ultraviolet C
UVR	ultraviolet radiation
VDRL	venereal disease research laboratory
VZV	varicella zoster virus

Introduction to Skin

Normal Processes of Skin and Subcutaneous Tissue

Embryonic Development of the Skin

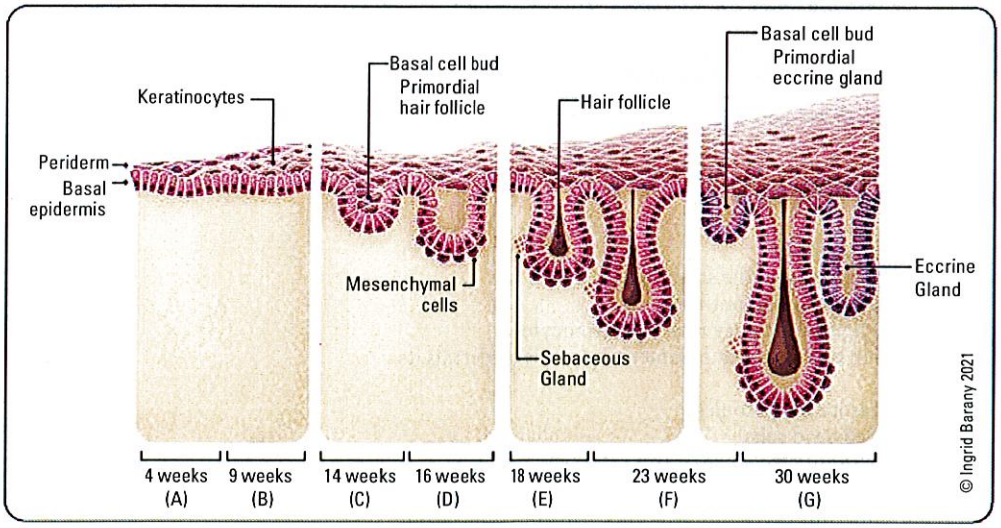


Figure 1. Fetal maturation of the skin
(A) 4 wk gestation: fetal skin has two distinct layers - the basal cell layer and outer layer (i.e. periderm). (B) 9 wk gestation: keratinization begins. (C) 14 wk gestation: stratification of epidermal layer; primordial hair follicle forms from the basal cell bud. (D) 16 wk gestation: local proliferation of mesenchymal cells associated with the epidermal buds as hair follicles develop and elongate. (E) 18 wk gestation: sebaceous gland develops; hair follicle elongates. (F) 23 wk gestation: continuous elongation of the hair follicle; primordial eccrine gland forms from the basal cell bud. (G) 30 wk gestation: continuous elongation and foiling coiling of the eccrine glands.
Modified from Facial Plastic Surgery Clinics of North America, 21(1), King A, Balaji S, Keswani SG, Biology and Function of Fetal and Pediatric Skin, 1-6, Copyright (2020), with permission from Elsevier

- **embryonic development and fetal maturation** (see *Figure 1*)
- **neonatal changes**
  - full-term infants have skin with all five layers, similar to adults
  - epidermal cells mature from columnar stratum basale to squamous keratinocytes of the stratum corneum
    - maturation occurs more rapidly in facial skin than trunk or limb skin
  - neonatal skin is coarser and develops into a more smooth texture homogeneously during the first 30 d of life
  - infants have smaller corneocytes and thinner stratum corneum until 2 y/o
  - from infancy to puberty, dermal thickness increases
- **repair, regeneration, and changes associated with stages of life**
  - regeneration relies on tissue-specific stem cells and restricted progenitor cells

- regenerative abilities decline with age as both cell types undergo:
  - a loss of self-renewing capacities
  - altered proliferative activity
  - functional decline
- with age, the skin becomes thinner and less able to withstand external stress because:
  - the epidermis attenuates with effacement of the rete ridges
  - keratinocytes lose proliferative abilities
  - the dermis loses volume
  - hyaluronic acid diminishes in the extracellular matrix of the dermis
- these changes lead to loss of skin and hair integrity, leading to conditions such as senile purpura and male pattern baldness (i.e. androgenic alopecia, see *D44*)
  - senile purpura (i.e. solar or actinic purpura): typically arise spontaneously; characterized by non-blanchable red-to-purple patches that resolve over 1-3 wk, leaving residual brown-yellow discolouration secondary to hemosiderin deposition
- the decline in regenerative ability can also be seen as postmenopausal hair changes (see *D46*)

Skin Anatomy

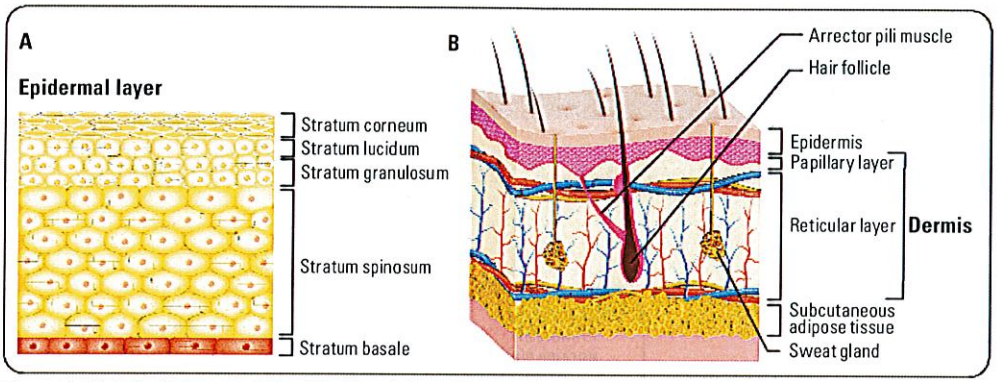


Figure 2. Histologic layers of the skin. A. epidermal layers of the skin. B. all layers of the skin

Layers of the Epidermis
"Californians Like Going Sun Bathing"
OR
"Canadians Like Good Sushi Boxes"

Skin

- divided anatomically into epidermis, dermis, and subcutaneous tissue
- **epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale
  - cells progress from stratum basale to stratum corneum in about 4 wk
    - stratum basale (i.e. germinativum): mitotic figures that give rise to keratinocytes
    - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
    - stratum granulosum: flat cells containing basophilic granules
    - stratum lucidum: transparent layers of packed dead cells
    - stratum corneum: flat scales of the water-resistant protein keratin
  - cells of the epidermis:
    - keratinocytes: located in all layers of the epidermis except the stratum corneum; connected to each other by desmosomes
    - melanocytes: located in the stratum basale; keratinocyte:melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races; produce melanosomes containing melanin, which are transferred to keratinocytes
    - Langerhans cells: dendritic cells which are important for immune surveillance
    - Merkel cells: located in the stratum basale; involved in touch sensation
- **dermis**
  - comprised of connective tissue divided into two regions
    - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
    - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
  - cells of dermis
    - fibroblasts: produce collagen, elastin, and ground substance
    - mast cells: release histamines which mediate type I hypersensitivity
  - other components of dermis include: blood vessels, nerves, pilosebaceous units, and sweat glands
- **subcutaneous tissue** (i.e. hypodermis)
  - consists primarily of adipose cells, larger calibre vessels, nerves, and fascia

Epidermal Appendages

- epidermal in origin, can extend into the dermis; includes hair, nails, and cutaneous glands
- pilosebaceous unit = hair + hair follicle + sebaceous gland + arrector pili muscle

Cutaneous Glands

- **sebaceous gland:** part of pilosebaceous unit; produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface and are absent only in non-hair bearing areas (e.g. palms, soles, lips)
- **apocrine sweat gland:** apocrine duct empties into hair follicle above sebaceous gland
  - not part of pilosebaceous unit
  - found concentrated in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- **eccrine sweat gland:** not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds, and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

Skin Function

- **protection**
  - due to continuous recycling and avascularity of epidermis, as well as normal skin flora
  - barrier to UV radiation (melanin), mechanical/chemical insults (sensory/mechanoreceptors), pathogens (immune cells), and dehydration (lipid rich barrier)
- **thermal regulation**
  - insulation to maintain body temperature in cool environments via peripheral vasoconstriction, hair, and subcutaneous adipose tissue
  - dissipation of heat in warm environments via increased activity of sweat glands and increased blood flow within dermal vascular networks
- **sensation**
  - touch, pain, and temperature sensation
- **metabolic function**
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

Morphology

Primary Lesions

Definition

- a de-novo initial lesion that has not been altered by trauma or manipulation, and has not regressed

Table 1. Types of Primary Morphological Lesions

Profile	<1 cm Diameter	≥1 cm Diameter
Flat Lesion	Macule (e.g. freckle)	Patch (e.g. vitiligo)
Raised Superficial Lesion	Papule (e.g. wart)	Plaque (e.g. psoriasis)
Deep Palpable (Dermal or Subcutaneous) Lesion	Nodule (e.g. dermatofibroma)	Tumour (e.g. lipoma)
Elevated Fluid-Filled Lesion	Vesicle (e.g. HSV)	Bulla (e.g. bullous pemphigoid)



Describe a Lesion with SCALDA

Size and Surface area
Colour (e.g. hyperpigmented, hypopigmented, erythematous)
Arrangement (e.g. solitary, linear, reticulated, grouped, herpetiform)
Lesion morphology
Distribution (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)
Always check hair, nails, mucous membranes, and intertriginous areas

Secondary Lesions

Definition

- develop during the evolutionary process of skin disease, created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)

Types of Secondary Morphological Lesions

- **crust:** dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- **scale:** excess keratin (e.g. seborrheic dermatitis)
- **lichenification:** thickening of the skin and accentuation of normal skin markings (e.g. chronic AD)
- **fissure:** a linear slit-like cleavage of the skin
- **excoriation:** a scratch mark
- **erosion:** a disruption of the skin involving the epidermis alone; heals without scarring
- **ulcer:** a disruption of the skin that extends into the dermis or deeper; may heal with scarring
- **xerosis:** pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes (xerostomia)
- **atrophy:** histological decrease in size or number of cells or tissues, resulting in thinning or depression of the skin

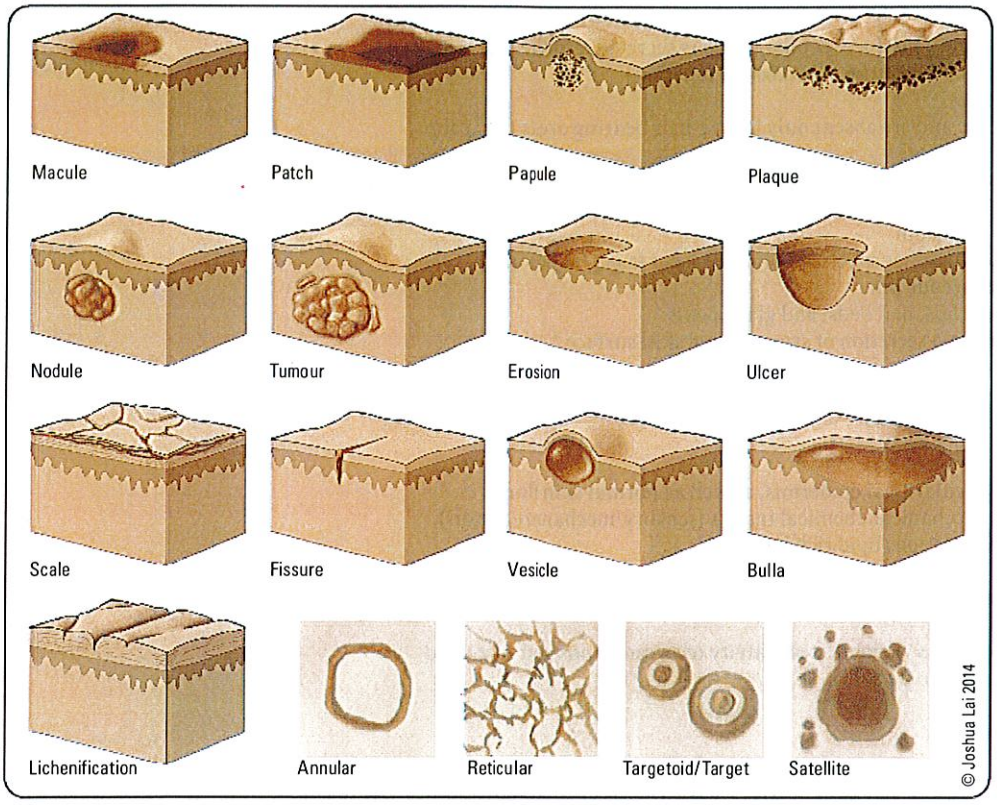


Figure 3. Examples of primary and secondary lesions

Other Morphological Terms

- **cyst**: an internally epithelial-lined structure containing semi-solid material or fluid
- pustule: an elevated lesion containing a collection of neutrophils (infectious or inflammatory in nature)
- **scar:** replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheal:** a special form of papule or plaque that is transient (<24 h) and blanchable, often with a halo and central clearing, formed by edema in the dermis (e.g. urticaria)
- **comedone:** a special collection of sebum and keratin
  - open comedone (blackhead)
  - closed comedone (whitehead)
- **petechiae:** pinpoint extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, <3 mm in size
- **purpura:** larger than petechiae, 3 mm-1 cm in size
- **ecchymosis (i.e. bruise):** larger than purpura, >1 cm in size
- **telangiectasia:** dilated superficial blood vessels; blanchable, reticulated, and of small calibre, can be associated with benign or malignant entities

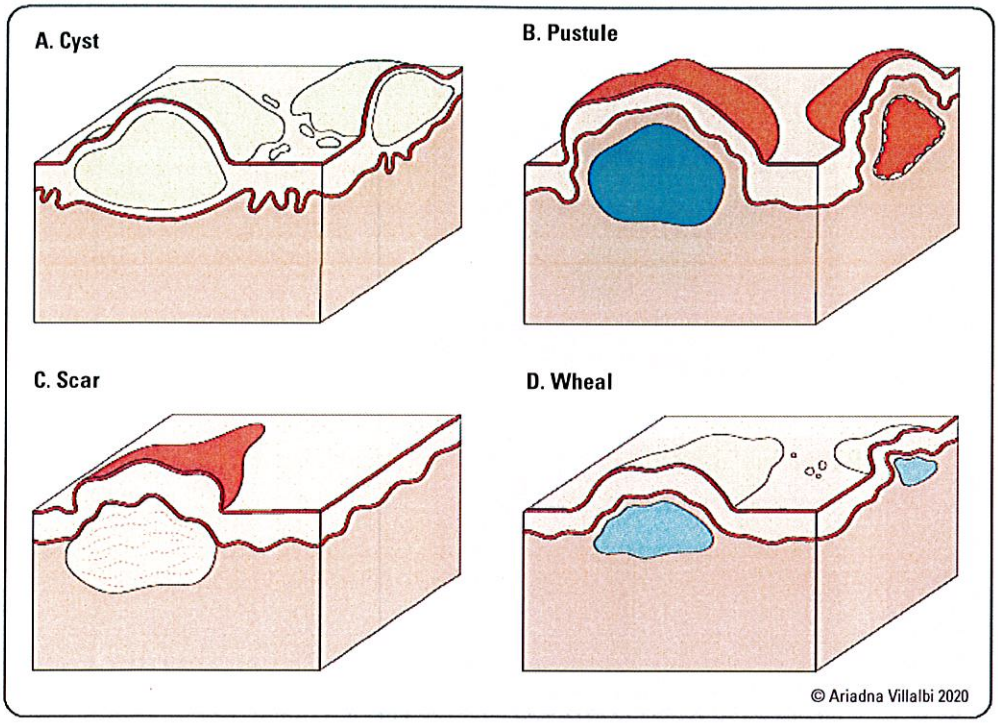


Figure 4. Examples of other morphological terms: cyst, pustule, scar, and wheal
Wolff K, Johnson R, Saavedra A, Fitzpatrick's Colour Atlas and Synopsis of Clinical Dermatology, Seventh Edition, copyright © 2020, Modified by Permission of McGraw-Hill Education

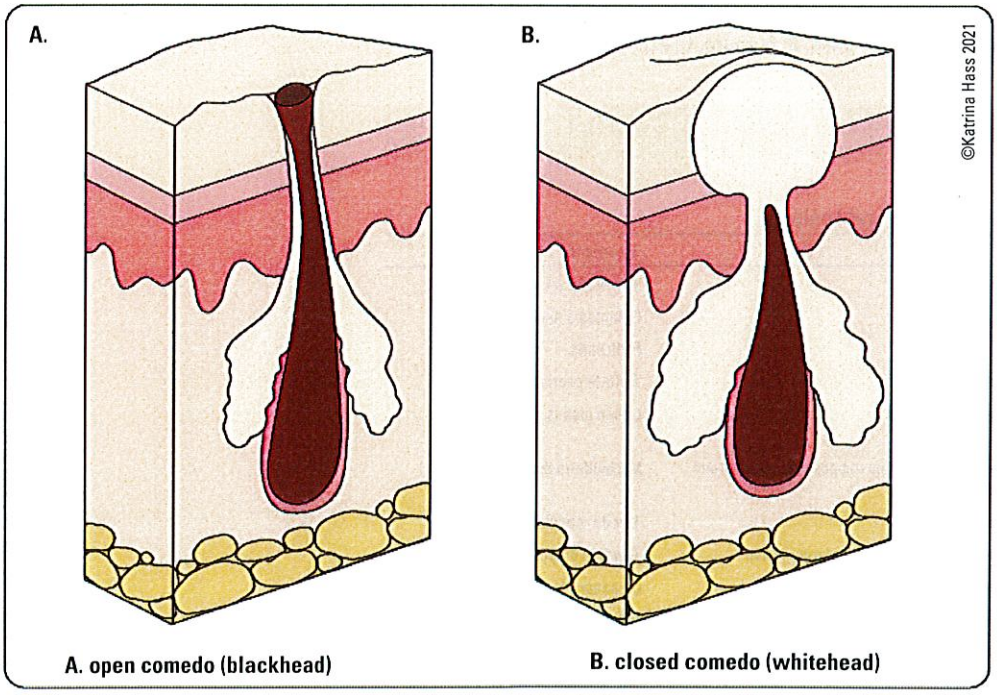


Figure 5. Examples of other morphological terms: open and closed comedone

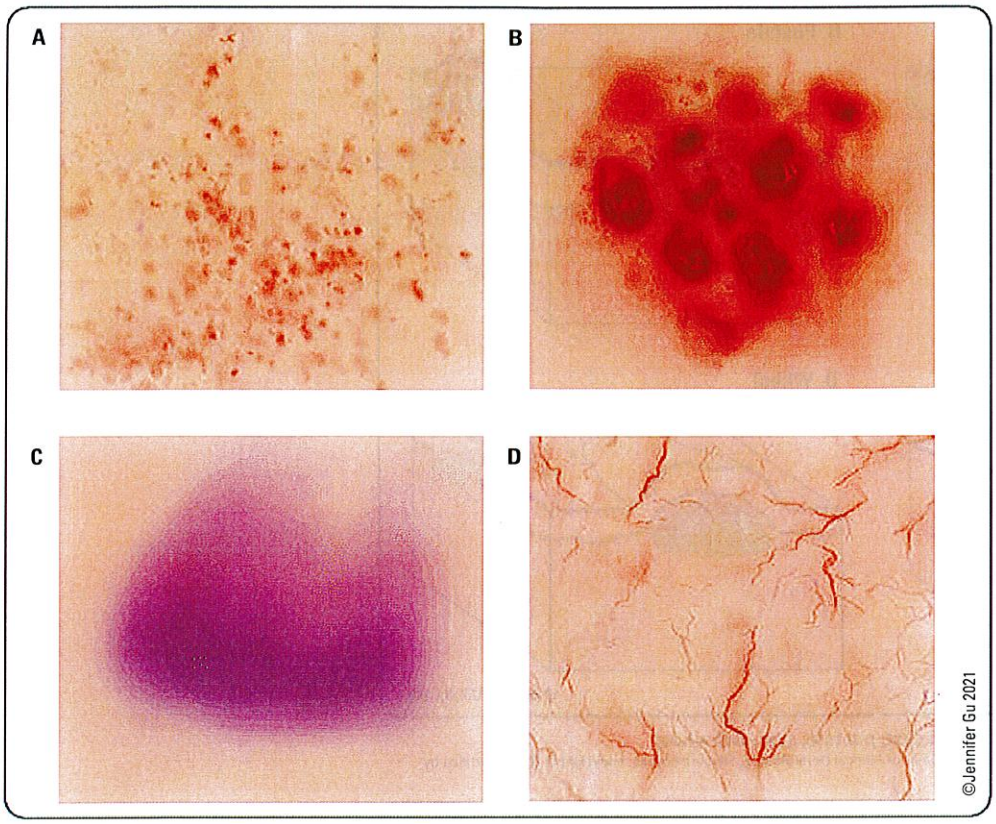


Figure 6. Examples of other morphological terms: A: petechiae, B: purpura, C: ecchymosis, and D: telangiectasia

Patterns and Distribution

Table 2. Patterns and Distribution of Morphological Lesions

Pattern or Distribution	Definition	Example
Acral	Relating to the hands and feet	Perniosis, secondary syphilis
Annular	Ring-shaped	Granuloma annulare
Follicular	Involving hair follicles	Folliculitis
Guttate	Lesions following a "drop-like" pattern	Guttate psoriasis
Koebner Phenomenon (i.e. isomorphic response)	Appearance of lesions at a site of skin injury	Lichen planus, psoriasis, vitiligo
Morbilliform	Literally means "measles-like," an eruption composed of macules and papules with truncal predominance	Morbilliform drug eruption
Reticular	Lesions following a "net-like" pattern	Livedo reticularis
Satellite	Small lesions scattered around the periphery of a larger lesion	Candida diaper dermatitis
Serpiginous	Lesions following a "snake-like" pattern	Cutaneous larva migrans
Target/Targetoid	Concentric ring lesions, like a bullseye	EM, urticaria, SJS/TEN

Other descriptive terms: discrete, clustered, linear, confluent, dermatitic, indurated (i.e. hard or firm)

Differential Diagnoses for Common Presentations

Table 3. Differential Diagnoses for Common Presentations

Lesion	Infectious	Inflammatory	Drug/Toxin	Miscellaneous
Brown Macule		Post-inflammatory hyperpigmentation	UV radiation, actinic/solar lentigo, freckle (i.e. ephelis)	Congenital: café-au-lait macule, congenital nevus, epidermal/junctional nevus Neoplasia: lentigo maligna, MM, pigmented BCC Other: melasma/chloasma (i.e. "mask of pregnancy")
Discrete Red Papule	Folliculitis Furuncle Scabies	Acne vulgaris Rosacea Psoriasis Urticaria	Bites/stings	Autoimmune: lichen planus Vascular: hemangioma, pyogenic granuloma Other: dermatofibroma, miliaria rubra

Table 3. Differential Diagnoses for Common Presentations

Lesion	Infectious	Inflammatory	Drug/Toxin	Miscellaneous
Red Scales	Pityriasis rosea Secondary syphilis Tinea	Dermatitis (atopic, contact, nummular, seborrheic) Discoid lupus Psoriasis	Gold	Autoimmune: lichen planus Neoplastic: mycosis fungoides
Vesicle	Cat scratch disease Impetigo Viral: HSV, HZV, VZV, Coxsackie virus Scabies	Acute contact dermatitis Dyshidrotic eczema		Other: dermatitis herpetiformis, porphyria cutanea tarda
Bulla	Bullous impetigo	Acute dermatitis EM, SLE, SJS/TEN	Fixed drug eruption SJS/TEN	Autoimmune: bullous pemphigoid, pemphigus vulgaris Other: dermatitis herpetiformis, porphyria cutanea tarda
Pustule	Candida Dermatophyte Impetigo Sepsis Varicella	Acne vulgaris Rosacea Dyshidrotic dermatitis Pustular folliculitis Pustular psoriasis Hidradenitis suppurativa	AGEP (usually secondary to drug reaction)	
Oral Ulcer	Aspergillosis CMV Coxsackie virus Cryptococcosis HSV/HZV HIV, TB, Syphilis	Allergic stomatitis EM Lichen planus Seronegative arthropathies, SLE Recurrent aphthous stomatitis Behçet's disease	Chemotherapy Radiation therapy SJS/TEN	Autoimmune: pemphigus vulgaris Congenital: XXY Hematologic: sickle cell disease Neoplasia: BCC, SCC
Skin Ulcer	Plague Syphilis TB Tularemia	RA, SLE, vasculitis UC, pyoderma gangrenosum		Autoimmune: necrobiosis lipoidica diabeticorum (e.g. DM) Congenital: XXY Hematologic: sickle cell disease Neoplasia: SCC Vascular: arterial, neurotrophic, pressure, venous, aphthous, leukoplakia, traumatic

Common Skin Lesions

Cysts

Table 4. Cysts

	Clinical Features	Pathophysiology	Epidemiology	Clinical Course	Management
Epidermal Cyst	Round, yellow/flesh-coloured, slow growing, mobile, firm, fluctuant, nodule, or tumour	Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris May be post-traumatic, rarely syndromic	Most common cutaneous cyst in youth-middle age	Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction Can increase in size and number over time	No treatment Elective excision
Pilar Cyst (i.e. Trichilemmal)	Multiple, hard, variable sized nodules under the scalp; lacks central punctum	Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin Idiopathic Post-trauma	2nd most common cutaneous cyst F>M, hereditary	Rupture causes pain and inflammation	No treatment Elective excision
Dermoid Cyst	Firm nodule most commonly found at lateral third of eyebrow or midline under nose	Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick-walled cyst filled with dense keratin	Rare	If nasal midline, risk of extension into CNS	No treatment Elective excision
Milium	1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead	Small epidermoid cyst, primarily arising from pluripotential cells in epidermal or adnexal epithelium Can be secondary to blistering, ulceration, trauma, TCS, atrophy, or cosmetic procedures	Any age 40-50% of infants	In newborns, spontaneously resolves in first 4 wk of life	No treatment Incision and expression of contents Electrodessication Topical retinoid therapy

GANGLION CYST: See Plastic Surgery PL27

Fibrous Lesions

DERMATOFIBROMA

Clinical Features

- firm dermal papule or nodule, skin-coloured to red-brown
- majority are asymptomatic but may be pruritic and/or tender
- sites: legs > arms > trunk
- dimple sign (i.e. Fitzpatrick's sign): lateral compression causes dimpling of the lesion

Pathophysiology
- benign tumour due to fibroblast proliferation in the dermis

Etiology
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibroma can be associated with SLE

Epidemiology
- adults, F>M

Differential Diagnosis
- dermatofibrosarcoma protuberans, melanoma

Investigations
- biopsy if diagnosis is uncertain

Management
- no treatment required
- excision if bothersome

SKIN TAGS

Clinical Features
- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

Pathophysiology
- benign outgrowth of skin

Epidemiology
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

Differential Diagnosis
- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, nevus lipomatosis superficialis

Management
- snip excision, electrodessication, cryosurgery

Hyperkeratotic Lesions

SEBORRHEIC KERATOSIS

Clinical Features
- i.e. 'wisdom spots,' 'age spots,' or 'barnacles of life'
- well-demarcated waxy papule/plaque with classic "stuck on" appearance
- occasionally pruritic
- over time lesions appear more warty, greasy, and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology
- very common benign epithelial tumour due to proliferation of keratinocytes and melanocytes

Epidemiology
- unusual <30 y/o
- M>F
- autosomal dominant inheritance
- Leser-Trelat sign: sudden appearance of seborrheic keratosis that can be associated with malignancy, commonly gastric adenocarcinomas

Differential Diagnosis
- melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented AK

Investigations
- biopsy only if diagnosis uncertain

Management
- none required, for cosmetic purposes only
- cryotherapy, electrodessication, shave excision

ACTINIC KERATOSES (SOLAR KERATOSES)
- see *Pre-Malignant Skin Conditions, D39*

KERATOACANTHOMA
- see *Malignant Skin Tumours, D40*

CORNS (HELOMATA)

Clinical Features
- firm papule with a central, translucent, cone-shaped, hard keratin core
- painful with direct pressure
- sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology
- localized hyperkeratosis induced by pressure on hands and feet

Epidemiology
- F>M, can be caused by chronic microtrauma

Differential Diagnosis
- calluses, plantar warts

Management
- relieve pressure with padding or alternate footwear, orthotics
- paring, topical salicylic acid, referral to podiatry



Corns vs. Warts vs. Calluses
- Corns have a whitish yellow central translucent keratinous core; painful with direct pressure; interruption of dermatoglyphics
- Warts bleed with paring and have a black speckled central appearance due to thrombosed capillaries; plantar warts destroy dermatoglyphics (epidermal ridges)
- Calluses have layers of yellowish keratin revealed with paring; there are no thrombosed capillaries or interruption of epidermal ridges



Keloids vs. Hypertrophic Scars

Keloids: extend beyond margins of original injury with claw-like extensions

Hypertrophic scars: confined to original margins of injury



DDx of Hyperpigmented Macules
- Purpura (e.g. solar, ASA, anticoagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

Keloids

Clinical Features
- firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for yr with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area, angle of mandible

Pathophysiology
- excessive deposition of randomly organized collagen fibres following trauma to skin

Epidemiology
- most common in Black patients, followed by those of Asian descent (predilection for darker skin)
- M=F, most commonly between ages 10-30

Management
- intralesional steroids
- silicone gel sheets

Pigmented Lesions

CONGENITAL NEVOMELANOCYTIC NEVI (CNN)

Clinical Features
- i.e. congenital hairy nevi
- sharply demarcated pigmented papule or plaque with regular borders ± coarse hairs
- classified by size: small (<1.5 cm), medium (M1: 1.5-10 cm, M2: >10-20 cm), large (L1: >20-30 cm, L2: >30-40 cm), giant (G1: >40-60 cm, G2: >60 cm)
- may be surrounded by smaller satellite nevi

Pathophysiology
- nevomelanocytes in epidermis (clusters) and dermis (strands)

Epidemiology
- present at birth or develops in early infancy to childhood
- malignant transformation is rare (1-5%) and more correlated with size of the lesion
- neurocutaneous melanosis can occur in giant CNN (melanocytes in the CNS)

Management
- take a baseline photo and observe lesion for change in shape, colour, or size out of proportion with growth
- surgical excision if suspicious, due to increased risk of melanoma
- MRI if suspicious for neurological involvement

Other Nevi
- Halo nevus: often appears as a typical nevus surrounded by a ring of depigmentation; common in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
- Blue nevus: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted



Other Nevi
Halo nevus: often appears as a typical nevus surrounded by a ring of depigmentation; common in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
Blue nevus: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted

OTHER CONGENITAL PIGMENTED LESIONS

Table 5. Comparison of Other Congenital Pigmented Lesions

	Clinical Features	Pathophysiology	Epidemiology	Differential Diagnosis	Clinical Course and Management
Café-au-lait Macule	Flat light-brown lesions with smooth or jagged borders	Areas of increased melanogenesis	Six or more is suggestive of neurofibromatosis type I Also associated with McCune-Albright syndrome	Flat congenital melanocytic nevus, speckled lentiginous nevus	Enlarge in proportion to the child No effective treatment
Speckled Lentiginous Nevus (i.e. nevus spilus)	Brown pigmented macular background (café-au-lait macule-like) with dark macular or papular speckles	Increased melanocyte concentration	Risk of melanoma similar to that of a CNN of the same size	Café-au-lait macule, agminated lentigines, Becker's nevus	Usually the light macular background is present at birth and speckles develop over time Management is similar to that of CNNs
Dermal Melanocytosis (historically known as Mongolian Spot)	Congenital grey-blue solitary or grouped macules commonly on lumbosacral area	Ectopic melanocytes in dermis	99% occurs in Asian and Indigenous infants	Ecchymosis	Usually fades in early childhood but may persist into adulthood
Xeroderma Pigmentosum	Extreme sensitivity to UV light, redness and blistering, xerosis, and changes in skin colour Typically affects the eyes and sun-exposed areas; may affect nervous system	Involves mutations in genes responsible for DNA repair (e.g. nucleotide excision repair genes)	More common in Japan, North Africa, and the Middle East	Freckles, Rothmund-Thomson syndrome, and porphyrin disease	Prevention by avoiding sun exposure (damage is irreversible) Reduce incidence of cancer using anticancer drugs (e.g. isotretinoin, fluorouracil) in adults only

ACQUIRED NEVOMELANOCYTIC NEVI (NMN)

Clinical Features
- common mole: well circumscribed, round, uniformly pigmented macules/papules <1.5 cm
- average number of moles per person: 18-40
- three stages of evolution: junctional NMN, compound NMN, and dermal NMN

Table 6. Evolution of Acquired Nevomelanocytic Nevi

Type	Age of Onset	Clinical Feature	Histology
Junctional	Childhood Majority progress to compound nevus	Flat, regularly bordered, uniformly tan-dark brown, sharply demarcated macule	Melanocytes at dermal-epidermal junction above basement membrane
Compound	Any age	Domed, regularly bordered, smooth, round, tan-dark brown papule Face, trunk, extremities, scalp NOT found on palms or soles	Melanocytes at dermal-epidermal junction; migration into dermis
Dermal	Adults	Soft, dome-shaped, skin-coloured to tan/brown papules or nodules Sites: face, neck	Melanocytes exclusively in dermis

Management
- new or changing pigmented lesions should be evaluated for atypical features which could indicate a melanoma
- excisional biopsy should be considered if the lesion demonstrates rapid change, asymmetry, varied colours, irregular borders, and persistent pain or bleeding

OTHER ACQUIRED PIGMENTED LESIONS

Table 7. Comparison of Other Acquired Pigmented Lesions

	Clinical Features	Pathophysiology	Epidemiology	Differential Diagnosis	Clinical Course and Management
Atypical Nevus (Dysplastic Nevus)	Variegated macule/papule with irregular distinct melanocytes in the basal layer	Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests	Five atypical nevi increase risk for melanoma Numerous dysplastic nevi may be part of familial atypical mole and melanoma syndrome Risk factor: family history	Melanoma	Follow with baseline photographs for changes Excisional biopsy if lesion changing or highly atypical Close surveillance with whole body skin examination
Ephelides (i.e. Freckles)	Small (<5 mm) well-demarcated light brown macules Sites: sun-exposed skin	Increased melanin within basal layer keratinocytes secondary to sun exposure	Skin phototypes I-II most commonly	Junctional nevi Juvenile lentigines	Multiply and darken with sun exposure, fade in winter No treatment required Sunscreen and sun avoidance may prevent the appearance of new freckles
Solar Lentigo (i.e. Liver Spot)	Well-demarcated brown/black macules Sites: sun-exposed skin	Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure	Most common in white individuals >40 yr Skin phototypes I-III most commonly	Lentigo maligna, seborrheic keratosis, pigmented AK	Laser therapy, cryotherapy
Becker's Nevus	Hairy, light brown macule/patch with a papular verrucous surface Sites: trunk and shoulders Onset in teen yr	Pigmented hamartoma with increased melanin in basal cells	M>F Often becomes noticeable at puberty	Hairy congenital melanocytic nevus	Hair growth follows onset of pigmentation Cosmetic management (usually too large to remove)
Melasma	Symmetrical hyperpigmentation on sun-exposed areas of face (forehead, upper lip, cheeks, chin)	Increase in number and activity of melanocytes Associated with estrogen and progesterone	F>M Common in pregnancy and women taking OCP or HRT Can occur with mild endocrine disturbances, antiepileptic medications, and other photosensitizing drugs Risk factors: sun exposure, dark skin tone	Post-inflammatory hyperpigmentation	Treatment: tinted mineral-based sunscreen hydroquinone, azelaic acid, retinoic acid, TCS, combination creams, destructive modalities (chemical peels), camouflage make-up. Very difficult to treat (can take months to improve)

Vascular Lesions

Table 8. Vascular Tumours Compared to Vascular Malformations

	Vascular Tumours	Vascular Malformations
Definition	Endothelial hyperplasia	Congenital malformation with normal endothelial turnover
Presence at Birth	Usually postnatal	100% at birth (not always obvious)
M:F	1:3-5	1:1
Natural History	Phases Proliferating Involuting Involuted	Proportionate growth (can expand)

HEMANGIOMAS

Clinical Features

- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a "bag of worms" when palpated

Pathophysiology

- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

Table 9. Vascular Tumours

	Clinical Features	Pathophysiology	Epidemiology	Clinical Course	Management
Hemangioma of Infancy	Hot, firm, red to blue plaques or tumours	Benign vascular proliferation of endothelial lining	Appears shortly after birth; rarely congenital	Appears shortly after birth, increases in size over mo, then regresses 50% of lesions resolve spontaneously by 5 yr	10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis Consider treatment if not gone by school age; topical timolol, propranolol; systemic corticosteroids; laser treatment; surgery Provide early specialist referral or treatment in infants with high-risk hemangiomas
Spider Angioma (i.e. Campbell Telangiectasia)	Central red arteriole with slender branches, blanchable	Can be associated with hyperestrogenic state (e.g. in liver disease, pregnancy, OCP) but more often is not	Any age	Increase in number over time	Reassurance Electrodesiccation or laser surgery if patient wishes
Cherry Angioma (i.e. Campbell De Morgan Spot)	Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm Site: trunk Less friable compared to pyogenic granulomas	Benign vascular neoplasm	>30 y/o	Lesions do not fade in time Lesions bleed infrequently	Usually no treatment needed Laser or electrocautery for small lesions Excision of large lesions if necessary
Pyogenic Granuloma	Bright red, dome-shaped sessile or pedunculated friable nodule Sites: fingers, lips, mouth, trunk, toes DDx: glomus tumour, nodular MM, SCC, nodular BCC	Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia	<30 y/o	Lesion grows rapidly over wk-mo, then stabilizes Lesion may persist indefinitely if untreated	Surgical excision with histologic examination Electrocautery; laser; cryotherapy

VASCULAR MALFORMATIONS

Table 10. Vascular Malformations

Type	Clinical Features	Pathophysiology	Management
Nevus Flammeus (i.e. Port-wine Stain)	Red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline Most common site: nape of neck Never spontaneously regresses but grows in proportion to the child	Congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution)	Laser or make-up
Nevus Simplex (i.e. Salmon Patch)	Pink-red irregular patches Midline macule on glabella known as "Angel Kiss;" in the nuchal region known as "Stork Bites" Present in 1/3 of newborns Majority regress spontaneously	Congenital dilation of dermal capillaries	No treatment required



Pyogenic granuloma is a misnomer: it is neither pyogenic nor granulomatous



Venous Lake: benign blue or violaceous papular lesion occurring on the face, lips, and ears due to dilation of a venule. Distinguished from malignant pigmented lesions through diascopy, as compression blanches the lesion



A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion

Lipoma

Clinical Features
- single or multiple non-tender subcutaneous tumours that are soft and mobile
- occurs most frequently on the trunk and extremities, but can be anywhere on the body

Pathophysiology
- adipocytes enclosed in a fibrous capsule

Epidemiology
- often solitary or few in number, if multiple can be associated with rare syndromes

Differential Diagnosis
- angiolipoma, liposarcoma

Investigations
- biopsy only if atypical features (painful, rapid growth, firm)
- ultrasound

Management
- reassurance
- excision or liposuction only if desired for cosmetic purposes

Xanthoma

Clinical Features
- localized lipid deposits that manifest as papules, plaques, or nodules in the skin
- several variants: eruptive xanthoma (1-5 mm erythematous-to-yellow papules); tuberous xanthoma (≤3 cm yellow-to-orange or erythematous papules or nodules); tendinous xanthoma (smooth, firm, mobile, skin-coloured nodules); plane xanthoma (soft, yellow, thin plaques)

Pathophysiology
- xanthoma associated with hyperlipidemia: formed from macrophages due to excessive uptake and oxidation of low density lipoprotein particles
- xanthoma not associated with hyperlipidemia (e.g. plane xanthoma): develop associated with monoclonal gammopathy, multiple myeloma, and other hematologic diseases; immune complexes form between antibodies and lipoproteins leading to lipid accumulation in macrophages
- xanthoma not associated with hyperlipidemia (e.g. verruciform xanthoma): may be response to immune reaction to local trauma or inflammation

Epidemiology
- often present in adulthood (except xanthoma associated with hypercholesterolemia, in which xanthoma develops before 10 y/o)
- occur in both males and females, no sex predilection

Differential Diagnosis
- xanthelasma: sebaceous hyperplasia, juvenile xanthogranuloma, syringoma, nodular BCC
- plane xanthoma: necrobiotic xanthogranuloma
- eruptive xanthoma: generalized granuloma annulare, xanthoma disseminatum
- tendinous xanthoma and tuberous xanthoma: other nodular eruptions over joints and tendons (e.g. rheumatoid nodules, gouty tophi, subcutaneous granuloma annulare, erythema elevatum diutinum)
- verrucous xanthoma: condylomata, oral papillomas, verrucous carcinoma, SCC

Investigations
- biopsy (shave, punch, or excisional)
- fasting lipid panel (except for xanthomas not associated with hyperlipidemia, e.g. verruciform xanthomas)

Management
- typically asymptomatic and therefore do not require treatment unless for cosmetic reasons
- options include surgical excision, cryotherapy, trichloroacetic acid 70% chemical peels, or Er:YAG or Nd-YAG lasers
- pharmacologic treatment of dyslipidemia usually indicated

Treatment of Acne Scars
Tretinoin creams
Glycolic acid
Chemical peels for superficial scars
Injectable fillers (collagen, hyaluronic acid) for pitted scars
Laser

Topical Benzoyl Peroxide for Acne
Cochrane DB Syst Rev 2020:CD011154
Purpose: Determine the efficacy and safety of topical benzoyl peroxide for the treatment of acne.
Methods: Systematic review of 120 clinical trials (n=29,592) comparing the use of topical benzoyl peroxide for the treatment of clinically-diagnosed acne as compared to placebo or other topical medication.
Results: Benzoyl peroxide was more effective than placebo or no treatment in participant global self-assessment of acne improvement (RR 1.27; 95% CI, 1.12-1.45; low-certainty evidence). Little to no difference existed between benzoyl peroxide and adapalene (RR 0.99; 95% CI, 0.90-1.10) or clindamycin (RR 0.95; 95% CI, 0.68-1.34). Withdrawal due to adverse effects was higher with benzoyl peroxide than with no treatment, or placebo (RR 2.13; 95% CI, 1.55-2.93, low-certainty evidence) and the most common cited adverse effects included erythema, pruritus, and skin burning.
Conclusion: Benzoyl peroxide as monotherapy or add-on therapy may be more effective in the treatment of acne when compared to placebo, but not when compared to adapalene or clindamycin.

Acneiform Eruptions

Acne Vulgaris/Common Acne

Clinical Features
- a common inflammatory pilosebaceous disease categorized according to severity
  - Type I: comedonal, sparse, no scarring
  - Type II: comedonal, papular, moderate ± little scarring
  - Type III: comedonal, papular, and pustular, with scarring
  - Type IV: nodulocystic acne, risk of severe scarring
- sites of predilection: face, neck, upper chest, and back

Pathophysiology
- hyperkeratinization at the follicular ostia (opening) blocks the secretion of sebum leading to the formation of microcomedones
- androgens promote excess sebum production
- *Cutibacterium acnes* (*C. acnes*) metabolizes sebum to free fatty acids and produces pro-inflammatory mediators

Epidemiology
- age of onset typically in puberty (10-17 yr in females, 14-19 yr in males)
- in prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
- incidence decreases in adulthood
- genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

Differential Diagnosis
- folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Table 11. Management of Acne

Compound/Drug Class	Product Names	Notes
MILD ACNE: OTC Topical Therapies		
Benzoyl peroxide (BPO)	Solugel®, Benzac®, Desquam®, Fostex®, CeraVe Acne Foaming Cleanser®	Helps prevent *Propionibacterium acnes* (*P. acnes*) resistance, is a bactericidal agent (targets *P. acnes*), and is comedolytic
Salicylic acid	CeraVe SA Cleanser	Used when patients cannot tolerate a topical retinoid due to skin irritation
MILD ACNE: Prescription Topical Therapies		
Antimicrobials	clindamycin (Dalacin T®), erythromycin	High rate of resistance when used as monotherapy
Retinoids	vitamin A acid (tretinoin, Stieva-A®, Retin A Micro®), adapalene (Differin®), ARAZLO® (tazarotene) Lotion 0.045%, AKLIEF® (trifarotene) Cream	Backbone of topical acne therapy All regimens should include a retinoid unless patient cannot tolerate
Combination products	clindamycin and BPO (Clindoxyl®) clindamycin and BPO (Benzaclin®) TactuPump® (adapalene and BPO) clindamycin and tretinoin (Biacna®)	Allows for greater adherence and efficacy Combines different mechanisms of action to increase efficacy and maximize tolerability
MODERATE ACNE		
Tetracycline/Minocycline/ Doxycycline	Sumycin®/Minocin®/Vibramycin®	Use caution with regard to drug interactions: do not use with isotretinoin Sun sensitivity Antibiotics require 3 mo of use before assessing efficacy
Cyproterone acetate-ethinyl estradiol	Diane-35®	After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance
Spironolactone	Aldactone®	May cause hyperkalemia if concurrent renal dx Black box warning for breast cancer
SEVERE ACNE		
Isotretinoin	Accutane®, Clarus®, Epuris®	See *Table 29, D53* for full side effect profile Most adverse effects are temporary and will resolve when the drug is discontinued Baseline lipid profile (risk of hypertriglyceridemia), LFTs and β-hCG before treatment May transiently exacerbate acne before patient sees improvement Refractory cases may require multiple courses of isotretinoin

Perioral Dermatitis

Clinical Features

- discrete erythematous papulopustular eruptions that often become confluent, forming inflammatory plaques on perioral, perinasal, and/or periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips

Epidemiology

- 15-40 y/o, occasionally in younger children
- predominantly females

Differential Diagnosis

- contact dermatitis, rosacea, acne vulgaris

Management

- avoid all TCS, avoid ointment/oil-based products, stop all cosmetic products
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: doxycycline (utilized for its anti-inflammatory properties)
- occasional use of a topical calcineurin inhibitor cream (i.e. pimecrolimus)

Rosacea

Clinical Features

- dome-shaped inflammatory papules ± pustules
- flushing, non-transient erythema, and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks, and chin; rarely on scalp, neck, and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, spices
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration, and lymphedema in the skin can develop



Acne Myths Debunked

- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized fatty acids, not dirt
- Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator



Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo)



Acne Exacerbating Factors

- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
- Topical agents: TCS, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress



A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone



Intralesional Injections

Intralesional steroids are effective in the cosmetic treatment of individual acne nodules



Isotretinoin and Pregnancy

- Use of isotretinoin during pregnancy is associated with spontaneous abortion and major birth defects such as facial dysmorphism and cognitive impairment
- Pregnancy should be ruled out before starting isotretinoin
- Patients should use two forms of contraception while on isotretinoin



Important Controversies Associated with Isotretinoin Therapy for Acne

Am J Clin Dermatol 2013;14:71-76

Main Points:

1. The evidence on whether isotretinoin causes depression and suicide is inconsistent; however, numerous controlled studies have shown an improvement in anxiety and depression scores in those taking isotretinoin.
2. There is no association between IBD and isotretinoin use. Only one study showed a significantly increased risk of UC. When considering using isotretinoin in a patient with IBD or with a strong family history, consider involving a gastroenterologist.

- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

Pathophysiology
- unknown

Epidemiology
- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 y/o; F>M

Differential Diagnosis
- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

Management
- year round sunscreen
- avoid common triggers (e.g. alcohol, spicy food)
- telangiectasia: treated by vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy (CO_2, argon, Nd:YAG)

Table 12. Specific Rosacea Treatments

First Line	Second Line	Third Line
Oral tetracyclines Topical metronidazole Oral erythromycin (250-500 mg PO bid) Topical azelaic acid Topical ivermectin	Topical clindamycin Oral metronidazole	Oral retinoids

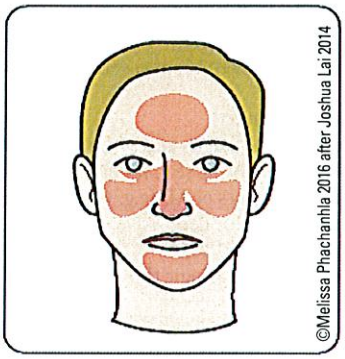


Figure 7. Rosacea distribution

Rosacea can be differentiated from acne by the absence of comedones, a predilection for the central face, and symptoms of flushing

Guidelines for the Diagnosis of Rosacea
J Drugs Dermatol 2012;11(6):725-730
Presence of one or more of the following primary features:
- Flushing (transient erythema)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

May include one or more of the following secondary features:
- Burning or stinging
- Dry appearance
- Edema
- Phymatous changes
- Ocular manifestations
- Peripheral location

Dermatitis (Eczema)

Definition
- inflammation of the skin

Clinical Features
- poorly demarcated erythematous plaques
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting, excoriations
- chronic dermatitis: lichenification, xerosis, fissuring

Asteatotic Dermatitis

Clinical Features
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (i.e. "winter itch") but starts in the fall
- shins predominate, looks like a "dried river bed"

Management
- skin rehydration with moisturizing routine (products with urea) ± TCS

Emollients and Moisturisers for Eczema
Cochrane DB Syst Rev 2017:CD012119
Purpose: To review the effects of moisturizers for eczema.
Methods: This review included 77 RCTs (n=6603) published prior to December 2015 on the effects of moisturizer on eczema.
Results: Moisturizers were more effective at reducing patient-reported eczema (RR 2.46; 95% CI, 1.16 to 5.23; low-quality evidence), itch (SMD -1.10; 95% CI, -1.83 to -0.38), investigator-assessed disease severity scores (SMD -1.04; 95% CI, -1.57 to -0.51; high-quality evidence), and flares (RR 0.33; 95% CI, 0.17 to 0.62; moderate-quality evidence), with no effect on adverse events (RR 1.03; 95% CI, 0.82 to 1.30; moderate-quality evidence).
Conclusion: Moisturizers are beneficial for eczema symptoms and severity. Greater benefits are observed when combined with active treatments. Evidence does not support the use of one moisturizer over another.

Atopic Dermatitis

Clinical Features
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution depends on age
- inflammation, lichenification, and excoriations are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with: keratosis pilaris (hyperkeratosis of hair follicles, "chicken skin"), xerosis, occupational hand dryness
- associated with severe or poorly controlled psychosocial distress and psychiatric comorbidities

Epidemiology
- frequently affects infants, children, and young adults
- 10-20% of children <5 yr in developed countries are affected
- associated with personal or family history of atopy (asthma, allergic rhinitis), anaphylaxis, eosinophilia
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

Pathophysiology
- a T-cell driven inflammatory process with epidermal barrier dysfunction

Triggers for Atopic Dermatitis
- Irritants (fragrance, detergents, solvents, clothing, water hardness)
- Contact allergens
- Inappropriate bathing habits (e.g. long hot showers)
- Sweating
- Microbes (e.g. *S. aureus*)
- Stress

Investigations
- clinical diagnosis
- consider: skin biopsy, serum IgE levels, patch testing if allergic contact dermatitis is suspected

Management
- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcomes (e.g. fewer flare-ups, modified course of disease) if diagnosis made early
- avoid triggers of AD (e.g. wool, fragrance, heat, etc.)
- be vigilant for depressive symptoms and the possible need for psychiatric referral, especially among those with severe disease
- non-pharmacologic therapy
  - moisturizers
    - apply liberally and reapply at least daily
    - bathe in plain warm water for a short period of time once daily followed by lightly, but not completely, drying the skin with a towel; immediately apply topical agents or moisturizers after this
  - use fragrance-free hypoallergenic non-soap cleansers
- pharmacologic therapy
  - topical corticosteroids
    - effective in reducing acute and chronic symptoms as well as prevention of flares
    - choice of steroid potency depends on age, body site, short vs. long-term use
    - apply one adult fingertip unit (0.5 g) to an area the size of two adult palms bid for at least 14 days for acute flares
    - most common local side effects: skin atrophy, purpura, telangiectasia, striae, and acneiform eruption
    - rare local side effects: hypopigmentation (more commonly seen in patients of colour, especially with higher potency TCS), hypertrichosis
  - topical calcineurin inhibitors
    - tacrolimus 0.03%, 0.1% (Protopic®) and pimecrolimus 1% (Elidel®)
    - can be used as acute treatments and as steroid-sparing agents in the long-term
    - advantages over long-term corticosteroid use: no skin atrophy; safe for sensitive areas such as the face and neck
    - apply bid for acute flares, and 2-3x/wk to recurrent sites to prevent relapses
    - local side effects: stinging, burning, cost
  - topical PDE-4 inhibitors
    - crisaborole (Eucrisa®)
  - topical small molecules
    - ruxolitinib (JAK-1/2 inhibitor) (OpzeluraTM)
  - oral small molecules
    - upadacitinib (JAK-1 inhibitor) (Rinvoq®)
    - abrocitinib (JAK-1 inhibitor) (Cibinqo®)
  - biologics
    - dupilumab (anti-IL 4/13) (Dupixent®)
    - tralokinumab (anti-IL 13) (Adtralza®)

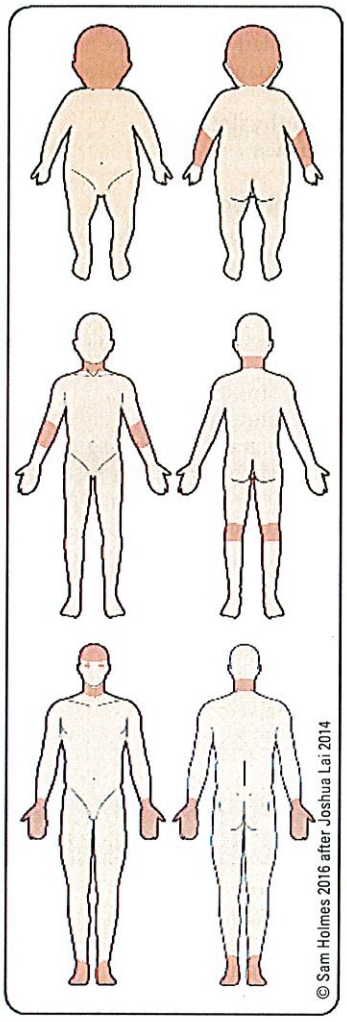


Figure 8. AD distribution
The typical distribution of AD in infants <6 mo (top), children >18 mo (middle), and adults ≥18 yr (bottom)

Complications
- infections
  - treatment of infections:
    - topical mupirocin, ozenoxacin, or fusidic acid (Canada only, not available in US)
    - oral antibiotics (e.g. cloxacillin, cephalexin) for widespread S. aureus infections

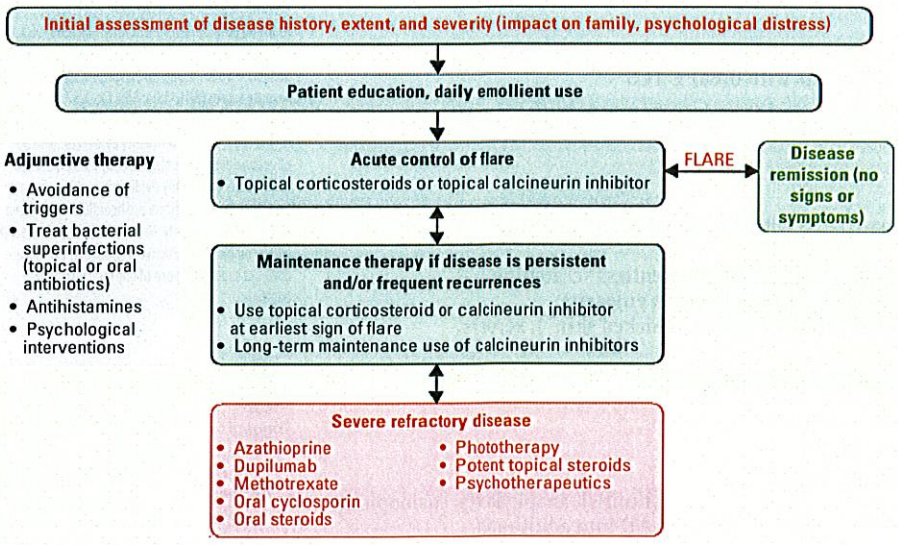


Figure 9. Atopic dermatitis treatment algorithm
Adapted from: Ellis C, et al. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. Br J Dermatol 2003;148(Suppl 63):3-10

Contact Dermatitis

Clinical Features
- cutaneous inflammation caused by an external agent(s)

Table 13. Contact Dermatitis

	Irritant Contact Dermatitis	Allergic Contact Dermatitis
Mechanism of Reaction	Toxic injury to skin; non-immune mechanism	Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2)
Type of Reaction	Erythema, dryness, fine scale, burning Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure) Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common	Erythema with a papulovesicular eruption, swelling, pruritus
Frequency	Majority; will occur in anyone given sufficient concentration of irritants	Minority; patient acquires susceptibility to allergen that persists indefinitely
Distribution	Hands are the most common site	Areas exposed to allergen
Examples	Soaps, weak alkali, detergents, organic solvents, alcohol, oils	Many allergens are irritants, so may coincide with irritant dermatitis Nickel Tattoos
Management	Avoidance of irritants Barrier moisturizers Topical/oral steroids	Patch testing to determine specific allergen Avoid allergen and its cross-reactants TCS bid prn Systemic steroids prn if extensive

Dyshidrotic Dermatitis

Clinical Features
- "tapioca pudding" papulovesicular or bullous dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infections common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

Pathophysiology
- unknown
- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate flares

Management
- topical: high potency TCS with plastic cling wrap occlusion to increase penetration
- systemic
  - prednisone in severe cases
  - alitretinoin (Toctino®) for all types of chronic hand dermatitis, including dyshidrotic dermatitis
  - antibiotics for secondary *S. aureus* infection

Nummular Dermatitis

Clinical Features
- nummular (coin-shaped), pruritic, dry, scaly, erythematous plaques
- secondary infection common

Pathophysiology
- little is known, but it is often accompanied by xerosis, which results from a dysfunction of the epidermal lipid barrier; this in turn can allow permeation of environmental agents, which can induce an allergic or irritant response

Management
- moisturization
- mid-high potency TCS ointment bid

Seborrheic Dermatitis

Clinical Features
- greasy, erythematous, yellow, scaling, papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: "cradle cap"

- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, nasolabial folds, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

Pathophysiology
- possible etiologic association with *Malassezia spp.* (yeast)

Epidemiology
- common in infants, adolescents, and males
- increased incidence and severity in immunocompromised patients and Parkinson's disease
- in adults can cause dandruff (pityriasis sicca)
- can overlap with psoriasis

Management
- face: ketoconazole (Ketoderm) cream bid prn and/or mild steroid cream bid prn
- scalp: ketoconazole 2% shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Dercos Anti-Dandruff Shampoo® or Head and Shoulders Clinical Strength®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

Stasis Dermatitis

Clinical Features
- erythematous, scaly, pruritic plaques on lower legs, particularly the medial ankle
- brown hemosiderin deposition, woody fibrosis, and lipodermatosclerosis in late stages
- usually bilateral, accompanied by swelling, oozing, crusting, may have accompanying varicosities

Pathophysiology
- chronic venous insufficiency leads to venous stasis
- surrounding soft tissue inflammation and fibrosis results

Investigations
- Doppler if suspicious for DVT, other vascular studies (e.g. venous duplex, ankle-brachial index)
- swab for bacterial culture if there is crusting

Management
- compression stockings are the most important therapy (if no peripheral arterial disease)
- rest and elevate legs
- moisturizer daily after shower to treat xerosis
- mid-high potency TCS to control inflammation

Complications
- ulceration (common at medial malleolus), secondary bacterial infections

Lichen Simplex Chronicus

Clinical Features
- well-defined plaque(s) of lichenified skin with increased pruritic skin markings ± excoriations
- common sites: neck, scalp, extremities, urogenital area
- often seen in patients with atopy, anxiety disorders, nonspecific emotional stress, among other conditions

Pathophysiology
- skin hyperexcitable to itch, resulting in continued rubbing/scratching of skin
- eventually lichenification occurs

Investigations
- histopathology/biopsy confirms diagnosis if clinical diagnosis uncertain
- if patient has generalized pruritus, rule out systemic cause: CBC with differential count, transaminases, bilirubin, ferritin, renal and thyroid function tests, TSH, glucose, SPEP
- CXR if lymphoma suspected

Management
- antipruritics (e.g. topical pramoxine hydrochloride, topical or intralesional steroids)

Papulosquamous Diseases

Lichen Planus

Clinical Features
- acute or chronic inflammation of skin or mucous membranes
- morphology: pruritic, well-demarcated, violaceous, polygonal, flat-topped papules and plaques
- common sites: wrists, nails, scalp, mucous membranes in 60% (mouth, vulva, glans)
- distribution: symmetrical and bilateral
- Wickham's striae: lacy, whitish reticular network mostly seen on oral mucosa; pathognomonic but may not be present
- other mucous membrane lesions: milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging, pterygium formation, complete dystrophy
- scalp: known as lichen planopilaris, scarring alopecia with perifollicular hyperkeratosis and erythema
- usually resolves spontaneously but may last for wk, mo, or yr
- rarely associated with hepatitis C
- Koebner phenomenon

The 6 Ps of Lichen Planus
Purple
Pruritic
Polygonal
Peripheral
Papules
Penis (i.e. mucosa)

Pathophysiology
- immune-mediated, antigen unknown
- lymphocyte activation leads to keratinocyte apoptosis

Epidemiology
- 1%, 30-60 yr, F>M

Investigations
- consider a skin biopsy
- hepatitis C serology if patient has risk factors

Management
- topical or intralesional steroids
- short courses of oral prednisone (rarely)
- phototherapy, oral retinoids, or systemic immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine) for extensive or recalcitrant cases

Pityriasis Rosea

Clinical Features
- acute, self-limiting eruption characterized by red or flesh-coloured oval plaques/patches with central scale that does not extend to edge of lesion
- lesions in darker skin tones may appear dusky violet or red-brown, and leave lingering hypo-/hyperpigmentation after the eruption clears
- long axis of lesions follows skin tension lines (i.e. Langer lines) parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a "herald" patch which precedes other lesions by 1-2 wk
- common sites: trunk, proximal aspects of arms and legs

Pathophysiology
- suspected HHV-7 or HHV-6 reactivation

Investigations
- none required

Management
- none required; clears spontaneously in 6-12 wk
- symptomatic: topical corticosteroids if pruritic, cool compresses, emollients

Skin Treatments for Chronic Plaque Psoriasis
Cochrane DB Syst Rev 2013:CD005028
Purpose: To review the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis.
Methods: This review identified RCTs comparing active topical treatments to either placebo or vitamin D analogues (used alone or in combination) in people with chronic plaque psoriasis.
Results: 170 studies including a total of 34808 participants were included in this review.
Conclusion: Both topical corticosteroids and vitamin D analogues were effective in treating chronic plaque psoriasis of the body. Corticosteroids showed benefits over vitamin D analogues in treating chronic plaque psoriasis of the scalp. Treatments combining vitamin D analogues and topical corticosteroids were more effective than using either vitamin D analogues or corticosteroids alone. Vitamin D analogues did result in more local adverse events than topical corticosteroids, the most common event being skin irritation or burning. People were more likely to discontinue using vitamin D analogues than topical corticosteroids.

Psoriasis

Classification
1. plaque psoriasis 2. guttate psoriasis 3. erythrodermic psoriasis
4. pustular psoriasis 5. inverse psoriasis

Pathophysiology
- not fully understood, genetic and immunologic factors
- shortened keratinocyte cell cycle correlates with Th1- and Th17-mediated inflammatory response

Epidemiology
- 1.5-2%, M=F
- all ages: peaks of onset: 20-39 yr and 50-60 yr
- polygenic inheritance: 8% with one affected parent, 41% with both parents affected
- risk factors: smoking, obesity, alcohol, drugs, infections, physical trauma (Koebner phenomenon)

Differential Diagnosis
- mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea corporis, nummular dermatitis, contact dermatitis, lichen planus, secondary syphilis, DLE

Investigations
- none required; biopsy if atypical presentation

PLAQUE PSORIASIS

Clinical Features
- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun)
- Auspitz sign: pinpoint bleeding observed when scale is removed
- common sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

Management
- depends on severity of disease, as defined by BSA affected or PASI
- mild (BSA <3%, PASI <3)
  - first line treatment includes TCS ± topical vitamin D analogue combination
  - topical retinoid ± TCS combination tends to be less tolerated than first line therapies
  - emollients
  - roflumilast
  - anthralin and tar are rarely used
  - phototherapy or systemic treatment may be necessary if the lesions are scattered or in difficult-to-treat areas (e.g. palms, soles, scalp, and genitals)
- moderate (BSA 3-10%, PASI 3-10) to severe (BSA >10%, PASI >10)
  - phototherapy if accessible
  - systemic or biological therapy based on patient's treatment history and comorbidities
  - TCS ± topical vitamin D3 analogue as adjunct therapy

Table 14. Topical Treatment of Psoriasis

Treatment	Mechanism	Comments
Emollients	Reduce fissure formation	
Salicylic acid 1-12%	Remove scales	
Tar (LCD: liquor carbonis detergens)	Inhibit DNA synthesis, increase cell turnover	Messy, poor long-term compliance
Topical corticosteroids	Reduce scaling, redness and thickness	Use appropriate potency steroid in different areas for degree of psoriasis
Vitamin D analogues: calcipotriene/ calcipotriol (Dovonex®, Silkis®)	Reduce keratinocyte hyperproliferation	
Betamethasone + calcipotriene (Dovobet®)	Combined TCS and vitamin D analogue. See above mechanisms	Not to be used on face or folds
Retinoid: Tazarotene (Tazorac®) (gel/cream)	Vitamin A derivative, reduce scaling	Irritating
Halobetasol propionate + tazarotene (Duobrii™) (lotion)	Combined TCS and vitamin A derivative, reduce scaling and inflammation	Irritating
PDE-4 inhibitor: Roflumilast (Zoryve™) (cream)	Reduce inflammation	Steroid sparing, can be used on face or folds

Table 15. Systemic Treatment of Psoriasis

Treatment	Considerations	Adverse Effects
Acitretin	More effective when used in combination with phototherapy	Alopecia, cheilitis, teratogenicity, hepatotoxicity, photosensitivity, epistaxis, xerosis, hypertriglyceridemia
Cyclosporine	Used for intermittent control rather than continuously Avoid using for >1 yr Non-melanoma skin cancer risk higher when combined with PUVA	Renal toxicity, hypertension, hypertriglyceridemia, immunosuppression, lymphoma, non-melanoma skin cancer
Methotrexate	Has been used for over 50 yr	Bone marrow toxicity, hepatic cirrhosis, teratogenicity
Apremilast (Otezla®)	Extremely safe	GI upset, headache, loose stool, weight loss
Deucravacitinib (Sotyktu™)	More effective than apremilast Well tolerated	Acne, increased risk of infection
PUVA	Highly effective in achieving remission Avoid >200 sessions in lifetime	Burning, skin cancer
Broadband UVB and NB-UVB (311 nm)	UVB is much less carcinogenic than PUVA. NB-UVB has not been shown to increase the risk of skin cancer	Rare burning

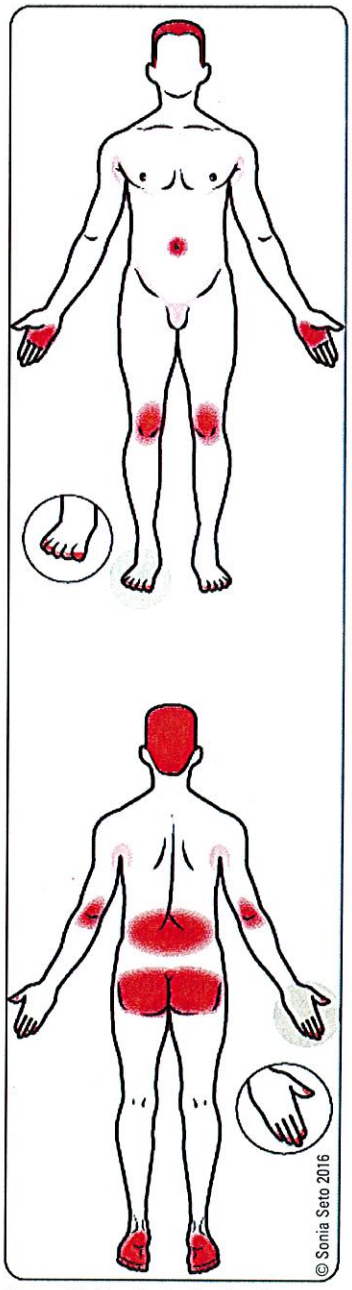


Figure 10. Psoriasis distribution

Mechanism of Biologics
"-mab" = monoclonal antibody
"-cept" = receptor

Table 16. Biologics Approved in Canada

Treatment	Route	Dosing Schedule	Effectiveness	Action
Etanercept (Enbrel®)*	SC	50 mg twice per wk for 3 mo, then 50 mg every wk	+++	Anti-TNF
Adalimumab (Humira®)*	SC	80 mg x 1, then 40 mg at wk 1, and every 2 wk thereafter	++++	Anti-TNF
Infliximab (Remicade®)*	IV	5 mg/kg at wk 0, 2, 6, and every 8 wk thereafter	+++++	Anti-TNF
Ustekinumab (Stelara®)*	SC	45 mg or 90 mg at wk 0, 4, and every 12 wk thereafter	++++	Anti-IL 12/23
Secukinumab (Cosentyx®)*	SC	300 mg at wk 0, 1, 2, 3, 4, and every mo thereafter	+++++	Anti-IL 17A
Ixekizumab (Taltz®)*	SC	160 mg at wk 0, then 80 mg at wk 2, 4, 6, 8, 10, 12, then 80 mg every 4 wk thereafter	+++++	Anti-IL 17A
Guselkumab (Tremfya®)*	SC	100 mg at wk 0, 4, and every 8 wk thereafter	+++++	Anti-IL 23
Brodalumab (Siliq®)	SC	210 mg at wk 0, 1, 2 and every 2 wk thereafter	+++++	Anti-IL 17RA (targets IL 17 receptor subunit A, rather than IL 17A itself)
Certolizumab pegol (Cimzia®)*	SC	400 mg every 2 wk	++++	Anti-TNF
Risankizumab (Skyrizi®)*	SC	150 mg at wk 0, 4, and every 12 wk thereafter	+++++	Anti-IL 23
Tildrakizumab (ILUMYA®)	SC	100 mg at wk 0, 4, and every 12 wk thereafter	++++	Anti-IL 23
Bimekizumab (BIMZELX®)	SC	320 mg at wk 0, 4, 8, 12, 16, and every 8 wk thereafter	+++++	Anti-IL 17A/IL 17F
Spesolimab (SPEVIGO®)**	IV	900 mg x 1 at wk 0, and if symptoms persist 900 mg x 1 at wk 1	n/a***	Anti-IL 36R

*Can also be used to treat psoriatic arthritis **Approved for generalized pustular psoriasis only ***Efficacy comparison not available

GUTTATE PSORIASIS ("RAIN DROP-LIKE")

Clinical Features
- discrete, scattered salmon-pink small scaling papules
- sites: diffuse, usually on trunk and legs, sparing palms and soles
- often antecedent streptococcal pharyngitis

Management
- UVB phototherapy, sunlight, emollients, TCS
- penicillin V, erythromycin, or azithromycin if GAS on throat culture

ERYTHRODERMIC PSORIASIS

Clinical Features
- generalized erythema (>90% of BSA) with fine desquamative scale on surface
- associated signs and symptoms: arthralgia, pruritus, dehydration, electrolyte imbalance
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management
- potentially life-threatening, requires immediate medical care
- IV fluids, monitor fluids and electrolytes, may require hospitalization
- treat underlying aggravating condition
- cyclosporine, acitretin, methotrexate, UV, biologics

PUSTULAR PSORIASIS

Clinical Features
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, can be painful
- may be generalized or localized
- patient can have a history of psoriasis; may occur with sudden withdrawal from steroid therapy

Management
- methotrexate, cyclosporine, acitretin, UV, biologics

INVERSE PSORIASIS

Clinical Features
- erythematous plaques on flexural surfaces such as axillae, inframammary folds, gluteal fold, inguinal folds
- lesions may be macerated

Management
- low potency TCS
- topical vitamin D analogues (e.g. calcipotriene, calcitriol)
- topical calcineurin inhibitors (e.g. tacrolimus, pimecrolimus)
- topical PDE-4 inhibitors (e.g. roflumilast)
- phototherapy

PSORIATIC ARTHRITIS
- 20-30% of patients with psoriasis also suffer from psoriatic arthritis
- psoriatic patients with nail or scalp involvement are at a higher risk for developing psoriatic arthritis
- see Rheumatology, RH25

Vesiculobullous Diseases

Bullous Pemphigoid

Clinical Features
- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- can present as urticarial plaques without bullae
- common sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth in 33%

Pathophysiology
- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leading to subepidermal bullae

Epidemiology
- mean age of onset: 60-80 yr, F=M

Investigations
- immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
- anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

Prognosis
- heals without scarring, usually chronic
- rarely fatal

Management
- prednisone 0.5-1 mg/kg/d until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclosporine, mycophenolate mofetil)
- potent TCS (clobetasol) may be as effective as systemic steroids in limited disease
- tetracycline ± nicotinamide is effective for some cases
- immunosuppressants such as azathioprine, mycophenolate mofetil, cyclosporine
- For refractory cases: IVIg, rituximab, dupilumab, or omalizumab

Pemphigus Vulgaris

Clinical Features
- autoimmune blistering disease characterized by flaccid, non-pruritic intraepidermal bullae/vesicles on an erythematous or normal skin base
- may present with erosions and secondary bacterial infection
- sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky's sign: epidermal detachment with shear stress
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

Pemphigus Vulgaris vs. Bullous Pemphigoid
VulgariS = Superficial, intraepidermal, flaccid lesions
PemphigoiD = Deeper, tense lesions at the dermal-epidermal junction

Pathophysiology
- IgG against epidermal desmoglein-1 and -3 lead to loss of intercellular adhesion in the epidermis

Epidemiology
- 40-60 yr, M=F, higher prevalence in Jewish, Mediterranean, Asian populations
- paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

Pemphigus Foliaceus
An autoimmune intraepidermal blistering disease that is more superficial than pemphigus vulgaris due to antibodies against desmoglein-1, a transmembrane adhesion molecule. Appears as crusted patches, erosions and/or flaccid bullae that usually start on the trunk. Localized disease can be managed with TCS. Active widespread disease is treated like pemphigus vulgaris

Investigations
- immunofluorescence: shows intraepidermal IgG and C3 deposition
- circulating serum anti-desmoglein IgG antibodies

Prognosis
- lesions heal with hyperpigmentation but do not scar
- may be fatal unless treated with immunosuppressive agents

Management
- prednisone 1-2 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclophosphamide, cyclosporine, IVIg, mycophenolate mofetil, rituximab)

Dermatitis Herpetiformis

Clinical Features
- grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations
- lesions grouped, bilaterally symmetrical
- common sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

Pathophysiology
- transglutaminase IgA deposits in the skin alone or in immune complexes leading to eosinophil and neutrophil infiltration
- almost all carry HLA-DQ2 or DQ8, other haplotypes include B8, DR3, and DQWZ
- 90% have gluten-sensitive enteropathy, 20% have intestinal symptoms of celiac disease
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

Epidemiology
- 20-60 yr, M:F=2:1

Investigations
- biopsy
- immunofluorescence shows IgA deposits in perilesional skin

Management
- dapsone (sulfapyridine if contraindicated or poorly tolerated)
- gluten-free diet for life: this can reduce risk of lymphoma

Porphyria Cutanea Tarda

Clinical Features
- skin fragility followed by formation of tense vesicles/bullae and erosions on photo-exposed skin
- gradual healing to scars, milia
- periorbital violaceous discolouration, diffuse hypermelanosis, facial hypertrichosis
- common sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

Pathophysiology
- uroporphyrinogen decarboxylase deficiency leads to excess heme precursors
- can be associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

Epidemiology
- 30-40 yr, M>F

Investigations
- urine and HCl 5% shows orange-red fluorescence under Wood's lamp (UV rays)
- 24 h urine has elevated uroporphyrins
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

Management
- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

Drug Eruptions

Exanthematous

EXANTHEMATOUS DRUG REACTION

Clinical Features
- morphology: erythematous macules and papules ± scale
- spread: symmetrical, trunk to extremities
- time course: 7-14 d after drug initiation, fades 7-14 d after withdrawal

Diagnosis of a Drug Reaction
Classification by Naranjo et al. has 4 criteria:
1. Temporal relationship between drug exposure and reaction
2. Recognized response to suspected drug
3. Improvement after drug withdrawal
4. Recurrence of reaction on re-challenge with the drug

Definite drug reaction requires all 4 criteria to be met
Probable drug reaction requires #1-3 to be met
Possible drug reaction requires only #1

Epidemiology
- most common cutaneous drug reaction; increased in presence of infections
- common causative agents: penicillin, sulfonamides, phenytoin

Management
- weigh risks and benefits of drug discontinuation
- antihistamines, emollients, TCS



Drug Hypersensitivity Syndrome Triad
Fever
Exanthematous eruption
Internal organ involvement

DRUG-INDUCED HYPERSENSITIVITY SYNDROME (DIHS)/DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Clinical Features
- morphology: morbilliform rash involving face, trunk, arms; can have facial edema
- systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- spread: starts with face or periorbitally and spreads caudally; no mucosal involvement
- time course: onset 1-6 wk after first exposure to drug; persists wk after withdrawal of drug

Epidemiology
- rare: incidence varies considerably depending on drug
- common causative agents: anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, lamotrigine), sulfonamides, and allopurinol
- 10% mortality if severe, undiagnosed, and untreated

Management
- discontinue offending drug ± prednisone 0.5 mg/kg/d, consider cyclosporine in severe cases
- may progress to generalized exfoliative dermatitis/erythroderma if drug is not discontinued

Urticarial

DRUG-INDUCED URTICARIA AND ANGIOEDEMA

Clinical Features
- morphology: wheals lasting >24 h unlike non-drug induced urticaria, angioedema (face and mucous membranes)
- systemic features: may be associated with systemic anaphylaxis (bronchospasm, laryngeal edema, shock)
- time course: h-d after exposure depending on the mechanism

Epidemiology
- second most common cutaneous drug reaction
- common causative agents: penicillins, ACEi, analgesics/anti-inflammatories, radiographic contrast media

Management
- discontinue offending drug, treatment with antihistamines, oral corticosteroids, epinephrine if anaphylactic

SERUM SICKNESS-LIKE REACTION

Clinical Features
- morphology: symmetrical cutaneous eruption (usually urticarial)
- systemic features: malaise, low grade fever, arthralgia, lymphadenopathy
- time course: appears 1-3 wk after drug initiation, resolves 2-3 wk after withdrawal

Epidemiology
- more prevalent in children (0.02-0.2%)
- common causative agents: cefaclor in children; bupropion in adults

Management
- discontinue offending drug ± topical/oral corticosteroids

Pustular

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

Clinical Features
- morphology: extensive erythematous, edematous, and sterile pustules
- systemic features: high fever, leukocytosis with neutrophilia
- spread: starts in face and intertriginous areas, spreads to trunk and extremities
- time course: appears 1 wk after drug initiation, resolves 2 wk after withdrawal

Epidemiology
- rare: 1-5/million
- common causative agents: aminopenicillins, cephalosporins, clindamycin, calcium channel blockers

Management
- discontinue offending drug and systemic corticosteroids

Bullous

STEVENS-JOHNSON SYNDROME (SJS)/TOXIC EPIDERMAL NECROLYSIS (TEN)

Clinical Features
- morphology: prodromal rash (morbilliform/targetoid lesions ± purpura, or diffuse erythema), confluence of flaccid blisters, positive Nikolsky sign (epidermal detachment with shear stress), full thickness epidermal loss; dusky tender skin, bullae, desquamation/skin sloughing, atypical targets
- classification:
  - BSA with epidermal detachment: <10% in SJS, 10-30% in SJS/TEN overlap, and >30% in TEN
- spread: face and extremities; may generalize; scalp, palms, soles relatively spared; erosion of mucous membranes (lips, oral mucosa, conjunctiva, GU mucosa)
- systemic features: fever (higher in TEN), cytopenias, renal tubular necrosis/AKI, tracheal erosion, infection, contractures, corneal scarring, phimosis, vaginal synechiae
- time course: appears 1-3 wk after drug initiation; progression <4 d; epidermal regrowth in 3 wk
- can have constitutional symptoms: malaise, fever, hypotension, tachycardia

Epidemiology
- SJS: 1.2-6/million; TEN: 0.4-1.2/million
- risk factors: SLE, HIV/AIDS, HLA-B1502 (reaction most prevalent in East Asians, associated with carbamazepine), HLA-B5801 (reaction most prevalent in Asian and White populations, associated with allopurinol)
- common causative agents: drugs (allopurinol, anti-epileptics, sulfonamides, NSAIDs, cephalosporins, immune checkpoint inhibitors) responsible in 50% of SJS and 80% of TEN; viral or mycoplasma infections
- prognosis: 5% mortality in SJS, 30% in TEN due to fluid loss and infection

Differential Diagnosis
- scarlet fever, phototoxic eruption, GVHD, SSSS, exfoliative dermatitis, AGEP, paraneoplastic pemphigus

Management
- discontinue offending drug
- admit to intermediate/intensive care/burn unit
- supportive care: IV fluids, electrolyte replacement, nutritional support, pain control, wound care, sterile handling, monitor for and treat infection
- IVIg, cyclosporine, corticosteroids, or etanercept

SCORTEN Score for TEN Prognosis
One point for each of: age ≥40, malignancy, initial BSA detached ≥10%, tachycardia ≥120 bpm, serum urea >10 mmol/L, serum glucose >14 mmol/L, serum bicarbonate <20 mmol/L

Used to determine appropriate clinical setting: score 0-1 can be treated in non-specialized wards; score ≥2 should be transferred to intensive care or burn unit

Score at admission is predictive of survival: 94% for 0-1, 87% for 2, 53% for 3, 25% for 4, and 17% for ≥5

Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis
JAMA Dermatol 2017;153:514-522
Purpose: To examine possible immunomodulating treatments for SJS/TEN and estimate mortality effect compared to supportive care.
Methods: Systematic review of randomized and nonrandomized studies on systemic immunomodulating therapies or supportive care for SJS/TEN.
Results: Ninety-six studies with 3248 patients were included in the final analysis. Glucocorticoids were associated with a survival benefit for patients (aggregate - OR 0.5, 95% CI 0.3-1.01). Though findings were limited to a small number of patients overall, cyclosporine was associated with significant benefit (OR 0.1; 95% CI 0.0-0.4). No beneficial effects were observed with other therapies, including IVIg.
Conclusion: Though based on limited evidence, glucocorticoids and cyclosporine were the most promising as SJS/TEN immunosuppressive therapies.

Other

FIXED DRUG ERUPTION

Clinical Features
- morphology: sharply demarcated erythematous oval patches on the skin or mucous membranes
- spread: commonly face, mucosa, genitalia, acral; recurs in same location upon subsequent exposure to the drug (fixed location)

Epidemiology
- common causative agents: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

Management
- discontinue offending drug ± prednisone 1 mg/kg/d x 2 wk for generalized lesions
- potent TCS for non-eroded lesions or antimicrobial ointment for eroded lesions

PHOTOSENSITIVITY REACTION

Clinical Features
- phototoxic reaction: "exaggerated sunburn" (erythema, edema, vesicles, bullae) confined to sun-exposed areas
- photoallergic reaction: pruritic eczematous eruption with papules, vesicles, scaling, and crusting that may spread to areas not exposed to light

Pathophysiology
- phototoxic reaction: direct tissue injury
- photoallergic reaction: type IV delayed hypersensitivity

Epidemiology
- common causative agents: chlorpromazine, doxycycline, thiazide diuretics, procainamide

Management
- sun protection ± topical/oral corticosteroids

Heritable Disorders

Ichthyosis Vulgaris

Clinical Features
- xerosis with fine scaling as well as large adherent scales ("fish-scales")
- affects arms, legs, palms, soles, back, forehead, and cheeks; spares flexural creases
- improves in summer, with humidity, and as the child grows into adulthood

Pathophysiology
- genetic deficiency in filaggrin protein leads to abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

Epidemiology
- 1:300 incidence
- autosomal dominant inheritance
- associated with AD and keratosis pilaris

Investigations
- electron microscopy: keratohyalin granules

Management
- immersion in bath and oils followed by an emollient cream, humectant cream, or creams/oil containing urea or α- or β-hydroxy acids
- intermittent systemic retinoids for severe cases

Epidermolysis Bullosa

Clinical Features
- blisters and erosions on skin and mucous membranes following minor trauma
- extracutaneous manifestation may occur in severe disease and include intraoral blistering and erosions, nail abnormalities, esophageal strictures, and genitourinary abnormalities

Pathophysiology
- group of rare inherited diseases caused by mutations in genes coding for structural proteins involved in basement membrane of skin

Differential Diagnosis
- friction blisters, epidermolysis bullosa acquisita

Investigations
- skin biopsy for immunofluorescence mapping

Management
- symptomatic management including supportive wound care
- avoid inducing friction on skin
- place padding on furniture
- wear loose clothing and appropriate footwear
- maintain cool ambient room temperature

Neurofibromatosis (Type I; von Recklinghausen's Disease)

Clinical Features
- diagnostic criteria includes 2 or more of the following, if parent not diagnosed with NF1:
  1. **6 or more café-au-lait patches >1.5 cm in an adult or 6 or more café-au-lait macules >0.5 cm in prepubertal individuals**
  2. **axillary or inguinal freckling**
  3. **2 or more iris hamartomas (Lisch nodules)**
  4. **optic glioma**
  5. **2 or more neurofibromas of any type or one plexiform neurofibroma**
  6. **distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)**
  7. **heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in normal tissue**
- a child of a parent who meets the diagnostic criteria above needs 1 or more to be diagnosed with NF1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P89)

Pathophysiology
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

Epidemiology
- incidence 1 in 3000

Investigations
- Wood's lamp to detect café-au-lait macules in patients with pale skin

Management
- refer to orthopedics, ophthalmology, plastics, and psychiatry
- follow-up annually for brain tumours (e.g. astrocytoma)
- excise suspicious or painful lesions
- see Pediatrics, P89

Oculocutaneous Albinism

Clinical Features
- hypopigmentation of skin and hair, including eyebrows and eyelashes, compared to family members and persons of same ethnicity
- ocular involvement: decreased retinal pigmentation, impaired vision, photophobia, nystagmus, strabismus

Pathophysiology
- group of genetic disorders of melanin biosynthesis
- autosomal recessive

Epidemiology
- 1 in 20000
- varies across ethnic groups

Investigations
- often clinical diagnosis, may consider molecular testing

Management
- sun protection
- close surveillance for skin cancers with whole body skin examinations

Vitiligo

Clinical Features
- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply demarcated white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

Pathophysiology
- acquired autoimmune destruction of melanocytes

Interventions for Vitiligo
Cochrane DB Syst Rev 2015;2:CD003263
Purpose: To assess the effects of existing interventions used in the management of vitiligo.
Method: Systematic review of RCTs assessing the effects of vitiligo treatments (topical treatments, light therapies, oral treatments, surgical methods). Primary outcomes were quality of life and >75% re-pigmentation.
Results: Ninety-six RCTs with 4512 participants were deemed eligible, of which only 25 reported on the primary outcomes and were finally included. Re-pigmentation was better with combination therapy (calcipotriol plus PUVA, than PUVA alone; hydrocortisone-17-butyrate plus excimer laser vs. excimer laser alone; oral minipulse of prednisolone (OMP) plus narrowband UVB (NB-UVB) vs. OMP alone; azathioprine with PUVA vs. PUVA alone; 8-methoxypsoralen (8-MOP) plus sunlight vs. psoralen). A non-significant increase in the proportion of participants with >75% re-pigmentation was noted in favour of NB-UVB compared to PUVA. Compared to PUVA, the NV-UVB group reported lower incidences of nausea and erythema, but not itching.
Conclusions: Some studies support existing therapies for vitiligo management, but follow-up is needed to assess the permanence of re-pigmentation and higher quality RCTs need to be conducted.

Epidemiology
- 1 in 100 incidence
- 30 in 100 with positive family history

Investigations
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison's disease, T1DM
- Wood's lamp to detect lesions: illuminates UV light onto skin to detect amelanosis (porcelain white discolouration)

Management
- sun avoidance and protection
- topical calcineurin inhibitor (e.g. tacrolimus, pimecrolimus) or TCS
- PUVA or NB-UVB
- Topical ruxolitinib (Janus kinase inhibitor) is a newly approved therapy for nonsegmental vitiligo in patients age 12 or older
- camouflage
- "bleaching" normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation

Infections

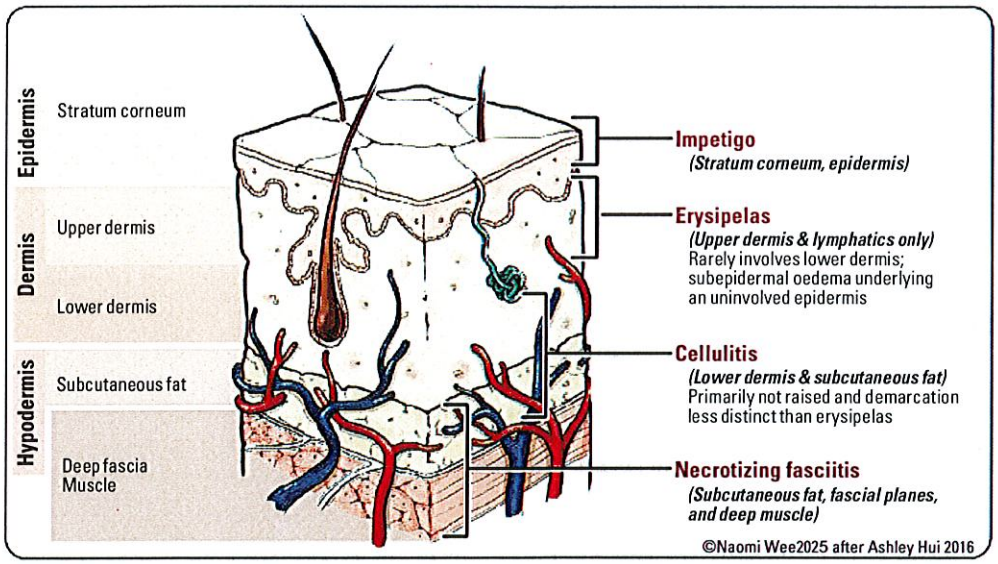


Figure 11. Layers of skin affected by bacterial infections

Bacterial Infections: Epidermis

IMPETIGO

Clinical Features
- acute purulent infection which appears vesicular; progresses to golden yellow "honey-crusted" lesions surrounded by erythema
- can present with bullae
- common sites: face, arms, legs, and buttocks

Etiology
- GAS, *S. aureus*, or both

Epidemiology
- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

Differential Diagnosis
- infected eczema, HSV, VZV

Investigations
- usually clinical diagnosis
- Gram stain and culture of lesion fluid or biopsy

Management
- remove crusts, use saline compresses, and topical antiseptic soaks bid
- localized: topical antibiotics (e.g. mupirocin 2% or fusidic acid 2% (Canada only) tid; continue for 7-10 d after resolution, or ozenaxacin 1% cream bid for 5 d)
- extensive: systemic antibiotics (e.g. dicloxacillin or cephalexin for 7-10 d)

Staphylococcal Scalded Skin Syndrome
- see Emergency Medicine, ER43

Bacterial Infections: Dermis

Table 17. Comparison of Erysipelas and Cellulitis

	Clinical Features	Etiology	Complications	Differential Diagnosis	Investigations	Management
Erysipelas	Involves upper dermis Confluent, erythematous, sharp raised edge, warm plaque, well demarcated Very painful ("St. Anthony's fire") Sites: face and legs Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection)	GAS	Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy Spreads via lymphatics	DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis	Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology	1st line: penicillin, cephalexin, cloxacillin or cefazolin 2nd line: clindamycin If allergic to penicillin, use erythromycin
Cellulitis	Involves lower dermis/subcutaneous fat Unilateral erythematous flat lesion, often with vesicles, poorly demarcated, not uniformly raised Tender Sites: commonly on legs Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy	GAS, *S. aureus* (large sized wounds), Haemophilus influenzae (periorbital), *Pasteurella multocida* (dog/cat bite)	Uncommon	Same as erysipelas	Same as erysipelas	1st line: cloxacillin or cefazolin/cephalexin clindamycin Hospitalized and MRSA positive: vancomycin Children: cefuroxime If DM (foot infections): TMP/SMX and metronidazole

COMMON HAIR FOLLICLE INFECTIONS

Table 18. Comparison of Superficial Folliculitis, Furuncles, and Carbuncles

	Clinical Features	Etiology	Management
Superficial Folliculitis	Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion) Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle Pustule ruptures to form a small crust Sites: primarily scalp, shoulders, anterior chest, upper back, other hair-bearing areas	Normal non-pathogenic bacteria (*Staphylococcus* – most common; Pseudomonas – hot tub) *Pityrosporum*	Antiseptic (Hibiclens®) Topical antibacterial (fusidic acid, mupirocin, erythromycin, or clindamycin) Oral cloxacillin or cephalexin for 7-10 d
Furuncles (Boils)	Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures Involves subcutaneous tissue that arises from a hair follicle Sites: hair-bearing skin (thigh, neck, face, axillae, perineum, buttocks)	*S. aureus*	Incise and drain large furuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&S) Cloxacillin or cephalexin for 1-2 wk (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy)
Carbuncles	Deep-seated abscess formed by multiple coalescing furuncles Usually in areas of thicker skin Occasionally ulcerates Lesions drain through multiple openings to the surface Systemic symptoms may be associated	*S. aureus*	Same as for furuncles

SKIN ABSCESS

Clinical Features
- painful, fluctuant, erythematous nodule, with or without surrounding cellulitis
- spontaneous drainage or purulent material may be discharged, regional adenopathy may be observed
- may progress to furuncle (deep infection of hair follicle) or carbuncle (collection of furuncles)
- sites: back of the neck, face, axillae, buttocks

Pathophysiology
- one or more pathogens; *S. aureus* with GAS and gram-negative bacilli with anaerobes is common in the perioral, perirectal, or vulvovaginal areas
- collection of pus within the dermis or subcutaneous tissue

Investigations
- clinical diagnosis; laboratory testing with uncomplicated infection in absence of comorbidities or complications is not required

Management
- if drainable abscess, incise and drain
- culture of debrided materials and antibiotics for the following circumstances:
  - severe local infection, systemic signs of infection, history of multiple/recurrent abscesses, presence of underlying comorbidities, immunosuppression, failure of initial antibiotic therapy, extremes of age (i.e. very young or very old), special exposures (e.g. animal bites), prophylaxis against infective endocarditis
- culture of debrided materials is not required in healthy patients who do not receive antibiotics

Bacterial Infections: Epidermis and Dermis

CUTANEOUS ANTHRAX

Clinical Features
- painless, pruritic, red-brown papule with surrounding edema and erythema
- lesions blister and then ulcerate, developing a black eschar
- often associated with systemic symptoms: lymphadenopathy, fever, myalgia, nausea, vomiting

Pathophysiology
- caused by Bacillus anthracis

Investigations
- Gram stain and culture
- polymerase chain reaction (PCR)
- full-thickness punch biopsy

Management
- oral antibiotic: ciprofloxacin, levofloxacin, or doxycycline

LEPROSY
- see Infectious Diseases, ID21

PILONIDAL CYST
- see General and Thoracic Surgery, GS49

Dermatophytoses

Clinical Features
- infection of skin, hair, and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

Pathophysiology
- digestion of keratin by dermatophytes resulting in scaly skin, broken hairs, crumbling nails/onycholysis

Etiology
- *Trichophyton, Microsporum, Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

Investigations
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

Management
- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type): clotrimazole, ketoconazole, terbinafine, or ciclopirox olamine cream applied bid
- oral therapy is indicated for onychomycosis and tinea capitis: terbinafine (Lamisil® – CYP2D6 inhibitor, liver toxicity) or itraconazole (Sporanox® – CYP3A4 inhibitor, liver toxicity)



A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses
NEJM 2017;376:2545-2555
Purpose: To determine the appropriate management of uncomplicated skin abscesses.
Study: Multi-centre, prospective, double-blind trial involving outpatient adults and children with abscesses 5 cm or smaller, stratified by presence of surgically drainable abscess, abscess size, number of sites of skin infection, and presence of non-purulent cellulitis. Following incision and drainage, participants were randomly assigned to 10 d courses of clindamycin, TMP-SMX or placebo. Primary outcome was clinical cure 7 to 10 d after treatment end. Intention-to-treat analyses were conducted.
Results: Seven hundred and eighty-six participants were enrolled (505 adults, 281 children). 10 d after therapy, the cure rate was similar between clindamycin and TMP-SMX (83.1% vs. 81.7%; P=0.73), and was higher than that of the placebo group (68.9%; P=0.001 for both comparisons). Among those who were cured, new infections at 1 mo follow-up were less common in the clindamycin group than the TMP-SMX or placebo groups (6.8% vs. 11.1%; P=0.03 vs. 12.4%; P=0.06). Adverse events were more frequent with clindamycin than either of the other groups (21.9% vs. 11.1% vs. 12.5%), though all resolved without sequelae.
Conclusions: Clindamycin or TMP-SMX in conjunction with incision and drainage for simple abscesses improves short-term outcomes compared to incision and drainage alone, though side effects must be considered.

Table 19. Different Manifestations of Dermatophyte Infection

	Clinical Features	Differential Diagnosis	Investigations	Management
Tinea Capitis	Round, scaly patches of alopecia, possibly with broken off hairs; pruritic Sites: scalp, eyelashes, and eyebrows; involving hair shafts and follicles Kerion (boggy, elevated, purulent inflamed nodule/plaque) may form secondary to infection by bacteria and result in scarring May have occipital lymphadenopathy Affects children (mainly Black), immunocompromised adults Very contagious and may be transmitted from barber, hats, theatre seats, pets	Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania	Wood's light examination of hair: green fluorescence only for Microsporum infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts	Terbinafine (Lamisil®) x 4 wk N.B.: oral agents are required to penetrate the hair root where dermatophyte resides Adjunctive antifungal shampoos or lotions may be helpful, and may prevent spread (e.g. selenium sulfide 2.5%, ketoconazole, ciclopirox)
Tinea Corporis (Ringworm)	Pruritic, scaly, round/oval plaque with active erythematous margin, ± central clearing Sites: trunk, limbs, face	Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis	Microscopic examinations of KOH prep of scales show hyphae Culture of scales	Topicals: clotrimazole 1%, ketoconazole 2%, miconazole 2%, terbinafine, or ciclopirox olamine cream bid for 2-4 wk Oral: terbinafine (Lamisil®), or itraconazole (Sporanox®), or fluconazole, or ketoconazole if extensive
Tinea Cruris ("Jock Itch")	Scaly patch/plaque with a well-defined, curved border and central clearing Pruritic, erythematous, dry/macerated Sites: starts medial thigh, spreads centrifugally to perineum, gluteal cleft, buttocks	Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma		
Tinea Pedis (Athlete's Foot)	Pruritic scaling and/or maceration of the web spaces, and powdery scaling of soles Acute infection: interdigital (especially 4th web space) red/white scales, vesicles, bullae, often with maceration Secondary bacterial infection may occur Chronic: non-pruritic, pink, scaling keratosis on soles, and sides of feet May present as flare-up of chronic tinea pedis Predisposing factors: heat, humidity, occlusive footwear	AD, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo, inverse psoriasis		
Tinea Manuum	Primary fungal infection of the hand is rare; usually associated with tinea pedis Acute: blisters at edge of red areas on hands Chronic: single dry scaly patch	AD, contact dermatitis, granuloma annulare, psoriasis		
Tinea Unguium (Onychomycosis)	Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris Toenail infections usually precede fingernail infections T. rubrum (90% of all toenail infections)	Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophy, bacterial infection	Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae Culture of subungual scraping or nail clippings on Sabouraud's agar Periodic acid-Schiff (PAS) stain of nail clipping by pathology	Terbinafine (Lamisil®) (6 wk for fingernails, 12 wk for toenails) Itraconazole (Sporanox®) 7 d on, 3 wk off (2 pulses for fingernails, 3 pulses for toenails) Topical: ciclopirox (Penlac®); nail lacquer (often ineffective), Efinaconazole (Jublia®) (48 wk)
Tinea Barbae	Superficial inflamed annular lesions; pustules and crusting around hairs Inflammatory kerion may occur and result in scarring hair loss Predominantly affects men who work with animals Site: beard area	Folliculitis, malignant lymphoma, sporotrichosis	Same as for tinea corporis	Terbinafine (Lamisil®) or Itraconazole (Sporanox®) x 4 wk

DIAPER RASH

• see Pediatrics, P15, P45

Parasitic Infections

CUTANEOUS LARVA MIGRANS

Clinical Features

- erythematous pruritic papules at site of initial infection
- larvae migrate under skin causing serpiginous eruption of red pruritic lines
- sites: often feet, legs, buttocks; anywhere skin comes into contact with contaminated sand or soil

Pathophysiology

- parasitic infection caused by hookworm larvae, most commonly from dog or cat feces

Epidemiology

- most common in tropical or subtropical regions

Management

- self-limiting, often resolves without treatment within a few wk
- consider treatment with anthelmintics, antihistamines

CUTANEOUS LEISHMANIASIS

Clinical Features

- begins as a solitary pink painless papule, enlarges to nodule or plaque-like lesion with central ulceration
- incubation time typically 2 wk to 6 mo

Pathophysiology
- transmitted by sandflies infected with Leishmania

Investigations
- histology, culture, and PCR

Management
- most cases resolve spontaneously
- may consider treatment with oral antifungals (e.g. fluconazole, ketoconazole) or parenteral treatment in severe or complicated cases

SCABIES

Clinical Features
- characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- common sites: axillae, groin, buttocks, hands/feet (especially web spaces); sparing of head and neck (except in infants)

Pathophysiology
- primarily transmitted through prolonged direct skin-skin contact, but scabies mites remain alive 2-3 d on clothing/sheets
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

Etiology
- Sarcoptes scabiei (a mite)
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

Differential Diagnosis
- atopic/contact dermatitis, arthropod bites, asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

Investigations
- microscopic examination of root and content of burrow and mineral oil mount for mites, eggs, feces
- skin biopsy may sometimes show scabies mite

Management
- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- Ivermectin
- change underwear and linens; wash twice with detergent in hot water cycle, then machine dry
- treat family and close contacts
- pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- mid-potency TCS and antihistamines for symptom management after treatment with permethrin

LICE (PEDICULOSIS)

Clinical Features
- intensely pruritic, red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs; red, excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs; excoriations
- body lice: nits and lice in seams of clothing; excoriations and secondary infection mainly on shoulders, belt-line, and buttocks

Etiology
- *Phthirus pubis* (pubic), *Pediculus humanus capitis* (scalp), *Pediculus humanus humanus* (body): attaches to body hair and feeds on the nearby body site
- can transmit infectious agents (e.g. Bartonella quintana, Rickettsia prowazekii)

Differential Diagnosis
- bacterial infection of scalp, seborrheic dermatitis

Diagnosis
- lice visible on inspection of affected area or clothing seams

Management
- permethrin 1%: Nix® cream rinse (ovicidal), RC & Cor® shampoo, or Kwellada-P® shampoo
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle, then machine dry
- children are medically cleared to return to school after first treatment

BED BUGS (HEMIPTERA)

Clinical Features
- burning wheals, turning to firm papules, often in groups of three – "breakfast, lunch, and dinner" – in areas with easy access (face, neck, arms, legs, hands)

Etiology
- caused by *Cimex lectularius*, a small insect that feeds mainly at night (hides in crevices in walls and furniture during the day)

Differential Diagnosis
- dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

Investigations
- none required, but lesional biopsy can confirm insect bite reaction

Management
- professional fumigation
- TCS and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture

Viral Infections

HERPANGINA

Clinical Features
- small vesicles form in mouth after exposure to virus
- lesions evolve into painful shallow oral ulcers, 1-5 mm in size, yellowish with an erythematous base
- often associated with sore throat, dysphagia, and headache

Pathophysiology
- caused by Coxsackie A viruses, highly contagious

Epidemiology
- most common in children and young adults

Investigations
- typically clinical diagnosis

Management
- self-limited
- symptomatic treatment, acetaminophen for fever and pain

HERPES SIMPLEX VIRUS

Clinical Features
- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- primary
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- secondary
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- complications: dendritic corneal ulcer, EM, herpes simplex encephalitis (infants at risk), HSV infection on AD causing Kaposi's varicelliform eruption (eczema herpeticum)

- two biologically and immunologically different subtypes: HSV-1 and HSV-2
  - HSV-1
    - typically "cold sores" (grouped vesicles at the mucocutaneous junction which quickly burst)
    - recurrent on face, lips, and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)
  - HSV-2
    - usually sexually transmitted; incubation 2-20 d
    - gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
    - vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
    - urethritis: watery discharge in males
    - recurrent on vulva, vagina, penis for 5-7 d
    - differential diagnosis of genital ulcers: candidal balanitis, chancroid, syphilitic chancres



Both HSV-1 and HSV-2 can occur on face or genitalia

Investigations

- Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
- viral culture, electron microscopy, PCR, and direct fluorescence antibody test of specimen taken from the unroofed base of a relatively new lesion
- serologic testing for antibody for current or past infection if necessary

Management

- oral herpes
  - treatment may or may not needed depending on length of episode
  - consider treating immunocompromised patients and recurrent/severe episodes with oral antivirals (i.e. acyclovir 400 mg orally 5 times daily for 5 days)
- genital herpes
  - test and treat concurrent STIs, pain control with sitz baths, and analgesia
  - first episode: acyclovir 400mg PO 3x daily for 7-10 days
  - recurrent genital herpes can be treated with daily suppressive therapy (i.e. acyclovir 400 mg PO bid) or episodic therapy (started during prodromal phase or within 1 day of lesion onset, i.e. acyclovir 800 mg orally twice daily for 5 days or 3 times daily for 2 days)
  - famciclovir and valacyclovir may be substituted and have better enteric absorption and less frequent dosing
  - for active lesions in pregnancy (see Obstetrics, OB31)



Erythema Multiforme
Etiology: most often HSV or *Mycoplasma pneumoniae*, rarely drugs
Morphology: macules/papules with central vesicles; classic bull's-eye pattern of concentric light and dark rings (typical target lesions)
Management: symptomatic treatment (oral antihistamines, oral antacids); corticosteroids in severely ill (controversial); prophylactic oral acyclovir for 6-12 mo for HSV-associated EM with frequent recurrences

HERPES ZOSTER VIRUS (SHINGLES)

Clinical Features

- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last d-wk
- pain can be pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Ramsay Hunt syndrome (see Otolaryngology, OT23)
- Hutchinson's sign: shingles on the tip of the nose signifies ocular involvement
  - shingles in this area involves the nasociliary branch of the ophthalmic branch of the trigeminal nerve (V1)
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV



HZV typically involves a single dermatome; and lesions rarely cross the midline

Etiology

- caused by reactivation of VZV
- risk factors: old age, immunosuppression, occasionally associated with hematologic malignancy

Differential Diagnosis

- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

Investigations

- none required, but can do Tzanck test, direct fluorescence antibody test, or viral culture to rule out HSV

Prevention

- routine vaccination in >50 yr with Shingrix® (recombinant zoster vaccine) preferred (can also use in >60 yr Zostavax® (live zoster vaccine))

Management

- compress with normal saline, Burow's or betadine solution
- oral antivirals: famciclovir, valacyclovir, or acyclovir for 7 d; must initiate within 72 h to be of benefit
- analgesia: NSAIDs, acetaminophen for mild-moderate pain; opioids if severe
- post-herpetic neuralgia: tricyclic antidepressants, anticonvulsants (gabapentin, pregabalin)

MOLLUSCUM CONTAGIOSUM

Clinical Features
- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus (Molluscum contagiosum virus)
- common sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology
- virus is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)
- virus is self-limited but can take 1-2 yr to resolve

Investigations
- none required, however can biopsy to confirm diagnosis

Management
- topical cantharidin
- cryotherapy
- curettage
- topical retinoids
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

WARTS (HUMAN PAPILLOMAVIRUS INFECTIONS)

Table 20. Different Manifestations of HPV Infection

	Definition and Clinical Features	Differential Diagnosis	Distribution	HPV Type
Verruca Vulgaris (Common Warts)	Hyperkeratotic, elevated, discrete epithelial growths with papillated surface caused by HPV Paring of surface reveals punctate, red-brown specks (thrombosed capillaries)	Molluscum contagiosum, seborrheic keratosis	Located at trauma sites: fingers, hands, knees of children and teens	At least 80 types are known
Verruca Plantaris (Plantar Warts) **Verruca Palmaris** (Palmar Warts)	Hyperkeratotic, shiny, sharply marginated growths Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges	May need to scrape ("pare") lesions to differentiate wart from callus and corn	Located at pressure sites: metatarsal heads, heels, toes	Commonly HPV 1, 2, 4, 10
Verruca Planae (Flat Warts)	Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration Common in children	Syringoma, seborrheic keratosis, molluscum contagiosum, lichen planus	Sites: face, dorsa of hands, shins, knees	Commonly HPV 3, 10
Condyloma Acuminata (Genital Warts)	Skin-coloured pinhead papules to soft cauliflower-like masses in clusters Can be asymptomatic, lasting mo to yr Highly contagious, transmitted sexually and non-sexually (e.g. Koebner phenomenon via scratching, shaving), and can spread without clinically apparent lesions Investigations: acetowhitening (subclinical lesions seen with acetic acid 5% x5 min and hand lens) Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts)	Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), molluscum contagiosum	Sites: genitalia and perianal areas	Commonly HPV 6 and 11 HPV 16, 18, 31, 33 cause cervical dysplasia, SCC, and invasive cancer

Treatment for Warts
- first line therapies
  - salicylic acid preparations (patches, solutions, creams, ointments), cryotherapy
- second line therapies
  - topical imiquimod, topical 5-fluorouracil, topical tretinoin, podophyllotoxin
- third line therapies
  - curettage, cautery, surgery for non plantar warts, CO2 laser, oral cimetidine (particularly children), intralesional bleomycin (plantar warts), trichloroacetic acid, diphencyprone

CHICKEN POX (VARICELLA)
- see Pediatrics, P63

ERYTHEMA INFECTIOSUM (FIFTH DISEASE)
- see Pediatrics, P62

HAND-FOOT-AND-MOUTH DISEASE
- see Pediatrics, P62

MEASLES
- see Pediatrics, P62

PARVOVIRUS
- see Pediatrics, P62

ROSEOLA
- see Pediatrics, P62

RUBELLA
- see Pediatrics, P63

VERRUCAE VULGARISMS
- see *Table 20, D36*

Yeast Infections

CANDIDIASIS

Etiology
- many species of Candida (70-80% of infections are from *Candida albicans*)
- opportunistic infection in those with predisposing factors (e.g. trauma, malnutrition, immunodeficiency)

Candidal Paronychia
- clinical features: painful red swelling of periungual skin
- management: topical agents not as effective; oral antifungals recommended

Candidal Intertrigo
- clinical features
  - macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
  - peripheral "satellite" pustules
  - starts as non-infectious maceration from heat, moisture, and friction
- predisposing factors: obesity, DM, systemic antibiotics, immunosuppression, malignancy
- management: keep area dry, terbinafine, ciclopirox olamine, ketoconazole/clotrimazole cream bid until rash clears

Oral terbinafine (Lamisil®) is not effective because it is not secreted by sweat glands

PITYRIASIS (TINEA) VERSICOLOR

Clinical Features
- asymptomatic superficial fungal infection with brown/white scaling macules
- affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
- common sites: upper chest and back

Pathophysiology
- microbe produces azelaic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
- affinity for sebaceous glands; requires fatty acids to survive

Etiology
- caused by *Malassezia* sp. (formerly known as *Pityrosporum*)
- also associated with folliculitis and seborrheic dermatitis
- predisposing factors: summer, tropical climates, excessive sweating, Cushing's syndrome, prolonged corticosteroid use

Investigations
- clinical diagnosis but can perform microscopic examination, KOH prep of scales for hyphae and spores

Management
- ketoconazole 2% shampoo or cream daily for 3 d
- selenium sulfide 2.5% lotion applied for 10 min for 7 d
- ciclopirox olamine bid
- systemic fluconazole or itraconazole for 7 d if extensive

Sexually Transmitted Infections

SYPHILIS

Clinical Features
- characterized initially by a painless ulcer (chancre)
- following inoculation, systemic infection with secondary and tertiary stages

Etiology
- Treponema pallidum
- transmitted sexually, congenitally, or rarely by transfusion

Table 21. Stages of Syphilis

	Clinical Features	Investigations	Management
Primary Syphilis	Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus Regional non-tender lymphadenopathy appears <1 wk after onset of chancre DDx: chancroid (painful), HSV (multiple lesions)	CANNOT be based on clinical features alone VDRL negative – repeat weekly for 1 mo FTA-ABS test has greater sensitivity and may detect disease earlier in course Dark field examination – spirochete in chancre fluid or lymph node	Penicillin G, 2.4 million units IM, single dose
Secondary Syphilis	Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre) Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia Lesions heal in 1-5 wk and may recur for 1 yr 3 types of lesions: 1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus) 2. Condyloma lata: wart-like moist papules around genital/perianal region 3. Mucous patches: macerated patches mainly found in oral mucosa	VDRL positive FTA-ABS +ve; –ve after 1 yr following appearance of chancre Dark field +ve in all secondary	Same as for primary syphilis
Tertiary Syphilis	Extremely rare 3-7 yr after secondary Main skin lesion: 'Gumma' – a granulomatous non-tender nodule	As in primary syphilis, VDRL can be falsely negative	Penicillin G, 2.4 million units IM weekly x 3 wk

GONOCOCCEMIA

Clinical Features
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- common sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis, and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

Etiology
- Neisseria gonorrhoeae

Investigations
- requires high index of clinical suspicion because tests are often negative
- bacterial culture of blood, joint fluid, and skin lesions
- joint fluid cell count and Gram stain

Management
- notify public health authorities
- screen for other STIs
- ceftriaxone 1 g IM or IV every 24 h

Herpes Simplex Virus
- see *Viral Infections, D34*

Human Papillomavirus
- see *Viral Infections, D36*

Pre-Malignant Skin Conditions

Actinic Keratoses (Solar Keratoses)

Clinical Features
- ill-defined, scaly, erythematous papules or plaques associated with sun-damaged skin (solar heliosis)
- initial lesion is a rough erythematous papule with white to yellow scale
- often easier to appreciate on palpation rather than inspection with a gritty, sandpaper-like texture
- sites: areas of sun exposure (face, helices of the ears primarily in men, hairless scalp, neck, upper trunk, dorsal aspects of the hands and forearms)

Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of AK to SCC (<1/1000 per yr), but higher likelihood if AK is persistent
- UV-induced p53 gene mutation
- risk factors: increased age, light skin/eyes/hair, immunosuppression, genetic syndromes such as albinism or xeroderma pigmentosum
- risk factors for malignant transformation of AK to SCC: immunosuppression, history of skin cancer, persistence of AK

Types of AK

Erythematous: typical AK lesion

Hypertrophic: thicker, rough papule/plaque

Cutaneous horn: firm hyperkeratotic outgrowth

Actinic cheilitis: confluent AKs on the lip

Pigmented: flat, tan-brown, scaly plaque

Spreading pigmented

Proliferative

Conjunctival: pinguecula, pterygium

Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III, rare in deeper skin tones as melanin is protective

Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis

Investigations
- biopsy refractory or suspicious lesions (infiltrative, tender, bleeding spontaneously)

Management
- destructive: shave excision and curettage with electrodesiccation, or cryotherapy
- topical pharmacotherapy (mechanism: destruction of rapidly growing cells or immune system modulation)
  - topical 5-fluorouracil cream (for 2-4 wk), imiquimod 5% (2x/wk for 16 wk), imiquimod 3.75% (daily for 2 wk, and then daily again for 2 wk more)
- photodynamic therapy
- chemical peels (e.g. TCA, phenol)
- excision
- laser resurfacing

Leukoplakia

Clinical Features
- a morphologic term describing homogeneous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

Pathophysiology
- precancerous or pre-malignant condition
- oral variant is strongly associated with tobacco use and alcohol consumption

Epidemiology
- 1-5% prevalence in adult population >30 y/o; peak at age >50
- M>F, fair-skinned
- most common oral mucosal pre-malignant lesion

Differential Diagnosis
- DLE, invasive SCC, candidiasis, lichen planus, oral hairy leukoplakia, white sponge nevus

Investigations
- biopsy due to risk of malignancy

Management
- low-risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, smoking cessation, follow-up
- moderate/dysplastic lesions: excision, cryotherapy
- primary aim of treatment is to decrease the risk of oral SCC

Malignant Skin Tumours

Nonmelanoma Skin Cancers

BASAL CELL CARCINOMA

Subtypes
- nodular BCC (most common)
  - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border, and depressed/eroded/ulcerated centre
- pigmented BCC
  - areas of pigment in translucent lesion with surface telangiectasia
  - may mimic MM
- superficial BCC
  - thin, tan to red-brown plaque, often with scaly, pearly border, and fine telangiectasia at margin
  - least aggressive subtype
- morpheaform or sclerosing BCC
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated

Pathophysiology
- malignant proliferation of basal keratinocytes of the epidermis
  - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
  - usually due to UVB light exposure, therefore >80% on sun exposed sites
  - typical latency period of 20-50 yr between time of UV damage and onset of BCC
  - also associated with previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin Syndrome)

Epidemiology
- most common malignancy in humans
- 75% of all malignant skin tumours in >40 y/o, increased prevalence in the elderly
- risk factors: M>F, skin phototypes I and II, chronic cumulative sun exposure, ionizing radiation, immunosuppression, arsenic exposure

Differential Diagnosis
- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular MM, SCC, merkel cell carcinoma (MCC)

Management
- see *Table 22, Management of Nonmelanoma Skin Cancers*
- follow-up for new primary disease or recurrence
- 95% cure rate if lesion <2 cm in diameter or if treated early

Workup/Investigations of Basal Cell Carcinoma and Other Nonmelanoma Skin Cancers
History: duration, growth rate, family/personal history of skin cancer, history of immunosuppression, history of sun exposure, medications, prior therapy to the lesion
Physical: location, size, whether circumscribed, tethering to deep structures, full skin exam, lymph node exam
Biopsy: if shallow lesion, can do shave biopsy; otherwise punch or excisional biopsy may be more appropriate

Surgical Margins
Smaller lesions: electrodessication and curettage with 2-3 mm margin of normal skin
Deep infiltrative lesions: surgical excision with 3-5 mm margins beyond visible and palpable tumour border, which may require skin graft or flap; or Mohs surgery, which conserves tissue and does not require margin control

Table 22. Management of Nonmelanoma Skin Cancers

Treatment Category	Treatment Options	Indications	Disadvantages
Topical	Imiquimod 5% cream (Aldara®)	Superficial BCCs, Bowen's Disease	Side effects: erythema, edema, ulceration, and, scaling
	Cryotherapy	Superficial BCCs, Bowen's Disease Advantages: minimal equipment, simple to perform, cost-effective, no restriction of activity after surgery	Margin around cancer may not be free, potential for scarring, minimally painful, no skin tissue for diagnosis
	5-fluorouracil (Efudex®)	Superficial BCCs, Bowen's Disease	Side effects: pain, burning, swelling
Procedural	Photodynamic therapy	Superficial BCCs Advantages: low cost, tolerable side effect profile	Side effects: pain
	Radiation therapy	Advanced cases of BCC, SCC Advantages: if lesions are located in cosmetically sensitive area	Side effects: alopecia, pigmentary changes, fibrosis, atrophy, buccal mucositis, gingivitis, telangiectasias
Surgical	Shave excision and electrodessication and curettage	Most types of BCCs, Bowen's Disease Advantages: minimal equipment needed, simple to perform, cost-effective, no restriction of activity after surgery	Not used for morpheaform BCC, margin around cancer may not be free, slow healing, possible scarring
	Mohs surgery	BCC and SCC lesions on the face or in areas that are difficult to reconstruct. Can be considered for lentigo maligna and/or melanoma in-situ. Advantages: highest cure rate, good cosmetic results, healthy skin tissue is preserved	Expensive, highly technical, resource intensive, activity restriction after surgery if skin graft/flap needed
	Traditional surgical excision	SCC Advantages: margin around cancer more likely to be free than shave excision, tissue is available for diagnosis, cosmetic satisfaction	Activity restriction after surgery if skin graft/flap needed, healthy tissue around cancer must be removed
Medical Therapy	Vismodegib	Metastatic BCC, Gorlin Syndrome (multiple BCCs)	Side effects: muscle spasms, hair loss, abnormal taste, weight loss, nausea, amenorrhea
	Cemiplimab	Metastatic SCC, metastatic BCC refractory to vismodegib	Side effects: musculoskeletal pain, fatigue, nausea

BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Clinical Features
- sharply demarcated erythematous patch/thin plaque with scale and/or crusting
- often 1-3 cm in diameter and found on the skin and mucous membranes
- evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

Management
- see *Table 22, Management of Nonmelanoma Skin Cancers, D40*

SQUAMOUS CELL CARCINOMA

Clinical Features
- hyperkeratotic indurated, pink/red/skin-coloured papule/plaque/nodule with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- exophytic (grows outward), may present as a cutaneous horn
- common sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology
- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: cumulative UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar, and nitrogen mustards), HPV 16 or 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

Epidemiology
- second most common type of cutaneous neoplasm in less pigmented skin types
- most common cutaneous neoplasm in patients with Type 6 skin, typically in non-photoexposed sites (risk factors include chronic wounds or chronically inflamed areas such as discoid lupus, or hidradenitis suppurativa)
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- SCC is the most common cutaneous malignancy in immunocompromised patients such as in organ transplant recipients, with increased mortality as compared to non-immunocompromised population

Differential Diagnosis
- benign: wart, psoriasis, irritated seborrheic keratosis
- pre-malignant: AK, Bowenoid papulosis
- malignant: keratoacanthoma, Bowen's disease, BCC, amelanotic melanoma

Management
- see *Table 22, Management of Nonmelanoma Skin Cancers, D40*
- may require lifelong follow-up (more aggressive treatment than BCC)

Prognosis
- good prognostic factors: early treatment, negative margins, and small size of lesion
- rate of metastasis from primary SCC is 2-5%
- higher risk of metastasis if diameter >2 cm, depth >2 mm, recurrent, involvement of bone/muscle/nerve, location on scalp/ears/nose/lips, immunosuppressed, caused by arsenic ingestion, or tumour arose from scar/chronic ulcer/burn/genital tract/sinus tract

KERATOACANTHOMA

Clinical Features
- rapidly growing, firm, dome-shaped, erythematous or skin-coloured volcano-like nodule with central keratin-filled crater
- may spontaneously regress
- sites: sun-exposed skin

Pathophysiology
- epithelial neoplasm with atypical keratinocytes in epidermis
- low grade variant of SCC

Etiology
- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology
- most common in >50 y/o, rare in <20 y/o

Differential Diagnosis
- treat as SCC until proven otherwise
- nodular BCC, MCC, hypertrophic solar keratosis, verruca vulgaris





Interventions for AK
Cochrane DB Syst Rev 2012;2:CD004415
Purpose: To assess the efficacy of treatments for AK.
Methods: Systematic review of RCTs.
Results: A total of 83 RCTs (10036 patients) were included, evaluating 24 treatments. Cryotherapy, diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, photodynamic therapy, resurfacing and trichloroacetic acid peel were all effective at treating AK and generally comparable with one another. Skin irritation was more common with diclofenac and 5-fluorouracil. Photodynamic therapy and imiquimod treatment resulted in better cosmetic appearance.
Conclusion: For individual lesions, photodynamic therapy is more effective than cryotherapy. For field-directed treatments, 5-fluorouracil, diclofenac, imiquimod, and ingenol mebutate had comparable efficacy.

Management
- surgical excision or saucerization (shave biopsy) followed by electrodesiccation of the base, treated similarly to SCC
- intralesional methotrexate or 5-fluorouracil injection

Malignant Melanoma

Clinical Features
- malignant characteristics of a mole: "ABCDE" mnemonic
- sites: skin, mucous membranes, eyes, CNS
- ~2/3 arise *de novo* without an associated nevus
- abnormal dermoscopic features

Clinical Subtypes of Malignant Melanoma
Listed from most to least common subtype
- **superficial spreading melanoma** (60-70% of all melanomas)
- atypical melanocytes initially spread laterally in epidermis, then invade the dermis
- irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
- ulcerate and bleed with growth
- subtype most likely associated with pre-existing nevus
- **nodular melanoma** (15-30% of all melanomas)
- atypical melanocytes that initially grow vertically with little lateral spread
- uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
- rapidly fatal
- may be pink or have no colour at all, this is called an amelanotic melanoma
- EFG = elevated, firm, growing
- **lentigo maligna**
  - MM *in situ* (normal and malignant melanocytes confined to the epidermis)
  - greater than 6 mm (up to several cm) in diameter, tan/brown/black uniformly flat macule or patch with irregular borders
  - lesion grows radially and produces complex colours
  - often seen in the elderly
  - 10% evolve to lentigo maligna melanoma
- **lentigo maligna melanoma (5-15% of all melanomas)**
  - older individuals, ~7th decade
  - malignant melanocytes invading into the dermis
  - associated with pre-existing solar lentigo, not pre-existing nevi
  - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  - with time, colour changes from uniform brown to dark brown with black and blue
  - found on all skin surfaces, especially those often exposed to sun, such as the face and hands
- **acral lentiginous melanoma (5-10% of all melanomas)**
  - ill-defined dark brown, blue-black macule
  - palmar, plantar, subungual skin
  - melanomas on mucous membranes have poor prognosis
  - most common subtype found in patients with Type 6 skin
- **amelanotic melanoma (2-8% of all melanomas)**
  - little to no pigment
  - pink or red macules, papules, or nodules, some may present with light-brown pigmentation
  - delay in diagnosis may contribute to its poor prognosis
  - MM in young children is more commonly amelanotic variant

Pathophysiology
- malignant neoplasm of pigment-forming cells (melanocytes and nevus cells)

Epidemiology
- 1 in 75 (Canada), 1 in 50 (US)
- risk factors: increasing age, fair skin, red hair, positive personal/family history, familial dysplastic nevus syndrome, large congenital nevi (>20 cm), any dysplastic nevi, >50 common nevi, immunosuppression, sun exposure with sunburns, tanning beds
- most common sites: back (M), calves (F)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

Differential Diagnosis
- benign: nevi, solar lentigo, seborrheic keratosis, dermatofibroma, spitz nevus
- malignant: pigmented BCC, dermatofibrosarcoma protuberans

Management
- excisional biopsy preferable (margin determined by Breslow depth), otherwise incisional biopsy, sentinel lymph node dissection controversial
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
- beware of lesions that regress – tumour is usually deeper than anticipated
- anti-CTLA-4 agents (e.g. ipilimumab), anti-PD1 agents (e.g. nivolumab, pembrolizumab), high-dose IFN, chemotherapy (e.g. dacarbazine) as options for unresectable stage II, stage III, and metastatic melanoma. These therapies can also be used as adjuvant therapy in resectable stage II, stage III disease



Does this Patient have a Mole or Melanoma?

ABCDE checklist
Asymmetry
Border (irregular and/or indistinct)
Colour (varied)
Diameter (increasing or >6 mm)
Enlargement, elevation, evolution (i.e. change in colour, size, or shape)
Sensitivity 92% (CI 82-96%)
Specificity 100% (CI 54-100%)
JAMA 1998;279:696-701



Risk Factors for Melanoma

no SPF is a SIN
Sun exposure
Pigment traits (blue eyes, fair/red hair, pale complexion)
Freckling
Skin reaction to sunlight (increased incidence of sunburn)
Immunosuppressive states (e.g. renal transplantation)
Nevi (dysplastic nevi; increased number of benign melanocytic nevi)



Node Dissection for Lesions

Offered to patients with stage IB or higher melanoma (>1 mm Breslow thickness OR 0.8-1 mm with or without ulceration OR <0.8 mm with ulceration)

May be considered in select patients with stage IA melanoma (<0.8 mm without ulceration with presence of risk factors such as age <40, >1 mitoses/ mm^2, lymphovascular invasion, positive deep biopsy margin)

Assess sentinel node at time of wide excision



See Landmark Dermatology Trials table for more information on the trial by Hodi et al. 2010, which details improved survival with Ipilimumab in patients with metastatic melanoma.



See Landmark Dermatology Trials table for more information on the BRIM-3 trial comparing the efficacy of BRAF kinase inhibitor vemurafenib (PLX4032) to dacarbazine in patients with metastatic melanoma.

- targeted small molecule BRAF inhibitors such as vemurafenib are an option in patients with BRAF V600E mutations and unresectable or metastatic melanoma
- radiotherapy may be used as adjunctive treatment

Table 23. American Joint Committee on Cancer Staging System Based on Breslow's Thickness of Invasion

Tumour Depth	Stage	Approximate 5-Yr Survival
T1 <1.0 mm	Stage I T1a – T2a	5-yr survival 90%
T2 1.01-2.0 mm	Stage II T2b – T4b	5-yr survival 70%
T3 2.01-4.0 mm	Stage III any nodes	5-yr survival 45%
T4 >4.0 mm	Stage IV any mets	5-yr survival 10%

a = no ulceration; b = ulceration

Other Cutaneous Cancers

CUTANEOUS T-CELL LYMPHOMA

Clinical Features
- Mycosis fungoides (limited superficial type)
  - characterized by slightly atrophic scaling, erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation, hypopigmentation)
  - common sites include: trunk, buttocks, proximal limbs
  - mildly symptomatic, usually excellent prognosis for early disease
  - hypopigmented subtype most commonly seen in children with deeper skin tones
- Sézary syndrome (widespread systemic type)
  - rare variant characterized by erythroderma, lymphadenopathy, WBC >20 x 109/L with Sézary cells
  - can be considered to have evolved from mycosis fungoides (not initially meeting diagnostic criteria), but more commonly arises de novo
  - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  - high mortality

Pathophysiology
- clonal proliferation of skin-homing CD4 T-cells

Epidemiology
- seen in >50 yr, M:F ratio is 2:1

Differential Diagnosis
- tinea corporis, atopic dermatitis, nummular dermatitis, psoriasis, DLE, Bowen's disease, adult T-Cell leukemia-lymphoma (ATL)

Investigations
- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is characteristic but not diagnostic of Sézary)
- imaging (for systemic involvement)

Management
- Mycosis fungoides
  - depends on stage of disease
  - early stage: TCS, topical chemotherapy, topical retinoids, topical imiquimod, local radiation, and/or PUVA, NB-UVB (311-313 mm)
  - advanced stage: biologics such as brentuximab, low-dose methotrexate, systemic retinoids, PUVA
- Sézary syndrome
  - oral retinoids and IFN
  - extra-corporeal photopheresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapy agents

KAPOSI SARCOMA

Definition
- an angioproliferative neoplasm that requires infection with human herpesvirus 8 (HHV-8)
- 4 types based on the clinical circumstance at which it develops
  - classical: develops in middle or old age in individuals of Mediterranean descent
  - endemic: seen in sub-Saharan indigenous Africans
  - iatrogenic: associated with immunosuppressive drug therapy and renal allograft recipients
  - AIDS associated

Clinical Features
- purplish, reddish blue, or dark brown/black macules, plaques, and nodules on the skin
- skin nodules can range in size from very small to several centimeters in diameter, and lesions may ulcerate and bleed
- lesions typically present on the distal extremities
- also affects the gastrointestinal tract and lymphatics leading to secondary lymphoedema

Epidemiology
- incidence is 0.02% to 0.06% of all malignant tumours, M>F

Differential Diagnosis
- well-differentiated angiosarcoma, benign lymphangiomatosis, hypertrophic lichen planus

Investigations
- biopsy
- PCR - can identify HHV-8 DNA sequences

Treatment
- surgery, cryotherapy, laser surgery, photodynamic therapy, topical retinoids, immunomodulators for superficial macules and plaques
- radiation therapy, systemic chemotherapy

Diseases of Hair Density

Hair Growth

- hair grows in a cyclic pattern that is defined in 3 stages (most scalp hairs are in anagen phase)
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and dihydrotestosterone (DHT); this response is genetically controlled

Hair Regrowth Potential
Ability to regrow hair depends on location of inflammatory infiltrates on hair follicle as stem cells are located at the upper part (bulge region) of the hair follicle
Scarring alopecia: Inflammatory infiltrates found in upper part of hair follicles, destroying stem cells
Non-scarring alopecia: Hair follicle is not permanently damaged, and therefore spontaneous or treatment-induced regrowth is possible

Non-Scarring (Non-Cicatricial) Alopecia

ANDROGENETIC ALOPECIA

Clinical Features
- male- or female-pattern alopecia
- males: fronto-temporal areas progressing to vertex, entire scalp may be bald
- females: widening of central part, "Christmas tree" pattern

Pathophysiology
- action of DHT on hair follicles

Epidemiology
- males: early 20s-30s
- females: 40s-50s

Management
- camouflage techniques (i.e. wigs, hair extensions, powders, concealing lotions or sprays)
- topical minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- females: spironolactone (anti-androgenic effects), cyproterone acetate (Diane-35®)
- males: finasteride (Propecia®) (5-α-reductase inhibitor) 1 mg/d
- oral minoxidil
- procedural (hair transplant, platelet-rich plasma)

DDx of Non-Scarring (Non-Cicatricial) Alopecia

Autoimmune
- Alopecia areata

Endocrine
- Hypothyroidism
- Androgens

Micronutrient deficiencies
- Iron
- Zinc

Toxins
- Heavy metals
- Anticoagulants
- Chemotherapy
- Vitamin A

Trauma to the hair follicle
- Trichotillomania
- Traction /Tight ponytail or braiding styles

Other
- Syphilis
- Severe illness
- Childbirth

TELOGEN EFFLUVIUM

Clinical Features
- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle

Pathophysiology
- variety of precipitating factors (i.e. post-partum, psychological stress, major illness)
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few mo but may not be complete

Precipitants of Telogen Effluvium

"SEND" hair follicles out of anagen and into telogen
Stress (biological and psychological) and **S**calp disease (surgery)
Endocrine (hypothyroidism, post-partum)
Nutritional (iron and protein deficiency)
Drugs (acitretin, heparin, lithium, IFN, β-blockers, valproic acid, SSRIs)

ANAGEN EFFLUVIUM

Clinical Features
- hair loss due to insult of hair follicle impairing its mitotic activity (growth stage)

Pathophysiology
- precipitated by chemotherapeutic agents (most common), other medications (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few wk after agent stopped



Hair Loss

TOP HAT
Telogen effluvium, Tinea capitis
Out of iron, zinc
Physical: trichotillomania, tight ponytail or braiding styles
Hormonal: hypothyroidism, androgenic
Autoimmune: SLE, alopecia areata
Toxins: heavy metals, anticoagulants, chemotherapy, vitamin A, SSRIs

ALOPECIA AREATA

Clinical Features
- autoimmune disorder characterized by patches of complete hair loss often localized to scalp, but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- "exclamation mark" pattern (hairs fractured and have tapered shafts, i.e. looks like "!")
- may be associated with autoimmune conditions: pernicious anemia, vitiligo, thyroid disease, Addison's disease
- spontaneous regrowth may occur within mo of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress
- alopecia totalis: complete loss of hair on scalp
- alopecia universalis: complete loss of scalp hair, eyelashes, eyebrows, and body hair



Non-scarring alopecia: intact hair follicles on exam → biopsy not required (but may be helpful)
Scarring alopecia: absent hair follicles on exam → biopsy required

Management
- excellent prognosis for localized disease
- TCS and intralesional steroids (triamcinolone acetonide) can be used for isolated patches
- topical immunotherapy (diphencyprone, anthralin)
- systemic immunosuppressants for refractory or extensive disease
- immunomodulatory (diphencyprone, anthralin)
- newer treatments: janus kinase inhibitors



Alopecia Areata Subtypes
Alopecia totalis: loss of all scalp hair and eyebrows
Alopecia universalis: loss of all body hair

OTHER
- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight braiding styles, wearing tight ponytails, tight tying of hair coverings)

Scarring (Cicatricial) Alopecia

Clinical Features
- irreversible loss of hair follicles with fibrosis

Etiology
- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HSV)
- primary inflammatory – subdivided into lymphocytic, neutrophilic, and mixed
  - lymphocytic:
    - lichen planus (lichen planopilaris) – white scale around hair follicles, up to 50% have lichen planus at other body sites
    - DLE (note that SLE can cause an alopecia unrelated to DLE lesions which are non-scarring)
    - central centrifugal cicatricial alopecia (CCCA): seen in up to 40% of Black women, starting at central scalp; one of the most commonly diagnosed scarring alopecias, may be associated with hair care practices
    - keratosis follicularis spinulosa decalvans (autosomal dominant, X-linked)
  - neutrophilic:
    - folliculitis decalvans – discharge of pus and blood, tufting of hair follicles
    - dissecting cellulitis of the scalp – follicular papules, pustules, nodules, and abscesses develop on the scalp
  - mixed
    - acne keloidalis nuchae – dome-shaped papules, pustules, and plaques on the occipital scalp
- morphea: "coup de sabre" with involvement of centre of scalp

Investigations
- biopsy from active border

Management
- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials, immunosuppressants (e.g. cyclosporine)

Postmenopausal Hair Changes

- estrogen regulates the growth and cycling of hair follicles
- hormonal changes (e.g. reduced estrogen) during menopause leads to decreased hair diameter, growth rate, and percentage of hairs in the anagen phase; moreover, chronological age affects hair density
- these compounded effects of the two factors above (hormone changes and aging) may lead to a perception of decreased scalp hairs in middle-aged women

Hypertrichosis

Clinical Features

- excessive hair growth that is an outlier for age, sex, or race
- is not associated with androgen sensitive areas
- can be localized/circumscribed, or generalized, acquired or congenital

Etiology

- congenital causes of hypertrichosis:
  - localized: congenital circumscribed hypertrichosis: congenital melanocytic nevus , congenital Becker nevus, smooth muscle hamartoma, underlying neurofibroma
  - generalized: congenital hypertrichosis lanuginosa, congenital generalized hypertrichosis, Brachmann-de-Lange syndrome, teratogen exposure
- acquired causes of hypertrichosis:
  - localized: acquired Becker nevus, chemicals (i.e. iodine, minoxidil, psoralens, TCS), orthopedic casts/splits, fracture, friction (i.e. scratching in lichen simplex) , trichomegaly (long eyelashes that can arise from local latanoprost treatment)
  - generalized: cerebral disturbances, acrodynia, infection, malnutrition, dermatomyositis, thyroid abnormalities

Management

- acquired: treat the underlying cause
- congenital: hair removal (i.e. shaving, waxing, laser hair removal), makeup, lighten hair with commercial bleach or 6% hydrogen peroxide

HIRSUTISM

- see Gynecology, GY25

Nails and Disorders of the Nail Apparatus

Table 24. Nail Changes in Systemic and Dermatological Conditions

Nail Abnormality	Definition/Etiology	Associated Disease
NAIL PLATE CHANGES		
Clubbing	Proximal nail plate has greater than 180° angle to nail fold, watch-glass nails, bulbous digits	Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.
Koilonychia	Spoon shaped nails	Iron deficiency, malnutrition, DM
Onycholysis	Separation of nail plate from nail bed	Psoriasis, dermatophytes, thyroid disease, repetitive trauma
Onychogryphosis	Hypertrophy of the nail plate producing a curved, claw-like deformity	Poor circulation, chronic inflammation, tinea
Onychohemia	Subungual hematoma	Trauma to nail bed
Onychomycosis	Fungal infection of nail (e.g. dermatophyte, yeast, mould)	HIV, DM, peripheral arterial disease
Onychomadesis	Nail plate detachment from proximal nail fold due to severe trauma that produces a complete arrest of nail matrix activity	Manicures, eczema, chronic paronychia, severe or febrile illness, erythroderma
SURFACE CHANGES		
V-Shaped Nicking	Distal margin has v-shaped loss of the nail plate	Darier's disease (keratosis follicularis)
Pterygium Inversum Unguis	Distal nail plate does not separate from underlying nail bed	Scleroderma
Pitting	Punctate depressions that migrate distally with growth	Psoriasis (random pattern), alopecia areata (geometric, grid-shaped arrangement), eczema
Transverse Ridging	Transverse depressions, often more in central portion of nail plate	Serious acute illness slows nail growth (when present in all nails = Beau's lines), eczema, chronic paronychia, trauma
Transverse White Lines	Bands of white discolouration	Poisons, hypoalbuminemia (Muehrcke's lines)
Onychorrhexis	Brittle nails leading to longitudinal ridging	Lichen planus, psoriasis, normal aging, fungal infection

Table 24. Nail Changes in Systemic and Dermatological Conditions

Nail Abnormality	Definition/Etiology	Associated Disease
COLOUR CHANGES		
Yellow		Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use
Green		Pseudomonas
Black		Melanoma, hematoma
Brown		Nicotine use, psoriasis, poisons, longitudinal melanonychia (more common in Fitzpatrick V and VI)
Splinter Hemorrhages	Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows	Trauma, bacterial endocarditis, blood dyscrasias, psoriasis
Oil Spots	Brown-yellow discolouration	Psoriasis
Leukonychia	White nails	Hypoalbuminemia, chronic renal failure
Terry's Nails	White proximal nail, darker distal nail with ground glass appearance, no lunula	Liver cirrhosis
NAIL FOLD CHANGES		
Herpetic Whitlow	HSV infection of distal phalanx	HSV infection
Paronychia	Local inflammation of the nail fold around the nail bed	Acute: painful infection Chronic: constant wetting (e.g. dishwashing, thumbsucking)
Nail Fold Telangiectasias	Cuticular hemorrhages, roughness, capillary changes	Scleroderma, SLE, dermatomyositis
LOSS OF NAILS		
Temporary Loss	Occurs without scarring	Trauma (especially toenails or fingernails after large subungual hematoma), Beau's lines after severe illness
Permanent Loss	Occurs with scarring	Lichen planus (pterygium), genetic abnormalities (rare)

Adnexal Disorders

HIDRADENITIS SUPPURATIVA

Definition
- a chronic scarring inflammatory skin condition that is a result of follicular occlusion and inflammation within intertriginous zones and areas rich in apocrine glands

Clinical Features
- primary lesions are inflammatory nodules
- presence of sinus formation, clusters of open comedones (double tombstone comedones), and hypertrophic scarring of intertriginous areas
- sites: occurs primarily in the intertriginous areas of the axillae (most common site), inguinal area, inner thighs, perianal and perineal areas, mammary and inframammary regions, buttocks, pubic region, scrotum, vulva, trunk, and occasionally the scalp and retroauricular areas
- additionally significant hyperpigmentation and keloid formation can be seen in more pigmented skin types

Pathophysiology
- follicular occlusion, follicular rupture, and an immune response

Epidemiology
- affects 1-4% of the population, F>M
- onset of symptoms occur between puberty and age 40, typically in 2nd or 3rd decade
- increased incidence in people of African descent
- associated with smoking and excess weight

Differential Diagnosis
- folliculitis, furuncles, carbuncles, acne vulgaris, Crohn's disease, granuloma inguinale, pyoderma gangrenosum, recurrent pilonidal sinus, abscess

Investigations
- clinical diagnosis
- ultrasound can be helpful for disease staging or detecting subclinical disease

Management
- behavioural: avoidance of triggers including shaving or wearing tight fitting clothing, smoking cessation, and weight management, laser hair removal
- pain management with NSAIDs

- mild disease: local therapy with topical antibiotics, topical resorcinol, and intralesional steroids
- moderate to severe disease: antibiotic therapy (oral tetracyclines, clindamycin and rifampin combination, dapsone), oral retinoids, hormonal therapy (metformin, OCPs), surgery (deroofing), laser and light-based therapies (CO_2 laser and Nd:YAG), and biologic therapy
- refractory moderate to severe disease: biologic therapy such as anti-TNFs i.e. adalimumab and infliximab, systemic glucocorticoids, cyclosporine, IV ertapenem, and combination therapies of any of the above treatments

PRIMARY HYPERHIDROSIS

Definition
- secretion of sweat in amounts greater than physiologically needed for thermoregulation

Clinical Features
- focal, visible, excessive sweating of at least 6 mo without apparent cause
- symptoms typically develop during childhood or adolescence and persist throughout life
- symptoms occur only during waking hours (diurnal)
- focal symptoms typically localized to the palms, soles, and axillae, and less commonly the scalp and face

Pathophysiology
- abnormal or exaggerated central response of the eccrine sweat glands to normal emotional stress

Epidemiology
- affects 1-5% of the population
- most patients have a family history of hyperhidrosis

Differential Diagnosis
- excessive heat, medications (e.g. antidepressants, antipyretics, cholinergic agonists, hormonal agents), menopause, and spinal cord injuries (autonomic dysreflexia, orthostatic hypotension, posttraumatic syringomyelia)

Investigations
- clinical diagnosis, iodine starch test

Management
- antiperspirants, botulinum toxin, microwave thermolysis, topical glycopyrronium bromide, suction curettage, systemic agents (oral glycopyrrolate, oral oxybutynin), iontophoresis, or endoscopic thoracic sympathectomy

Oral Diseases

LEUKOPLAKIA
- see *Leukoplakia, D39*

RECURRENT APHTHOUS STOMATITIS

Clinical Features
- also known as "canker sores"
- painful, shallow, typically less than 5 mm in diameter, round to oval shaped, covered by a creamy-white pseudomembrane with an erythematous halo
- sites: labial and buccal mucosa, floor of the mouth, ventral surface of the tongue, soft palate, and oropharyngeal mucosa

Pathophysiology
- dysfunction in the immune system resulting in immunologically mediated damage to epithelial cells
- triggered by trauma, emotional stress, infectious agents, genetic factors, HIV infection, and hormonal fluctuations
- early lesions can show a neutrophilic vessel-based submucosal infiltrate

Epidemiology
- women more commonly affected than men
- peak prevalence in ages 20-30

Differential Diagnosis
- Behçet syndrome, SLE, gluten-sensitive enteropathy, HSV

Investigations
- diagnosis is made clinically

Management
- oral hygiene: soft toothbrush, waxed tape-style dental floss, soft-tipped gum stimulator for plaque removal, and nonalcoholic mouthwash

- reduce traumatic factors inside the mouth such as biting cheeks or lips, and sharp/rough dental restorations
- pain control: lidocaine viscous 2%, diphenhydramine liquid (12.5 mg/5 mL), dyclonine lozenges
- severe refractory cases: colchicine

Skin Manifestations of Systemic Disease

Table 25. Skin Manifestations of Internal Conditions

Disease	Related Dermatoses
AUTOIMMUNE DISORDERS	
Behçet's Disease	Painful aphthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acneiform papules
Buerger's Disease	Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital resorptions
Dermatomyositis	Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron's papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis
Polyarteritis Nodosa	Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis, ulceration
Reactive Arthritis	Keratoderma blennorrhagica (on feet), balanitis circinata (on male penis)
Rheumatic Fever	Petechiae, urticaria, erythema nodosum, rheumatoid nodules, evanescent rash
Sarcoidosis	Heterogeneous cutaneous manifestations ranging from plaques, erythema nodosum, pink, brownish to violaceous nodules/plaques (lupus pernio)
Scleroderma	Raynaud's, non-pitting edema, ulcers, cutaneous calcification, periungual telangiectasia, acrosclerosis, salt-and-pepper pigmentation. Localized scleroderma presenting with waxy/shiny/tense atrophic skin is known as "morphea"
SLE	Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity
Crohn's Disease/UC	Pyoderma gangrenosum, erythema nodosum, Sweet's syndrome
ENDOCRINE DISORDERS	
Addison's Disease	Generalized hyperpigmentation or limited to skin folds, buccal mucosa, and scars
Cushing's Syndrome	Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia
DM	Infections (e.g. boils, carbuncles, candidiasis, S. aureus, dermatophytoses, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipoidica diabeticorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis
Hyperthyroidism	Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, onycholysis
Hypothyroidism	Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows
HIV-RELATED	
Infections	Viral (e.g. HSV, HZV, HPV, CMV, Molluscum contagiosum, oral hairy leukoplakia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epithelioid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis)
Inflammatory Dermatoses	Seborrhea, psoriasis, pityriasis rosea, vasculitis
Malignancies	Kaposi's sarcoma, lymphoma, BCC, SCC, MM
MALIGNANCY	
Adenocarcinoma Gastrointestinal Cervix/anus/rectum	Peutz-Jeghers: pigmented macules on lips/oral mucosa Paget's disease: eroding scaling plaques of perineum
Carcinoma Breast GI Thyroid Breast/lung/ovary	Paget's disease: eczematous and crusting lesions of the skin of the nipple and usually areola of the breast Palmoplantar keratoderma: thickened skin of palms/soles Sipple's syndrome: multiple mucosal neuromas Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles
Lymphoma/Leukemia Hodgkin's Acute leukemia	Ataxia telangiectasia: telangiectasia on pinna, bulbar conjunctiva Ichthyosis: generalized scaling especially on extremities, Sweet's syndrome Bloom's syndrome: butterfly erythema on face, associated with short stature
Multiple Myeloma	Amyloidosis: large, smooth tongue with facial petechiae and waxy papules on eyelids, nasolabial folds, and lips
OTHERS	
Liver Disease	Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry's nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice
Renal Disease	Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis
Pruritic Urticarial Papules and Plaques of Pregnancy	Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms, and lower back
Cryoglobulinemia	Palpable purpura in cold-exposed areas, Raynaud's, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection



Raynaud's Phenomenon DDx

COLD HAND
Cryoglobulins/Cryofibrinogens
Obstruction/Occupational
Lupus erythematosus, other connective tissue disease
DM/Drugs
Hematologic problems (polycythemia, leukemia, etc.)
Arterial problems (atherosclerosis)
Neurologic problems (vascular tone)
Disease of unknown origin (idiopathic)



Acanthosis Nigricans
An asymptomatic dark thickened velvety hyperpigmentation of flexural skin most commonly peri nuchal. Associated with DM, obesity, and other endocrine disorders, and malignancy. It is a cutaneous marker of tissue insulin resistance

Pediatric Exanthems

• see Pediatrics, P62

Miscellaneous Lesions

Angioedema and Urticaria

Angioedema

- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  - onset in childhood; 80% have positive family history
  - recurrent attacks; 25% die from laryngeal edema
  - triggers: minor trauma, emotional upset, temperature changes
- types of acquired angioedema
  - acute allergic angioedema (allergens include food, drugs, contrast media, insect venom, latex)
  - non-allergic drug reaction (drugs include ACEI)
  - acquired C1 inhibitor deficiency
- treatment
  - prophylaxis with danazol or stanozolol for hereditary angioedema
  - epinephrine pen to temporize until patient reaches hospital in acute attack

Urticaria

- also known as "hives"
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen

Table 26. Classification of Urticaria

Type	Etiology
Acute Urticaria >2/3 of cases Attacks last <6 wk Individual lesions last <24 h	Drugs: especially ASA, NSAIDs Foods: nuts, shellfish, eggs, fruit Idiopathic Infection Drugs (antibiotics, hormones, local anesthetics) Foods Parasitic infections Insect stings (bees, wasps, hornets) Physical contact (animal saliva, plant resins, latex, metals, lotions, soap) Direct mast cell release Opiates, muscle relaxants, radio-contrast agents Complement-mediated Serum sickness, transfusion reactions Infections, viral/bacterial (>80% of urticaria in pediatric patients)
Chronic Urticaria <1/3 of cases Attacks last >6 wk Individual lesion lasts <24 h	Idiopathic (90% of chronic urticaria patients) IgE-dependent: trigger associated Aeroallergens Urticarial vasculitis Arachidonic acid metabolism ASA, NSAIDs Physical Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat Other Mastocytosis, urticaria pigmentosa Parasitic infections Systemic diseases: SLE, endocrinopathy, neoplasm Stress
Urticarial Vasculitis Individual lesions last >24 h Often painful, less likely pruritic, wheals with bruise type lesions Biopsy indicated	Idiopathic Infections Hepatitis Autoimmune diseases SLE Drug hypersensitivity Cimetidine and diltiazem

DDx for Urticaria

MAD HIVES
Malignancy
Allergic
Drugs and foods
Hereditary
Infection
Vasculitis
Emotions
Stings

Approach to Urticaria

- Thorough Hx and physical exam
- **Acute:** no immediate investigations needed; consider referral for allergy testing
- **Chronic:** further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- **Vasculitic:** biopsy of lesion and referral to dermatology

Wheal

- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 h
- Associated with mast cell release of histamine
- May be pruritic

Mastocytosis (Urticaria Pigmentosa)
Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier's sign), due to mast cell degranulation; this occurs within minutes of rubbing

Erythema Nodosum

Clinical Features
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs (typically shins), knees, arms
- associated with arthralgia, fever, malaise

Etiology
- 40% are idiopathic
- drugs: sulfonamides, OCPs (also pregnancy), analgesics, all-trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn's > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

Epidemiology
- 15-30 y/o, F:M=3:1
- lesions last for days and spontaneously resolve in 6 wk

Investigations
- CXR (to rule out chest infection and sarcoidosis)
- throat culture, ASO titre, PPD skin test

Management
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids, oral potassium iodide
- treat underlying cause

DDx of Erythema Nodosum

NODOSUMM
NO cause (idiopathic) in 40%
Drugs (sulfonamides, OCP, etc.)
Other infections (Group A Strep)
Sarcoidosis
UC and Crohn's
Malignancy (leukemia, Hodgkin lymphoma)
Many Infections

Pruritus

Clinical Features
- a sensation provoking a desire to scratch, with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

Etiology
- dermatologic – generalized
  - asteatotic dermatitis ("winter itch" due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - immunoglobulins disease (bullous pemphigoid)
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin's lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, iron deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkin's lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis

Investigations
- blood work: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture, and serology for parasites
- biopsy

Management
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- TCS and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria

DDx of Pruritus

SCRATCHED
Scabies
Cholestasis
Renal
Autoimmune
Tumours
Crazies (psychiatric)
Hematology (polycythemia, lymphoma)
Endocrine (thyroid, parathyroid, iron)
Drugs, Dry skin

Consider biopsy of any non-healing wound to rule out cancer

- phototherapy with UVB or PUVA
- doxepin, amitriptyline
- immunosuppressive agents if severe: steroids and steroid-sparing

Wounds and Ulcers

- see Plastic Surgery, PL8

Sunscreens and Preventative Therapy

Sunburn (Solar Erythema)

- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVA and UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am-4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens

- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
- topical chemical: absorbs UV light
  - requires application at least 15-30 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
- topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride, and melanin
  - all are effective against the UVA and UVB spectrum
  - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management

- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, TCS)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

Topical Steroids

Table 27. Potency Ranking of Topical Steroids

Relative Potency	Relative Strength	Generic Names	Trade Names	Usage
Weak	x1	hydrocortisone – 2.5% (1%, 0.5% available OTC)	Emo Cort® Hydrocort®	Intertriginous areas, children, face, thin skin
Moderate	x3	hydrocortisone 17-valerate – 0.2% desonide mometasone furoate	Westcort® Hydrovalt® Tridesilon® Elocom®	Arm, leg, trunk
Potent	x6	betamethasone – 0.1% 17-valerate – 0.1% amcinonide	Betnovate® Celestoderm – V® Cyclocort®	Body
Very Potent	x9	betamethasone dipropionate – 0.05% fluocinonide – 0.05% halcinonide	Diprosone® Lidex, Topsyn gel® Lyderm® Halog®	Palms and soles
Extremely Potent	x12	clobetasol propionate – 0.05% (most potent) betamethasone dipropionate ointment halobetasol propionate – 0.05%	Dermovate® Diprolene® Ultravate®	Palms and soles

Skin Phototypes (Fitzpatrick)

Phototype	Colour of Skin	Skin's Response to Sun Exposure (without SPF protection)
I	White	Always burns, never tans
II	White	Always burns, little tan
III	White	Slight burn, slow tan
IV	Pale brown	Slight burn, faster tan
V	Brown	Rarely burns, dark tan
VI	Dark brown or black	Never burns, dark tan

SPF = burn time with cream/burn time without cream

UV Radiation

UVA (320-400 nm): Aging
- Penetrates skin more effectively than UVB or UVC
- Responsible for tanning, burning, wrinkling, photoallergy, and premature skin aging
- Penetrates clouds, glass, and is reflected off water, snow, and cement

UVB (290-320 nm): Burning
- Absorbed by the outer dermis
- Is mainly responsible for burning and premature skin aging
- Primarily responsible for BCC, SCC
- Does not penetrate glass and is substantially absorbed by ozone

UVC (200-290 nm)
- Is filtered by ozone layer

Body Site: Relative Percutaneous Absorption

Forearm	1.0
Plantar foot	0.14
Palm	0.83
Back	1.7
Scalp	3.7
Forehead	6.0
Cheeks	13.0
Scrotum	42.0

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption

Side Effects of Topical Steroids

Local: atrophy, perioral dermatitis, steroid acne, rosacea, contact dermatitis, tachyphylaxis (tolerance), telangiectasia, striae, hypertrichosis, hypopigmentation

Systemic: suppression of HPA axis, mood changes, nervousness, insomnia, hyperglycemia, fluid/sodium retention, increased appetite, weight gain, muscular weakness (Note: significant systemic absorption to cause systemic side effects is rare)

Dermatologic Therapies

Table 28. Common Topical Therapies

Drug Name	Dosing Schedule	Indications	Comments
Calcipotriol (Dovonex®)	0.005% cream, ointment, scalp solution, apply bid For maintenance therapy, apply once daily	Psoriasis	Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk >14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)
Imiquimod (Aldara®)	5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wk	Genital warts Cutaneous warts AK Superficial BCC	Avoid natural/artificial UV exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Works best for warts on mucosal surfaces May induce inflammation and erosion
Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)	1% or 5% cream, applied once overnight to all skin areas from neck down, repeated one wk later	Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)	Do not use in children <2 yr Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritus Low toxicity, excellent results Consider second application after 7 d
Pimecrolimus (Elidel®)	1% cream bid (>3 mo old) Use for as long as lesions persist and discontinue upon resolution of symptoms	AD (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive
Tacrolimus Topical (Protopic®)	0.03% (2-15 y/o) or 0.1% (>15 y/o) ointment bid Continue for duration of disease plus 1 wk after clearing	AD (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive
Crisaborole (Eucrisa®)	> 3 mos of age	AD mild to moderate	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive

Topical Vehicles

Ointment (water in oil): hydrate, greasy

Cream (oil in water): hydrate, variable

Lotion (powder in water): drying, cosmesis

Solutions (water, alcohol, propylene glycol)

Gel (solution that melts on contact with skin, alcohol): drying

Foam is a newer vehicle and several agents are now available in foam vehicles. Examples include Olux-E™ (clobetasol), Verdeso™ (desonide), Luxiq™ (betamethasone), and Enstilar™ (betamethasone propionate and calcipotriol))

Sprays: Lamisil™ (terbinafine) spray, Clobex™ spray (clobetasol)

Lacquers: Penlac® (ciclopirox), Jublia® (efinaconazole)

Deciding on the Amount of Steroid to Use (Adults)

1 palm = 1% BSA

1 fingertip unit (FTU) = amount of topical medication (from 5 mm nozzle) placed on pad of index finger from distal tip to DIP = 500 mg = 2% BSA

Therefore give 30 g for every 2 palms of area to cover (if applying steroid bid, 1 mo supply)

note ¼ to ½ FTU for younger children

Table 29. Common Oral Therapies

Drug Name	Dosing Schedule	Indications	Comments
Acitretin (Soriatane®)	25-50 mg PO once daily; maximum 75 mg/d	Severe psoriasis Other disorders of hyperkeratinization (ichthyosis, Darier's disease)	Monitoring Cr at baseline; LFTs at baseline, then q1-2 wk until stable, then as clinically indicated; fasting lipid panel at baseline, then q1-2 wk until stable, then if long-term treatment or high-risk patient, continue periodically; urine or serum pregnancy test x 2 at baseline, qmo during treatment, then q3 mo for >3 yr after discontinuation; glucose if diabetes; radiography periodically if long-term treatment Contraindications Women of childbearing potential unless strict contraceptive requirements are met Drug interactions Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives May be combined with PUVA phototherapy (known as re-PUVA)
Antivirals	famciclovir (Famvir®) 250 mg PO tid x 7-10 d (for 1st episode of genital herpes) 125 mg PO bid x 3 d (for recurrent genital herpes)	Chickenpox HZV Genital herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis	Side effects Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function Drug interactions Cladribine, varicella vaccine, zoster vaccine
	valacyclovir (Valtrex®) 1000 mg PO bid x 3 d (for 1st episode of genital herpes) 500 mg PO bid x 5 d (for recurrent genital herpes)		Side effects Dizziness, depression, abdominal pain Reduce dose if impaired renal function Drug interactions cladribine, foscarnet, varicella vaccine, zoster vaccine
Cyclosporine (Neoral®)	2.5-4 mg/kg/d PO divided bid Max 4 mg/kg/d After 4 wk may increase by 0.5 mg/kg/d q2 wk Concomitant dose of magnesium may protect the kidneys	Psoriasis May also be effective in: Lichen planus EM Recalcitrant urticaria Recalcitrant AD	Monitoring BUN/Cr x2 at baseline, then q2 wk x 3 mo, then if stable, qmo; BP x 2, CBC, K+, Mg2+, lipid panel, uric acid at baseline, then q2 wk x 3 mo, then qmo if stable, or more frequently if adjust dose; LFTs Contraindications Abnormal renal function, uncontrolled hypertension, malignancy (except NMSC), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long-term effects preclude use of cyclosporine for >2 yr; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug

Table 29. Common Oral Therapies

Drug Name	Dosing Schedule	Indications	Comments
Dapsone	50-100-150 mg PO once daily tapering to 25-50 mg PO once daily to as low as 50 mg 2x/wk	Dermatitis herpetiformis, neutrophilic dermatoses	Monitoring G6PD before treatment starts; CBC qwk x 4, qmo x 6, then q6 mo thereafter; LFTs at baseline, then periodically Side effects Neuropathy Hemolysis (Vitamin C and E supplementation can help prevent this) Drug interactions Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major) Often a dramatic response within hours
Doxycycline	100 mg PO bid	Acne vulgaris Rosacea Bullous pemphigoid	Contraindications Pregnancy, hepatic impairment, drug hypersensitivity Taking acitretin, isotretinoin, or penicillin antibiotic Oral typhoid vaccine
Isotretinoin (Accutane®, Clarus®, Epuris®)	0.5-1 mg/kg/d given once daily to achieve a total dose of 120 mg/kg (20-24 wk)	Severe nodular and/or inflammatory acne Acne conglobata Recalcitrant acne Widespread comedonal acne	Monitoring Fasting lipid panel at baseline, then q1-2 wk until lipid response to isotretinoin is established or if risk factors more frequently; LFTs at baseline, then q1-2 wk until stable; pregnancy test x 2 at baseline; glucose frequently if risk factors Contraindications Teratogenic – in sexually active females, 2 forms of reliable contraception necessary Generally regarded as unsafe in lactation Side effects Decreased night vision, decreased tolerance to contact lenses, dry mucous membranes May transiently exacerbate acne, dry skin Depression, myalgia Drug interactions Caution if used at the same time as tetracycline family antibiotics – both may cause pseudotumour cerebri Discontinue vitamin A supplements Drug may be discontinued at 16-20 wk when nodule count has dropped by >70%; a second course may be initiated after 2 mo prn Refractory cases may require >3 courses
Itraconazole (Sporanox®)	100-400 mg PO once daily, depending on infection Tinea corporis/cruris/versicolor: 200 mg PO once daily x 7 d Tinea pedis: 200 mg PO bid x 3 d Toenails: 200 mg PO bid x 3 d once per mo, repeated 3x Fingernail involvement only: 200 mg bid PO x 3 d once per mo	Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis	Contraindications CHF Side effects Serious hepatotoxicity Drug Interactions Inhibits CYP3A4 Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs) Give capsules with food, capsules must be swallowed whole
Ivermectin (Mectizan®, Stromectol®)	200-250 µg/kg PO weekly x 2 Take once as directed; repeat one wk later	Onchocerciasis (USA only) Not licensed for use in Canada Also effective for: scabies	No significant serious side effects Efficacious
Methotrexate	10-25 mg qwk, PO, IM, or IV Max: 30 mg/wk To minimize side effects, administer with folic acid supplementation: 1-5 mg once daily	Psoriasis AD Lymphomatoid papulosis May also be effective in: cutaneous sarcoidosis	Monitoring Pregnancy test at baseline; CBC at baseline, then q6 mo or more frequently if initial treatment, dose change, elevated serum level risk, or chemotherapy use; BUN/Cr, LFTs at baseline, then q4-8 wk or more frequently if initial Tx, dose change, elevated serum level risk, or chemotherapy use; serum albumin at baseline if psoriasis, then continue periodically; CXR at baseline; liver biopsy at baseline if psoriasis or if RA with history of alcoholism, persistently abnormal baseline LFTs, or chronic HBV or HCV infection, then if psoriasis repeat after total cumulative dose 1.5 g and each additional 1-1.5 g; serum drug levels if renal impairment, or high dose chemotherapy use Contraindications Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy May be combined with cyclosporine to allow lower doses of both drugs
OCPs (TriCyclen®, Diane 35®, Alesse®)	1 pill PO once daily	Hormonal acne (chin, jawline) Acne associated with polycystic ovarian syndrome or other endocrine abnormalities	All combined OCPs are helpful in acne but those listed on the left have undergone RCTs Contraindications Smoking, HTN, migraines with aura, pregnancy Routine gynecological health maintenance should be up to date
Spironolactone	50-100 mg PO once daily alone or with OCPs	Hormonal acne (chin, jawline) Acne with endocrine abnormality	Contraindications Pregnancy Side effects Menstrual irregularities at higher doses if not on OCPs Breast tenderness, mild diuresis common Risk of hyperkalemia – counsel patients to reduce intake of potassium rich foods such as bananas
Terbinafine (Lamisil®)	250 mg PO once daily x 2 wk Fingernails x 6 wk Toenails x 12 wk Confirm diagnosis prior to treatment	Onychomycosis Tinea corporis, cruris, pedis, capitis	Contraindications Pregnancy, chronic or active liver disease Drug interactions Potent inhibitor of CYP2D6; use with caution when also taking β-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics Drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity
Tetracycline	250-500 mg PO bid to tid Taken 1 h before or 2 h after a meal	Acne vulgaris Rosacea Bullous pemphigoid	Contraindications Severe renal or hepatic dysfunction

Traumatic and Mechanical Disorders

PERNIOSIS

Definition
- abnormal inflammatory response to cold, damp, non-freezing conditions

Epidemiology
- common in the United Kingdom and northwestern Europe; common for those whose homes lack central heating
- women, the elderly, and children are most affected

Clinical Features
- single or multiple erythematous to blue-violet macules, nodules, or papules
- blistering or ulceration seen in severe cases
- lesions present on the distal toes and fingers, and less often on the heels, ears, and nose
- symptoms of burning, itching, or pain, lasting 1-3 wk

Pathophysiology
- unknown but may be associated with cryoglobulins or cold agglutinins

Differential Diagnosis
- chilblain lupus erythematosus, lupus pernio

Treatment
- warming clothing, avoidance of cold, damp conditions, keeping feet dry, smoking cessation
- nifedipine, nicotinamide, phenoxybenzamine, sympathectomy, and erythemogenic UVB phototherapy

TRAUMATIC AURICULAR HEMATOMA (CAULIFLOWER EAR)
- see Plastic Surgery, PL34

ANIMAL BITES
- see *Cellulitis, D30*

BITES
- see Plastic Surgery, PL11

BURN INJURIES
- see Plastic Surgery, PL18

FROSTBITE
- see Emergency Medicine, ER46

KELOIDS
- see *Keloids, D10*

THERMAL INJURY
- see Plastic Surgery, PL18

UV LIGHT INJURIES
- see *Sunscreens and Preventative Therapy, D52*

Landmark Dermatology Trials

Trial Name	Reference	Clinical Trial Details
MELANOMA		
NCT00094653	NEJM 2010; 363:711-723	**Title:** Improved Survival with Ipilimumab in Patients with Metastatic Melanoma **Purpose:** To compare ipilimumab administered with or without a glycoprotein 100 (gp100) peptide vaccine to gp100 alone in patients with previously treated metastatic melanoma. **Methods:** 676 HLA-A*0201–positive patients with unresectable stage III or IV melanoma, were randomized in a 3:1:1 ratio to receive ipilimumab+gp100 (n=403), ipilimumab alone (n=137), or gp100 alone (n=136). **Results:** Median survival was 10 mo among patients receiving ipilimumab plus gp100, as compared with 6.4 mo among patients receiving gp100 alone and 10.1 mo median survival with ipilimumab alone. No significant difference in survival between ipilimumab groups was noted. Grade 3 or 4 immune-related adverse events occurred in 10-15% of patients treated with ipilimumab and 3% treated with gp100 alone. **Conclusions:** Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma.
BRIM-3	NEJM 2011; 364:2507-2516	**Title:** Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation **Purpose:** To compare the efficacy of BRAF kinase inhibitor vemurafenib (PLX4032) vs. dacarbazine in patients with metastatic melanoma. **Methods:** Phase 3 RCT comparing vemurafenib with dacarbazine in 675 patients with untreated, metastatic melanoma with BRAF V600E mutation. Patients were randomized to receive vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg/m2 of body-surface area intravenously every 3 wk). Co-primary endpoints: overall and progression-free survival. **Results:** At 6 mo, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group. Vemurafenib was associated with a relative reduction of death risk by 63% and a reduction of 74% in the risk of either death or disease progression vs. dacarbazine. Response rates were reported to be 48% for vemurafenib and 5% for dacarbazine. Common adverse events associated with vemurafenib: arthralgia, rash, fatigue, alopecia, keratoacanthoma, photosensitivity, nausea, and diarrhea. **Conclusions:** Vemurafenib improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation.
RELATIVITY-047	NEJM 2022;386:24-34	Title: Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma Purpose: To assess the efficacy of relatlimab (LAG-3-blocking antibody) plus nivolumab (PD-1-blocking antibody) as compared to nivolumab alone on previously untreated metastatic or unresectable melanoma. Methods: Phase 2-3, double-blind, randomized trial of 714 patients with previously untreated stage III or IV metastatic or unresectable melanoma. Patients were randomized to receive relatlimab-nivolumab or nivolumab alone q4 wk. Primary end-point was progression-free survival. Results: Patients receiving relatlimab-nivolumab had a median progression-free survival of 10.1 mo as compared to 4.6 mo in those receiving nivolumab alone (HR, 0.75; 95% CI, 0.62-0.92; p=0.006). Conclusions: Relatlimab plus nivolumab displays greater progression-free survival than nivolumab alone in patients with previously untreated metastatic or unresectable melanoma.
NCT03698019	NEJM 2023;388:813-823	**Title:** Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma **Purpose:** To determine the effect of neoadjuvant and adjuvant pembrolizumab on event-free survival in patients with resectable stage III-IV melanoma as compared to adjuvant therapy alone. **Methods:** Patients with resectable stage IIIB to IVC melanoma (n=313) were randomly assigned to receive neoadjuvant-adjuvant pembrolizumab (before and after surgery) or adjuvant therapy alone (after surgery) for 1 yr, or until the development of toxic effects or disease recurrence. Primary endpoint was event-free survival. **Results:** Event-free survival was significantly longer in patients receiving neoadjuvant-adjuvant pembrolizumab compared to adjuvant therapy alone (p=0.004). Event-free survival was 72% (95% CI, 64-80) and 49% (95% CI, 41-59) in the neoadjuvant-adjuvant and adjuvant groups, respectively. **Conclusions:** Neoadjuvant-adjuvant treatment with pembrolizumab results in longer event-free survival in patients with resectable stage III or IV melanoma than adjuvant treatment alone.
PSORIASIS		
BE VIVID	Lancet 2021, 397: 475-486	**Title:** Bimekizumab versus Ustekinumab for the Treatment of Moderate to Severe Plaque Psoriasis (BE VIVID): Efficacy and Safety from a 52 wk, Multicentre, Double-blind, Active Comparator and Placebo-Controlled Phase 3 Trial **Purpose:** To compare the efficacy and safety of a 52 wk treatment with bimekizumab vs. placebo vs. ustekinumab in patients with moderate to severe plaque psoriasis. **Methods:** Multicentre RCT involving adults 18 yr of age or older with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index [PASI] score ≥12, ≥10% body surface area affected by psoriasis, and Investigator's Global Assessment [IGA] score ≥3 on a five-point-scale). Patients were randomly assigned (4:2:1) to bimekizumab 320 mg every 4 wk, ustekinumab 45 mg or 90 mg at wk 0 and 4, then every 12 wk, or placebo every 4 wk. At 16 wk, patients in the placebo group were switched to bimekizumab. **Results:** The study enrolled 567 patients. At wk 16, 85% of patients in the bimekizumab group had PASI90 vs. 50% in the ustekinumab group, and 5% in the placebo group. Approximately 84% of patients in the bimekizumab group had an IGA response vs. 53% in the ustekinumab group, and 5% in the placebo groups. Major cardiac adverse events occurred in 5 patients with pre-existing CV risk factors in the bimekizumab group, whereas none occurred in the ustekinumab group. Additionally, oral candidiasis rates were higher than placebo and ustekinumab, and one case of IBD was recorded. **Conclusions:** Bimekizumab was more efficacious than ustekinumab and placebo in the treatment of moderate to severe plaque psoriasis. Additional studies may be needed to assess safety.
ADVANCE	J Am Acad Dermatol 2022;86:77-85	**Title:** Efficacy and Safety of Apremilast (Phosphodiesterase Inhibitor) in Patients with Mild-to-moderate Plaque Psoriasis **Purpose:** To evaluate the effectiveness of apremilast in treating mild-to-moderate plaque psoriasis. **Methods:** A phase 3, double-blind, placebo-controlled study was conducted in 595 adults with mild-to-moderate psoriasis. Patients were randomized to either 30 mg twice daily oral apremilast or placebo (oral tablets of no pharmacological significance) for the first 16 wk. The outcome of interest was the achievement of a static Physician Global Assessment score of 0 (clear) or 1 (almost clear). **Results:** A significantly larger proportion of the apremilast group met the desired static Physician Global Assessment response rate when compared to the placebo group (21.6% vs. 4.1%). **Conclusions:** Apremilast proved effective as a treatment for mild-to-moderate plaque psoriasis.

Trial Name	Reference	Clinical Trial Details
ATOPIC DERMATITIS		
ECZTRA	Br J Dermatol 2021;184:450-463	**Title:** Tralokinumab (Monoclonal Antibody) Plus Topical Corticosteroids (TCS) for the Treatment of Moderate-to-severe Atopic Dermatitis **Purpose:** To evaluate the safety and effectiveness of tralokinumab in treating moderate to severe atopic dermatitis. **Methods:** A double-blind placebo study was conducted using 380 patients, 253 of which were randomized to the treatment group (subcutaneous tralokinumab 300 mg every 2 wk with TCS as needed over 16 wk) and the remainder to the placebo group (placebo every 2 wk with TCS as needed over 16 wk). The outcome of interest was a 75% improvement in the Eczema Area and Severity Index (EASI). **Results:** After 16 wk of treatment, there was a significantly larger proportion of patients treated with tralokinumab (56%) that achieved the EASI benchmark when compared to the placebo group (35.7%). **Conclusions:** Tralokinumab in combination with the current standard of care was proven to be effective and well-tolerated in treatment for atopic dermatitis.
ADvocate 1 and ADvocate2	NEJM 2023;388:1080-1091	**Title:** Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis **Purpose:** To assess the efficacy of lebrikizumab, an IL-13 monoclonal antibody, on moderate to severe AD. **Methods:** Two RCTs were conducted (n=379 and n=427) in which adults (≥18 y/o) or adolescents (12-18 y/o) with moderate to severe AD were randomly assigned to receive lebrikizumab or placebo (SC every 2 wk) for 16 wk. Primary outcome was an Investigator's Global Assessment (IGA) score of 0-1 (range 0-4 from clear to severe disease). Secondary outcomes included 75% improvement in the Eczema Area and Severity Index (EASI-75). **Results:** The primary outcome was met in 43.1% and 12.7% of patients on lebrikizumab and placebo, respectively ($p<0.001$). EASI-75 was attained in 58.8% and 16.2% of patients on lebrikizumab and placebo, respectively ($p<0.001$). **Conclusions:** Lebrikizumab is effective in the treatment of moderate to severe AD in adolescent and adult patients.
VITILIGO		
TRuE-V1 & TRuE-V2	NEJM 2022;387:1445-1455	**Title:** Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo **Purpose:** To determine the effect of ruxolitinib cream (JAK1/2 inhibitor) on repigmentation in adults with vitiligo. **Methods:** Two RCTs were conducted (n=330 in TRuE-V1, n=334 in TRuE-V2) in which patients aged >12 with non-segmental vitiligo (≤10% BSA depigmentation) were randomly assigned to receive 1.5% ruxolitinib cream or vehicle control bid for 52 wk. Primary endpoint was a 75% or greater decrease in the facial Vitiligo Area Scoring Index (F-VASI75 response). **Results:** Treatment with ruxolitinib resulted in a F-VASI75 response in 29.8% as compared to 7.8% in controls in TRuE-V1 (RR, 4.0; 95% CI, 1.9 to 8.4; $p<0.001$). Similarly, treatment with ruxolitinib resulted in a F-VASI75 response in 30.9% as compared to 11.4% in controls in TRuE-V2 (RR, 2.7; 95% CI, 1.5 to 4.9; $p<0.001$). Adverse events of application-site acne, nasopharyngitis, and application-site pruritus were observed in 54.8% and 62.3% of patients on ruxolitinib in TRuE-V1 and TRuE-V2 trials, respectively. **Conclusions:** Ruxolitinib cream is superior to vehicle control in the repigmentation of vitiligo in adult patients at 52 wk, but use is associated with application-site adverse events such as acne and pruritus.
ALOPECIA AREATA		
BRAVE-AA1 & BRAVE-AA2	NEJM 2022;386:1687-1699	**Title:** Two Phase 3 Trials of Baricitinib for Alopecia Areata **Purpose:** To assess the efficacy of baricitinib (JAK1/2 inhibitor) on alopecia areata. **Methods:** Two RCTs were conducted (n=654 in BRAVE-AA1, n=546 in BRAVE-AA2) in which adult patients with severe alopecia areata were randomly assigned to receive oral baricitinib 1x daily (2mg or 4mg) or placebo for 36 wk. Primary outcome was assessment of the Severity of Alopecia Tool (SALT) score (range 0-100, no scalp hair loss to complete scalp hair loss). **Results:** In BRAVE-AA1, SALT scores ≤20 were achieved in 38.8% of patients in the 4mg baricitinib group, 22.8% in the 2mg baricitinib group, and 6.2% in the placebo group ($p<0.001$ for each dose vs. placebo). In BRAVE-AA2, SALT scores ≤20 were achieved in 35.9% of patients in the 4mg baricitinib group, 19.4% in the 2mg baricitinib group, and 3.3% in the placebo group ($p<0.001$ for each dose vs. placebo). **Conclusions:** This study suggests that baricitinib is more effective in the hair regrowth of patients with severe alopecia areata as compared to placebo.

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ER Emergency Medicine

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Acronyms

AAA	abdominal aortic aneurysm	D10W	dextrose 10% in water	IVC	inferior vena cava	RUSH	rapid ultrasound for shock and hypotension
ABG	arterial blood gas	D50W	dextrose 50% in water	LBBB	left bundle branch block	SAH	subarachnoid hemorrhage
ACEI	angiotensin-converting enzyme inhibitor	D25W	dextrose 25% in water	LOC	level of consciousness	SBP	spontaneous bacterial peritonitis
ACLS	Advanced Cardiac Life Support	DGI	disseminated gonococcal infection	LP	lumbar puncture	SCI	spinal cord injury
ACS	acute coronary syndrome	DIC	disseminated intravascular coagulation	LSD	lysergic acid diethylamide	SHoC	sonography in hypotension and cardiac arrest
AED	automatic external defibrillator	DKA	diabetic ketoacidosis	LVH	left ventricular hypertrophy	SJS	Stevens-Johnson syndrome
AFib	atrial fibrillation	DRE	digital rectal exam	MAP	mean arterial pressure	SNS	sympathetic nervous system
AG	anion gap	DT	delirium tremens	MDI	metered dose inhaler	SOB	shortness of breath
AHA	American Heart Association	DVT	deep vein thrombosis	MDMA	methylenedioxy-methamphetamine	SSRI	selective serotonin reuptake inhibitor
ARDS	acute respiratory distress syndrome	ED	emergency department	MMSE	mini-mental state examination	SSSS	staphylococcal scalded skin syndrome
AVN	avascular necrosis	EM	erythema multiforme	MVC	motor vehicle collision	STEMI	ST elevation myocardial infarction
AVPU	alert, voice, pain, unresponsive	ESR	erythrocyte sedimentation rate	NS	normal saline	TBI	traumatic brain injury
AXR	abdominal x-ray	ETT	endotracheal tube	NSTEMI	non-ST elevation myocardial infarction	TCA	tricyclic antidepressant
Bi-PAP	bilevel positive airway pressure	FAST	focused assessment with sonography for trauma	PID	pelvic inflammatory disease	Tdap	tetanus, diphtheria, acellular pertussis
BSA	body surface area	FEV1	forced expiratory volume in 1 second	PNS	parasympathetic nervous system	TEN	toxic epidermal necrolysis
BUN	blood urea nitrogen	FFP	fresh frozen plasma	POG	plasma osmolar gap	TIA	transient ischaemic attack
CAS	Children's Aid Society	GERD	gastroesophageal reflux disease	pRBC	packed red blood cells	TSS	toxic shock syndrome
CIWA	Clinical Institute Withdrawal Assessment for Alcohol	GCS	Glasgow Coma Scale	PT	prothrombin time	VBG	venous blood gas
CNS	central nervous system	HEENT	head eyes ears nose throat	PTT	partial thromboplastin time	VFib	ventricular fibrillation
CPAP	continuous positive airway pressure	HI	head injury	RAPD	relative afferent pupillary defect	VTach	ventricular tachycardia
CPP	cerebral perfusion pressure	H&N	head and neck	RBBB	right bundle branch block	VTE	venous thromboembolism
CRP	c-reactive protein	IBD	inflammatory bowel disease	ROM	range of motion		
CVA	costovertebral angle	IBS	irritable bowel syndrome	RPS	rapid primary survey		
CVS	cardiovascular system	ICS	intercostal space	RSI	rapid sequence induction		
D5W	dextrose 5% in water	INR	international normalized ratio	rt-PA	recombinant tissue plasminogen activator		

Patient Assessment/Management

1. Rapid Primary Survey

- Airway maintenance with C-spine control
- Breathing and ventilation
- Circulation (pulses, hemorrhage control)
- Disability (neurological status)
- Exposure (complete) and Environment (temperature control)
  - continually reassessed during secondary survey
  - changes in hemodynamic and/or neurological status necessitates a return to the primary survey beginning with airway assessment
- **IMPORTANT:** always watch for signs of shock while doing primary survey
- addressing the "ABCs" is the hallmark of the emergency department
  - in the setting of cardiac arrest, the approach changes to the "CABs": chest compressions, airway, and breathing
  - CAB can also be applied in massive trauma situations in the setting of massive blood loss to treat hypovolemic shock

Approach to the Critically Ill Patient
1. Rapid Primary Survey (RPS)
2. Resuscitation (often concurrent with RPS)
3. Detailed Secondary Survey
4. Definitive Care

Signs of Airway Obstruction
- Agitation, confusion, "universal choking sign"
- Respiratory distress
- Failure to speak, dysphonia, stridor
- Cyanosis

A. AIRWAY
- first priority is to secure airway
- assume a cervical injury in every trauma patient and immobilize with collar
- assess ability to breathe and speak
- listen for evidence of airway obstruction (e.g. stridor)
- can change rapidly, therefore reassess frequently
- assess for facial fractures/edema/burns (impending airway collapse)

Airway Management
- anatomic optimization to allow for oxygenation and ventilation

1. Basic Airway Management
- protect the C-spine
- chin lift (if C-spine injury not suspected) or jaw thrust to open the airway
- sweep and suction to clear mouth of foreign material

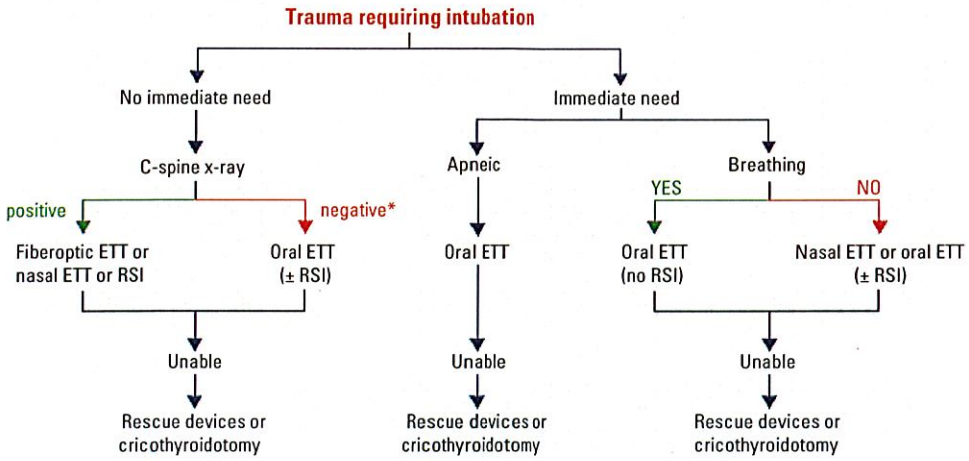
2. Temporizing Measures
- nasopharyngeal airway (if gag reflex present, i.e. conscious)
- oropharyngeal airway (if gag reflex absent, i.e. unconscious)
- "rescue" airway devices (e.g. laryngeal mask airway, Combitube®)
- especially for children <8 yo, transtracheal jet ventilation through cricothyroid membrane (rarely used and best to consider opting for a definitive airway)

3. Definitive Airway Management

- ETT intubation (with in-line stabilization of C-spine if applicable)
  - orotracheal ± RSI preferred
  - nasotracheal may be better tolerated in conscious patient
- surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
- cricothyroidotomy

Contraindications to Intubation

- see Table 2, Anesthesia, A8
- supraglottic/glottic pathology that would preclude successful intubation
- provider safety: e.g. SARS-CoV-2 (COVID-19) precludes intubation, CPR, and other aerosol generating procedures in the absence of full PPE



*** Note:** clearing the C-spine requires radiologic and clinical assessment

Figure 1. Approach to endotracheal intubation in an injured patient

B. BREATHING

Breathing Assessment

- quantitative measures of respiratory function: rate, oximetry, ABG, A-a gradient
- **Look**
  - mental status (anxiety, agitation, decreased LOC), chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring, increased work of breathing, midline trachea, flail chest
- **Listen**
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping, adventitious sounds (e.g. wheezes, crackles)
- **Feel**
  - tracheal shift, chest wall for crepitus (e.g. subcutaneous emphysema, rib fracture), flail segments, sucking chest wounds

Management of Breathing

- treat likely underlying cause (e.g. bronchodilators, epinephrine, diuresis)
- optimize oxygenation: nasal prongs → simple face mask → venturi mask → non-rebreather mask → high-flow nasal cannula → CPAP/BiPAP (in order of increasing FiO_2)
- bag-valve mask and CPAP to supplement inadequate ventilation

C. CIRCULATION

Definition of Shock

- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities)

Table 1. Major Types of Shock

Hypovolemic	Cardiogenic	Distributive	Obstructive
Hemorrhage (external and internal)	Myocardial ischaemia	Septic (see *Sepsis, ER38*)	Cardiac tamponade (see *Chest Trauma, ER11*)
Severe burns	Dysrhythmias	Anaphylactic (see *Anaphylaxis and Allergic Reactions, ER29*)	Tension pneumothorax (see *Chest Trauma, ER11*)
High output fistulas	CHF	Neurogenic (spinal cord injury)	PE (see *Venous Thromboembolism, ER32*)
Dehydration (diarrhea, DKA)	Cardiomyopathies		Aortic stenosis
	Cardiac valve problems		Constrictive pericarditis

Clinical Evaluation

- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities (except neurogenic and septic shock), and reduced central venous pressure
- late: hypotension, altered mental status, reduced urine output



Medications that can be Delivered via ETT

NAVEL
Naloxone (Narcan®)
Atropine
Ventolin® (salbutamol)
Epinephrine
Lidocaine



Indications for Intubation (4 P's)
Patent airway
Protects against aspiration (e.g. decreasing GCS <8)
Positive pressure ventilation
Pulmonary toilet (suction)



Rescue Techniques in Intubation
- Bougie (used like a guidewire)
- GlideScope®
- Lighted stylet (uses light through skin to determine if ETT in correct place)
- Fiberoptic intubation (uses fiberoptic cable for indirect visualization)



Video Laryngoscopes

Stylets
Bonfil
Rigid and flexible laryngoscope (RIFL)
SensaScope®

Guide Channels
AirTraq™
Pentax AWS®
Res-Q-Scope II®
Traditional (non-guided)
GlideScope®



Noisy breathing is obstructed breathing until proven otherwise



O_2 Delivery Methods

	FiO_2	Amount Given
Nasal Prongs	25-40%	1-6 L/min
Face Mask	40-60%	5-10 L/min
Non-rebreather	80-90%	15 L/min
High-flow Nasal Cannula	up to 100%	15-60L/min
CPAP/BiPAP	up to 100%	



Shock in a trauma patient is hemorrhagic until proven otherwise

Table 2. Estimation of Degree of Hemorrhagic Shock

Class	I	II	III	IV
Blood Loss	<750 cc	750-1500 cc	1500-2000 cc	>2000 cc
% of Blood Volume	<15%	15-30%	30-40%	>40%
Pulse	<100	>100	>120	>140
Blood Pressure	Normal	Normal	Decreased	Decreased
Respiratory Rate	20	30	35	>45
Capillary Refill	Normal	Decreased	Decreased	Decreased
Urinary Output	30 cc/h	20 cc/h	10 cc/h	None
Fluid Replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

Management of Hemorrhagic Shock

- clear airway and assess breathing either first or simultaneously
- apply direct pressure on external wounds while elevating extremities. Do not remove impaled objects in the emergency room setting as they may tamponade bleeds
- start two large bore (14-16 G) IVs in the brachial/cephalic vein of each arm
- permissive hypotension with pRBC transfusion, ideally crossmatched. If crossmatched blood is unavailable in a timely manner, consider O- for women of childbearing age and O+ for men. Use FFP, platelets or tranexamic acid in early bleeding. If available, activate 'massive transfusion protocol'
- consider common sites of internal bleeding (abdomen, chest, pelvis, long bones, GI tract) where surgical intervention may be necessary

D. DISABILITY

- assess LOC using GCS
- pupils
  - assess equality, size, symmetry, reactivity to light
- unequal or sluggish suggests local eye problem or lateralizing CNS lesion
- non-reactive pupils + decreased LOC: structural cause (especially if asymmetric)
- lateralizing motor deficits

Glasgow Coma Scale

- GCS is for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated; change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3-part score: Eyes + Verbal + Motor = Total
- if patient intubated, GCS score reported out of 10 + T (T = tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

Eyes Open		Best Verbal Response		Best Motor Response	
Spontaneously	4	Answers questions appropriately	5	Obeys commands	6
To voice	3	Confused, disoriented	4	Localizes to pain	5
To pain	2	Inappropriate words	3	Withdraws from pain	4
No response	1	Incomprehensible sounds	2	Decorticate (flexion)	3
		No verbal response	1	Decerebrate (extension)	2
				No response	1

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury See *Table 36, ER57 for Modified GCS for infants and children*

E. EXPOSURE/ENVIRONMENT

- expose patient completely and assess entire body for injury; log roll to examine back
- DRE for trauma patients
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation

- done concurrently with primary survey
- attend to ABCs
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP, and O_2 monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

Causes of Shock

SHOCKED
Septic, spinal/neurogenic
Hemorrhagic
Obstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
anaphylactiK
Endocrine (e.g. Addison's, myxedema, coma)
Drugs

Common Sites of Bleeding

- External (e.g. scalp)
- Chest
- Abdomen (peritoneum, retroperitoneum)
- Pelvis
- Long bones
- GI

Fluid Resuscitation
Give bolus until HR decreases, urine output increases, and patient stabilizes

- Maintenance: 4:2:1 rule
- 0-10 kg: 4 cc/kg/h
- 10-20 kg: 2 cc/kg/h
- Remaining weight: 1 cc/kg/h
- Replace ongoing losses and deficits (assume 10% of body weight)

Shortcut for calculating maintenance fluids for any patient ≥20 kg: Fluid rate (in cc/hr) = 40 + patient's weight in kg

Unilateral, Dilated, Non-Reactive Pupil

- Focal mass lesion
- Epidural hematoma
- Subdural hematoma

Contraindications to Foley Insertion
Blood at urethral meatus
Scrotal hematoma
High-riding prostate on DRE

NG Tube Contraindications
Significant mid-face trauma
Basal skull fracture

Table 4. 2010 AHA CPR Guidelines with 2020 Updates

Step/Action	Adult: >8 yr	Child: 1-8 yr	Infant: <1 yr
Airway	Head tilt-chin lift; jaw thrust without head extension if concern for spinal injury		
Breaths	2 breaths at 1 s/breath – stop once see chest rise		
Severe Foreign-Body Airway Obstruction	Abdominal thrust (if conscious)		Back blows and chest compressions
Compressions			
Compression landmarks	In the centre of the chest, lower half of the sternum		Just below nipple line
Compression method: push hard and fast, and allow for complete recoil	2 hands: heel of 1 hand with heel of second hand on top	2 hands: heel of 1 hand with second on top, or 1 hand: heel of 1 hand only	2 fingers, or thumbs
Compression depth	2-2.4 inches	About 1/3 to 1/2 the depth of the chest	
Compression rate	100-120/min with complete chest wall recoil between compressions		
Compression-ventilation ratio	30 compressions to 2 ventilations	15 compressions to 2 ventilations	
Compression-only CPR	Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only		
Defibrillation	Immediate defibrillation if a shockable rhythm (ventricular fibrillation or ventricular tachycardia) is identified Compressions (5 cycles/2 min) and use AED if unwitnessed arrest Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available		

See Anesthesia, *A32 for ACLS Guidelines*

Sodium Bicarbonate Use During Pediatric Cardiopulmonary Resuscitation
Pediatr Crit Care Med 2022;23:784
Purpose: To determine the relationship between sodium bicarbonate use and outcomes during pediatric cardiac arrest.
Methods: Secondary analysis of the prospective, multicenter RCT (ICU-RESUscitation Project) in patients between 37 weeks post-conceptual age and 18 years old who received CPR.
Results: In patients who received sodium bicarbonate, there was a lower survival to hospital discharge (adjusted odds ratio [aOR], 0.7; 95% CI, 0.54–0.92; p = 0.01) and lower survival to hospital discharge with favorable neurologic outcome rates (aOR, 0.69; 95% CI, 0.53–0.91; p = 0.007).
Conclusions: Sodium bicarbonate use in pediatric CPR is associated with poorer outcomes.

3. Secondary Survey

- start after primary survey completed and initial resuscitation and stabilization initiated
- identify other injuries or areas of concern
- full physical exam and CT if indicated by history and exam findings (C-spine, chest, abdomen, and pelvis – required in blunt trauma, consider T-spine and L-spine if indicated)

HISTORY

- "SAMPLE": Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury or illness

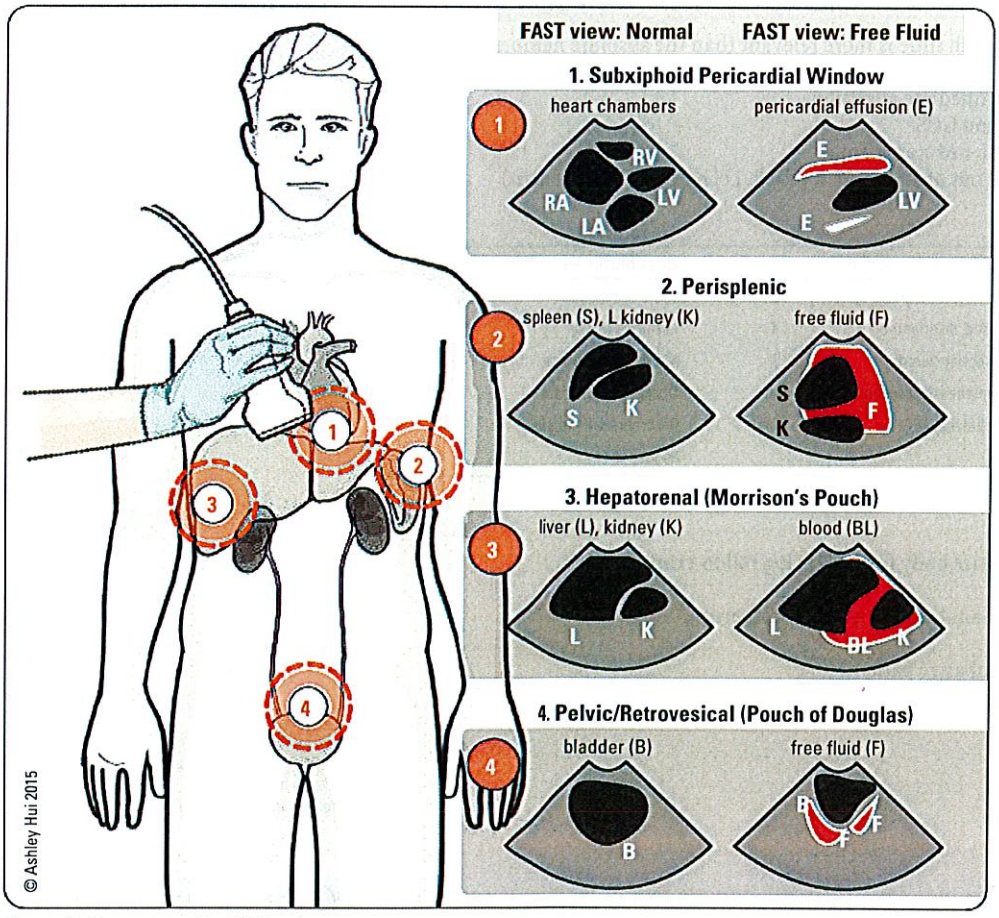


Figure 2. Four areas of a FAST

PHYSICAL EXAM *(see Traumatology, ER7)*

Head and Neck
- inspect for periorbital bruising, mastoid bruising, ocular injuries
- palpate facial bones, scalp
- bite occlusion test with tongue depressor (if patient awake)

Chest
- inspect for equal chest rise, and work of breathing
- auscultate lung fields
- palpate for subcutaneous emphysema, step off and deformities

Abdomen
- assess for peritonitis, abdominal distention, focal areas of tenderness
- DRE for select cases: suspected GI bleed, and in trauma (if pelvic fracture or frank hematuria)

Musculoskeletal
- examine all extremities for swelling, deformity, contusions, tenderness, ROM
- check for pulses (using Doppler probe if not palpable)
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis and assess pelvic stability (lateral, AP, vertical)

Neurological
- GCS
- full cranial nerve exam
- assess limb strength and sensation with coarse and fine touch in the cooperative patient
- unconscious patient: assess GCS, breathing pattern, pupils and reaction to light/RAPD, limb tone, reflexes (including corneal and gag), posturing



Non-contrast head CT is the best imaging modality for intracranial injury



Consider use of **POCUS** to guide resuscitation

If hypotensive: consider using **RUSH** or **SHoC** protocol

If trauma: use **eFAST**

INITIAL IMAGING
- non-contrast CT head/face/C-spine (rule out fractures and bleeds)
- CXR
- FAST (see *Figure 2, ER5*) or CT abdomen/pelvis (if stable)
- pelvis x-ray

Ethical Considerations

Consent to Treatment: Adults
- see Ethical, Legal, and Organizational Medicine, ELOM12
- Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury AND obtaining consent is either: a) not possible, OR b) would increase risk to the patient
  - assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
- be aware of who the legal substitute decision maker (SDM) is and contact them early
- exceptions to the Emergency Rule – treatment cannot be initiated if:
  - a competent patient has previously refused the same or similar treatment and there is no evidence to suggest t he patient's wishes have changed (e.g. after an SDM has been contacted to clarify patient's wishes)
  - an advanced directive is available (e.g. do not resuscitate order), though this is still controversial
  - NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
- if in doubt, initiate treatment
- care can be withdrawn if necessary at a later time or if wishes are clarified by family

Consent to Treatment: Children
- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions, unless the child is an emancipated or mature minor (age cut-off varies by province)
- if parents refuse treatment that is considered life-saving or will potentially alter the child's quality of life, act in the best interest of the child, while involving local child protection services and continuing to engage with parents/guardians

Duty to Report
- law may vary depending on province and/or state
- e.g. gunshot wounds, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others

Jehovah's Witnesses
- capable adults have the right to refuse medical treatment
- some patients may decline whole blood, pRBCs, platelets, and plasma, even if considered life-saving
- clarify the use of albumin, immunoglobulins, hemophilic preparations, or other derived products
- parents can refuse care for their child if it is against their belief; evaluate risk of treatment refusal and ensure parents are making an informed decision. If life-saving treatment is refused, can act in the child's interest but will need to involve CAS immediately
- document discussion about treatments, alternatives offered, and potential risks (and their likelihood)

Traumatology

- epidemiology
  - 4.9 million deaths are caused by injuries worldwide (data from 2016)
  - in Canada, traumatic injuries contributed more than 269000 hospitalizations and 17000 deaths (data from 2018)
  - leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
  - minutes: death usually at the scene from lethal injuries
  - early: death within 4-6 h – "golden hour" (decreased mortality with trauma care)
  - days-weeks: death from multiple organ dysfunction, sepsis, VTE, etc.
- injuries fall into two categories
  - blunt (most common): MVC, pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - penetrating (increasing in incidence): gunshot wound, stabbing, impalement



Always completely expose and count the number of wounds

Considerations for Traumatic Injury

- important to know the mechanism of injury to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about HI, loss of consciousness, amnesia, vomiting, headache, and seizure activity

Table 5. Mechanisms and Considerations of Traumatic Injuries

Mechanism of Injury	Special Considerations	Associated Injuries
MVC	Vehicle(s) involved: weight, size, speed, damage Location of patient in vehicle Use and type of seatbelt Ejection of patient from vehicle Entrapment of patient under vehicle Airbag deployment Helmet use in motorcycle collision	Head-on collision: head/facial, thoracic (aortic), lower extremity Lateral/T-bone collision: head, C-spine, thoracic, abdominal, pelvic, and lower extremity Rear-end collision: hyper-extension of C-spine (whiplash injury) Rollover: all of the above may be associated injuries
Pedestrian-Automobile Impact	High morbidity and mortality Vehicle speed is an important factor Site of impact on car	Adults tend to be struck in lower legs (lower extremity injuries), impacted against car (truncal injuries), and thrown to ground (HI)
Falls	Distance of fall: 50% mortality at 4 storeys and 95% mortality at 7 storeys (1 storey = 12 ft = 3.6 m) Landing position (vertical vs. horizontal)	Vertical: lower extremity, pelvic, and spine fractures; HI Horizontal: facial, upper extremity, and rib fractures; abdominal, thoracic, and HI



High-Risk Injuries
- MVC at high speed, resulting in ejection from vehicle
- Motorcycle collisions
- Vehicle vs. pedestrian crashes
- Fall from height >12 ft (3.6 m)



Vehicle vs. Pedestrian Crash

In all patients, don't assume injuries are isolated

Waddell's triad in pediatric patients: Tibia-fibula or femur fracture; Truncal or abdominal injury; Craniofacial injury

Head Trauma



- see Neurosurgery, NS35

ASSESSMENT OF BRAIN INJURY

History
- prehospital status
- mechanism of injury

Physical Exam
- assume C-spine injury until ruled out
- isolated penetrating trauma can forego c-spine mobilization if a neurological exam can be performed
- vital signs
  - shock (not likely due to isolated brain injury, except in infants; assume other injury and/or spinal shock)
  - look for Cushing's response to increasing ICP (bradycardia, HTN, irregular respirations)
- severity of injury determined by
  1. LOC
     - GCS ≤8 intubate, any change in score of 3 or more = serious injury
     - GCS of mild TBI = 13-15, moderate = 9-12, severe = 3-8
  2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)
     - may become subtler with increasing severity of injury
     - reassess frequently



Signs of Increased ICP
- Deteriorating LOC (hallmark)
- Deteriorating respiratory pattern
- Cushing reflex (high BP, low HR, irregular respirations)
- Lateralizing CNS signs (e.g. cranial nerve palsies, hemiparesis)
- Seizures
- Papilledema (occurs late)
- N/V and headache



Signs of Basal Skull Fracture
- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF rhinorrhea/otorrhea

Investigations
- labs: CBC, electrolytes, INR/PTT, glucose, toxicology screen
- CT head (non-contrast) to exclude intracranial hemorrhage/hematoma
- C-spine imaging



Warning Signs of Severe Head Injury
GCS <8
Deteriorating GCS
Unequal pupils
Lateralizing signs
N.B. Altered LOC is a hallmark of brain injury

Management
- goal in ED: reduce secondary injury by avoiding hypoxia, ischaemia, decreased CPP, seizure
- general
  - ABCs
  - ensure oxygen delivery to brain through intubation and prevent hypercarbia
  - maintain BP (sBP >90)
  - treat other injuries
- early neurosurgical consultation for acute and subsequent patient management after imaging
- seizure treatment/prophylaxis
  - phenytoin,levetiracetam
- treat suspected raised ICP
  - intubate (neuroprotective RSI where possible)
  - administer fentanyl or lidocaine at least 2 minutes prior to RSI
  - calm (sedate) if risk for high airway pressures or agitation
  - hyperventilate (100% O_2) to a pCO_2 of 30-35 mmHg
  - elevate head of bed to 20°
  - adequate BP to ensure good cerebral perfusion
  - give mannitol 1g/kg infused rapidly (contraindicated in shock/renal failure) or 3 mL/kg of hypertonic (3%) saline
  - remove c-collar if possible

Disposition
- neurosurgical ICU admission for severe HI
- in a hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor HI not requiring admission, provide 24 h HI protocol (regular assessment of the patient for signs of loss of consciousness, confusion or amnesia) to competent caregiver, follow up with concussion and/or sports clinic as even seemingly minor HI may cause lasting deficits



Canadian CT Head Rule
Lancet 2001;357:1391-1396
CT Head is only required for patients with minor HI and with any one of the following
- High-Risk (for neurological intervention)
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture
- Vomiting ≥2 episodes
- Age ≥65 yr

Medium-Risk (for brain injury on CT)
- Amnesia before impact >30 min (i.e. cannot recall events just before impact)
- Dangerous mechanism (pedestrian struck by MVC, occupant ejected from motor vehicle, fall from height >3 ft or five stairs)

Minor HI is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.
NB: Canadian CT Head Rule does not apply for non-trauma cases, for GCS <13, ages <16, for patients on Coumadin® and/or having a bleeding disorder, or having an obvious open skull fracture.

Specific Injuries
- fractures
  - Investigation: non-contrast head CT and physical exam

A. skull fractures
- vault fractures
  - suspect if non-frontal injury and/or boggy hematoma
  - linear, non-depressed
    - most common
    - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
  - depressed
    - open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
- basal skull fractures
  - typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
  - can be a radiological or clinical diagnosis
  - associated with Battle's sign, racoon eyes, hemotympanum, and/or CSF otorrhea/rhinorrhea; though classic signs are often delayed

B. facial fractures (see Plastic Surgery, PL31)
- neuronal injury
- beware of open fracture or sinus fractures (risk of infection)
- severe facial fractures may pose risk to airway from profuse bleeding

- scalp laceration
  - can be a source of significant bleeding
  - achieve haemostasis, inspect and palpate for skull bone defects ± CT head (rule out skull fracture)
- neuronal injury

A. diffuse
- mild TBI = concussion (GCS 13-15, patients are awake, may be confused but able to communicate and follow commands)
  - transient alteration in mental status that may involve loss of consciousness
  - hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later
  - loss of consciousness (if present) must be less than 30 min and post-traumatic amnesia must be less than 24 h
- diffuse axonal injury (requires MRI; diagnosis rarely made in the ED)
  - mild: coma 6-24 h, possibly lasting deficit
  - moderate: coma >24 h, little or no signs of brainstem dysfunction
  - severe: coma >24 h, frequent signs of brainstem dysfunction

B. focal injuries
- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

Mild Traumatic Brain Injury

Epidemiology
- TBI results in 1.7 million deaths, hospitalizations, and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see Neurosurgery, NS35)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
- somatic: headache, sleep disturbance, N/V, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe symptoms not improving can be a sign of diffuse axonal injury

Extent of retrograde amnesia correlates with severity of injury

Etiology
- falls, MVC, struck by an object, assault, sports

Investigations
- neurological exam
- concussion recognition tool (see parachute.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

For minor pediatric HI (up to 16 yo with GCS ≥13 and injury within the last 24 h), use Canadian Assessment of Tomography for Childhood Head Injury (CATCH) rule to determine need for CT. CT head required if any of the following findings are exhibited
- GCS <15 at two hours after injury
- Suspected open or depressed skull fracture
- History of worsening headache
- Irritability on examination
- Signs of basal skull fracture
- Hematoma on scalp
- Dangerous mechanism of injury (MVC, fall from ≥3 ft or 5 stairs, fall from bicycle with no helmet)

Treatment
- close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family; watch for changes to clinical features of more severe TBI (see above), and if change, return to ED
- arrange immediate CT and neurological consultation if seizures, bradycardia, hypotension, sluggish pupils and/or focal deficits
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- pharmacological management of pain, depression, headache
- follow Return to Play/Return to Learn guidelines

Prognosis
- most recover with minimal treatment
  - athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life-threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

Every Patient with One or More of the Following Signs or Symptoms should be Placed in a C-Spine Collar
- Midline tenderness
- Neurological symptoms or signs
- Significant distracting injuries
- HI
- Intoxication
- Dangerous mechanism
- History of altered LOC

History
- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Physical Exam
- ABCs
- abdominal: ecchymosis, tenderness
- neurological: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine, assess rectal tone
  - when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
- extremities: check capillary refill, suspect thoracolumbar injury with calcaneal fractures

Of the investigations, CT is the best modality to assess C-Spine injuries. If unavailable and significant trauma is suspected, protect C-Spine and transfer for definitive imaging. If minor trauma of C-Spine, may consider x-ray imaging

Investigations
- bloodwork: CBC, electrolytes, Cr, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - CT of the spine; if not available, protect spine and transfer for definitive imaging
  - indications
    - unconscious patients (with appropriate mechanism of injury)
    - neurological symptoms or findings
    - deformities that are palpable when patient is log rolled
    - back pain

Cauda Equina Syndrome can occur with any spinal cord injury below T10 vertebrae. Look for incontinence, anterior thigh pain, quadriceps weakness, abnormal sacral sensation, decreased rectal tone, and variable reflexes

- bilateral calcaneal fractures (due to fall from height)
  - concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
- MRI (for soft tissue injuries) if appropriate (persistent pain, paresthesia, or focal deficits despite normal CT imaging)

Can Clear C-Spine if:

- oriented to person, place, time, and event
- no evidence of intoxication
- no posterior midline cervical tenderness
- no focal neurological deficits
- no painful distracting injuries (e.g. long bone fracture)
- able to rotate neck 45 degrees in each direction without midline tenderness

Management of Cord Injury

- immobilize
- evaluate ABCs
- treat neurogenic shock (maintain sBP >100 mmHg)
- insert NG once facial fractures are excluded (for decompression of paralytic ileus)
- insert Foley catheter (only if no concerns about urethral injury)
- continually reassess high spinal cord injuries as edema can travel up the spine
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact but loss of innervation of intercostals and other accessory muscles of breathing)
  - high cervical cord injury (above C4) may require intubation and ventilation; soft tissue swelling and hematoma can cause airway compromise, therefore low threshold for intubation, even if patient is otherwise well
- if patient is in shock, treat with: volume infusion, consider vasopressors, maintain normothermia and euglycemia

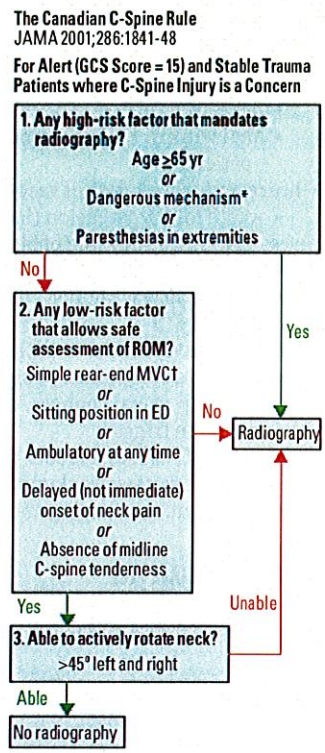
Approach to C-Spine Imaging

- CT of the spine is the screening modality of choice
- C-Spine CT can detect 97-100% of injuries
- compared to radiography, CT scans allows for more rapid clearance of the C-Spine
- MRI of C-Spine is the preferred technique for soft tissue injuries (spinal cord lesions, intervertebral discs, and spinal ligaments)
- If only C-Spine x-rays are available, radiography can be assessed as follows

Table 6. Interpretation of Lateral View: The ABCS

A	**Adequacy and Alignment**
	Follow the anterior and posterior contour lines
	Translation of the vertebra >3.5 mm and angulation of >11 degrees is considered significant for spinal instability
	Next, follow the spinolaminar line; the diameter between the posterior cortex and the spinolaminar line should be >18 mm
	Fanning of spinous processes suggests posterior ligamentous disruption
	Widening of facet joints
	Check atlanto-occipital joint
	Line extending inferiorly from clivus should transect odontoid
	Atlanto-axial articulation, widening of predental space (normal: <3 mm in adults, <5 mm in children) indicates injury of C1 or C2
	In children, there is a phenomenon called pseudosubluxation where there is a normal "translation" of C2 on C3 (less often C3 on C4)
	The translation may be seen in the flexed or neutral position and is not associated with soft tissue swelling (see below)
	The line of Swischuk is helpful in differentiating pathological cervical spine displacement from pseudosubluxation
	The line is drawn from the anterior aspect of the posterior arch from C1-C3
	The anterior aspect of the posterior arch of C2 should not be more than 2 mm from this line (>2mm is indicative of true subluxation)
B	**Bones**
	Follow the bony contours of the vertebrae to look for any breaks in the cortex
	Height, width, and shape of each vertebral body
	Pedicles, facets, and laminae should appear as one – doubling suggests rotation
C	**Cartilage**
	Look at the disk spaces to ensure that they are of equal length throughout
	The anterior and posterior aspect of the individual discs should be equal
	Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression
	Measure the pre-dental space (distance from dens to C1 body); it should be <3 mm
	The distance between the lowest part of the occiput base and the dens should be <2 mm
	The facet joints should be stacked on top of each other at a 45-degree angle
S	**Soft Tissues**
	The retropharyngeal space lies anteriorly to the C-Spine; it widens around C4 due to the esophagus
	The retropharyngeal space normally measures less than 7 mm at C2 and 21 mm at C7; may be wide in children <2 yr on expiration (alternatively, less than the height of the vertebra at C2 and less than the width of the vertebra at C7)
	Assess retrotracheal spaces (normal: <22 mm at C6-T1, <14 mm in children <5 yr)

- plain films of C-Spine are not reliable in patients with significant trauma and should be used with caution



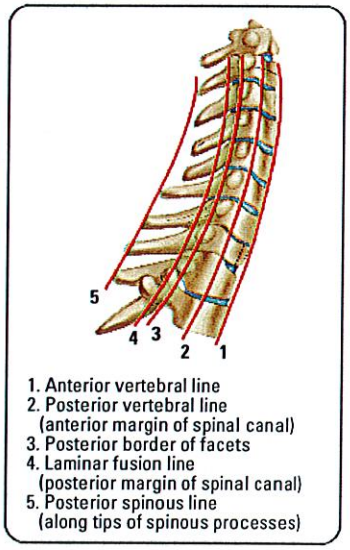


Figure 3. Lines of contour on a lateral C-spine x-ray

Prevertebral soft tissue swelling is only 49% sensitive for injury

Sequelae of C-Spine Fractures

- see Neurosurgery, NS38
- acute phase of SCI
  - spinal shock: absence of all voluntary and reflex activity below level of injury
    - decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
    - anal wink or bulbocavernosus reflex more reliable than anal tone, especially in comatose patients
  - neurogenic shock: loss of vasomotor tone, SNS tone
    - watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
    - occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
    - provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
- chronic phase of SCI
  - autonomic dysreflexia: in patients with an SCI at level T6 or above
    - signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
    - common triggers
      - GU causes: bladder distention, urinary tract infection, and kidney stones
      - GI causes: fecal impaction or bowel distension
    - treatment: monitoring and controlling BP, prior to addressing causative issue

Chest Trauma

- two types: those found and managed in 1° survey and those found and managed in 2° survey

Table 7. Life-Threatening Chest Injuries Found in Primary Survey

	Physical Exam	Investigations	Management
Airway Obstruction	Anxiety, stridor, hoarseness, altered mental status Apnea, cyanosis	Do not wait for ABG to intubate	Definitive airway management Intubate early Remove foreign body with magill forceps prior to the intubation. Be prepared for a potential surgical airway
Tension Pneumothorax Clinical diagnosis One-way valve causing accumulation of air in pleural space	Respiratory distress, tachycardia, hypoxia, distended neck veins, cyanosis, asymmetry of chest wall motion Tracheal deviation away from pneumothorax Percussion hyperresonance Unilateral absence of breath sounds	Non-radiographic diagnosis	Needle thoracostomy – large bore needle, 2nd ICS mid clavicular line or finger thoracostomy. Definitive management is a chest tube
Open Pneumothorax Air entering chest from wound rather than trachea	Gunshot or other wound (hole >2/3 tracheal diameter) ± exit wound Unequal breath sounds	ABG: decreased pO_2	Air-tight dressing sealed on 3 sides Chest tube Surgery
Massive Hemothorax >1500 cc blood loss in chest cavity	Pallor, flat neck veins, shock Unilateral dullness Absent breath sounds Hypotension	Usually only able to do supine CXR – entire lung appears radiopaque as blood spreads out over posterior thoracic cavity	Restore blood volume Chest tube Thoracotomy if: >1500 cc total blood loss ≥200 cc/h continued drainage
Flail Chest Free-floating segment of chest wall due to >2 rib fractures, each at 2 sites Underlying lung contusion (cause of morbidity and mortality)	Paradoxical movement of flail segment Palpable crepitus of ribs Decreased air entry on affected side	VBG: decreased pO_2, increased pCO_2 CT: rib fractures, lung contusion	
Cardiac Tamponade Clinical diagnosis Pericardial fluid accumulation impairing ventricular function	Penetrating wound (usually) Beck's triad: hypotension, distended neck veins, muffled heart sounds Tachycardia, tachypnea Kussmaul's sign (increased JVP with inspiration)	Echocardiogram FAST	

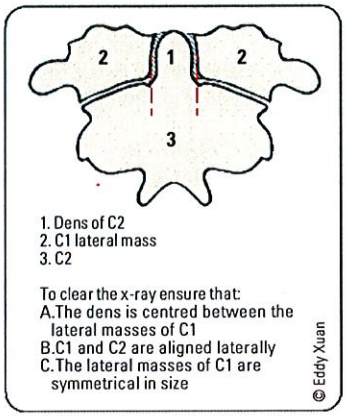


Figure 4. C-spine x-ray; odontoid view

Cardiac Box: sternal notch, nipples, and xiphoid process; penetrating injuries inside this area should increase suspicion of cardiac injury

Supine Oblique Views

Rarely used

Better visualization of posterior element fractures (lamina, pedicle, facet joint)

Good to assess patency of neural foramina

Can be used to visualize the C7-T1 junction

20% of C-spine fractures are accompanied by other spinal fractures, so ensure thoracic and lumbar spine CT is normal before proceeding to OR

Trauma to the chest accounts for 50% of trauma deaths

80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control

3-way Seal for Open Pneumothorax (i.e. sucking chest wound)
Allows air to escape during the expiratory phase (so that you do not get a tension pneumothorax) but seals itself to allow adequate breaths during the inspiratory phase

Pulsus Paradoxus: a drop in BP of >10 mmHg with inspiration. Recall that BP normally drops with inspiration, but what's "paradoxical" about this is that it drops more than it should

Table 8. Potentially Life-Threatening Chest Injuries Found in Secondary Survey

	Physical Exam	Investigations	Management
Pulmonary Contusion	Blunt trauma to chest Interstitial edema impairs compliance and gas exchange	CT: areas of opacification of lung within 6 h of trauma	Maintain adequate ventilation Monitor with ABG, pulse oximeter, and ECG Chest physiotherapy Positive pressure ventilation if severe
Ruptured Diaphragm	Blunt trauma to chest or abdomen (e.g. high lap belt in MVC)	CXR: abnormality of diaphragm/ lower lung fields/NG tube placement CT scan and endoscopy: sometimes helpful for diagnosis Laparoscopy for definite diagnosis	Laparotomy for diaphragm repair and associated intra-abdominal injuries
Esophageal Injury	Usually penetrating trauma (pain out of proportion to degree of injury) or caustic ingestion	CXR: mediastinal air (not always) Esophagram (Gastrografin®) Flexible esophagoscopy	Early repair (within 24 h) improves outcome)
Aortic Tear 90% tear at subclavian (near ligamentum arteriosum), most die at scene Salvageable if diagnosis made rapidly	Sudden high speed deceleration (e.g. MVC, fall, airplane crash), complaints of chest pain, dyspnea, hoarseness (frequently absent) Decreased femoral pulses, differential arm BP (arch tear)	CXR, CT scan, transesophageal echocardiogram, aortography (gold standard)	Thoracotomy (may treat other severe injuries first)
Blunt Myocardial Injury (rare)	Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose) Physical exam: overlying injury (e.g. fractures, chest wall contusion)	ECG: dysrhythmias, ST changes Cardiac blood work (e.g. troponin) 2-D Echo: Can assess for tamponade, wall motion, valve function, or thrombi Patients with a normal ECG, normal troponin, and normal hemodynamics rarely get dysrhythmias	O_2 Antidysrhythmic agents Analgesia

Other Potentially Life-Threatening Injuries Related to the Chest

Penetrating Neck Trauma

- includes all penetrating trauma to the three zones of the neck
- management: injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery
- do not explore penetrating neck wounds except in the OR

Airway Injuries

O_2 + fluid therapy + pain control
Judicious fluid therapy in absence of systemic hypotension
Positive pressure ventilation
± intubation and ventilation if persistently hypoxic or unable to ventilate

IV fluids
Open thoracotomy

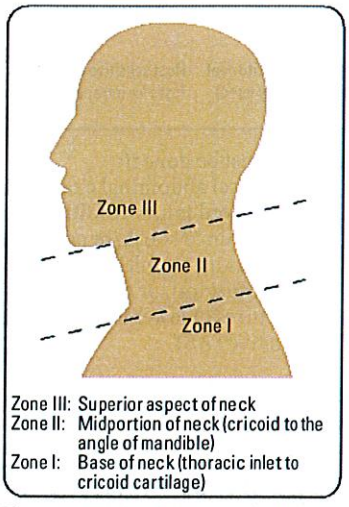
- always maintain a high index of suspicion
- larynx
  - history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma, inhalational injury (e.g. burns)
  - triad: hoarseness, subcutaneous emphysema, palpable fracture
  - other symptoms: hemoptysis, dyspnea, dysphonia
  - investigations: CXR, CT scan, arteriography (if penetrating), CT angiography of the neck
  - management
    - airway: manage early because of edema; if comfortable, can intubate through defect
    - C-spine may also be injured, consider mechanism of injury
    - surgical: tracheotomy vs. repair
- trachea/bronchus
  - frequently missed
  - history: deceleration, penetration, increased intrathoracic pressure, complaints of dyspnea, hemoptysis
  - examination: subcutaneous emphysema, Hamman's sign (crunching sound synchronous with heartbeat)
  - CXR: mediastinal air, persistent pneumothorax, or persistent air leak after chest tube inserted for pneumothorax
  - management
    - surgical repair if >1/3 circumference

Ruptured diaphragm is more often diagnosed on the left side, as the liver conceals right side defects

Aortic Tear

ABC WHITE
X-ray features of **A**ortic tear
Depressed left mainstem **B**ronchus
pleural **C**ap
Wide mediastinum (most consistent)
Hemothorax
Indistinct aortic knuckle
Tracheal deviation to right side
Esophagus (NG tube) deviated to right
(Note: these features are present in 85% of cases, but cannot rule out if absent)

If Penetrating Neck Trauma Present, DON'T:
- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object



Zone III: Superior aspect of neck
Zone II: Midportion of neck (cricoid to the angle of mandible)
Zone I: Base of neck (thoracic inlet to cricoid cartilage)

Figure 5. Zones of the neck in trauma

Abdominal Trauma

- two mechanisms
  - blunt: usually causes solid organ injury (spleen = most common, liver = second most common)
  - penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA

- results in two types of hemorrhage: intraperitoneal and retroperitoneal
- adopt high clinical suspicion of bleeding in multi-system trauma

History

- mechanism of injury, SAMPLE history

Physical Exam

- often unreliable in multi-system trauma, wide spectrum of presentations
  - slow blood loss not immediately apparent
  - tachycardia, tachypnea, oliguria, febrile, hypotension
  - other injuries may mask symptoms
  - serial examinations are required
- abdomen
  - inspect: contusions, abrasions, seat-belt sign, distention
  - auscultate (rare): bruits, bowel sounds
  - palpate: tenderness, rebound tenderness, rigidity, guarding
  - DRE: rectal tone, blood, bone fragments, prostate location
  - placement of NG and Foley catheter should be considered part of the abdominal exam
- assess each system, including cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

Investigations

- labs: CBC, electrolytes, coagulation, fibrinogen, cross and type, glucose, Cr, CK, lipase, amylase, liver enzymes, VBG, blood EtOH, β-hCG, U/A, toxicology screen

Table 9. Imaging in Abdominal Trauma

Imaging	Strengths	Limitations
Ultrasound: FAST	Identifies presence/absence of free fluid in peritoneal cavity RAPID exam: less than 5 min Can also examine pericardium and pleural cavities Can do serial examinations quickly	NOT used to identify specific organ injuries If patient has ascites, FAST will be falsely positive False negatives with small amounts of blood, retroperitoneal blood, delayed presentations, prior abdominal surgery, or incorrect positioning Technically difficult if patient is obese
X-Ray	Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines	Soft tissue not well visualized
CT Scan	Most specific test	Radiation exposure 20x more than x-ray Use with caution if hemodynamic instability: decide in trauma bay if patient should go directly to the OR (if unstable and FAST +'ve) or is stable enough to go to the CT scanner
Diagnostic Peritoneal Lavage (rarely used)	Most sensitive test Tests for intraperitoneal bleed	Cannot test for retroperitoneal bleed or diaphragmatic rupture Cannot distinguish lethal from trivial bleed Results can take up to 1 h

- imaging must be done if:
  - equivocal abdominal examination, altered sensorium, or distracting injuries (e.g. head trauma, spinal cord injury resulting in abdominal anesthesia)
  - unexplained shock/hypotension
  - patients have multiple traumas and must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
  - fractures of lower ribs, pelvis, spine
  - positive FAST

Management

- general: ABCs, early blood products, and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

PENETRATING TRAUMA

- high-risk of gastrointestinal perforation and sepsis
- high risk of cardiac injury if wound is in the cardiac box
- history: size of blade, calibre/distance from gun, route of entry



Seatbelt Injuries May Cause

- Retroperitoneal duodenal trauma
- Intraperitoneal bowel transection
- Mesenteric injury
- L-spine injury



Indications for Foley and NG Tube in Abdominal Trauma

Foley Catheter: unconscious or patient with multiple injuries who cannot void spontaneously

NG Tube: used to decompress the stomach and proximal small bowel. Contraindicated if suspected facial or basal skull fractures



Point-of-Care Ultrasonography for Diagnosing Thoracoabdominal Injuries in Patients with Blunt Trauma

Cochrane DB Syst Rev 2018:CD012669

Purpose: Determine the diagnostic accuracy of POCUS for detecting and excluding free fluid, organ injuries, vascular lesions, and other injuries compared to diagnostic reference standards in patients with blunt trauma.

Methods: Systematic review of prospective or retrospective diagnostic cohort studies of patients with any type of blunt trauma.

Results: 34 studies, 8635 participants. For abdominal trauma, POCUS had a sensitivity of 0.68 (95% CI 0.59-0.75) and a specificity of 0.95 (95% CI 0.92-0.97). In children, pooled sensitivity of POCUS was 0.63 (95% CI 0.46-0.77), as compared to 0.78 (95% CI 0.69-0.84) in an adult/mixed population. For chest injuries, POCUS had a sensitivity of 0.96 (95% CI 0.88-0.99) and a specificity of 0.95 (95% CI 0.97-1.00).

Conclusions: In patients with blunt thoracoabdominal trauma, positive POCUS findings are helpful for guiding treatment decisions. However, with regard to abdominal trauma, a negative POCUS does not rule out injuries and must be verified. This is of particular importance in pediatric trauma, where the sensitivity of POCUS is poor. Based on a small number of studies in a mixed population, POCUS may have a higher sensitivity in chest injuries.



Laparotomy is Mandatory if Penetrating Trauma and:

- Shock
- Peritonitis
- Evisceration
- Free air in abdomen
- Blood in NG tube, Foley catheter, or on DRE



"Rule of Thirds" for Stab Wounds

1/3 do not penetrate peritoneal cavity
1/3 penetrate but are harmless
1/3 cause injury requiring surgery

- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
  - back or flanks (muscles too thick)

Management
- general: ABCs, fluid resuscitation, and stabilization
- gunshot wounds may require laparotomy if signs of peritonitis, hemodynamic instability or hematemesis

Genitourinary Tract Injuries

- see Urology, U35

Etiology
- blunt trauma: often associated with pelvic fractures
  - upper tract
    - renal
      - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    - ureter: rare, at uretero-pelvic junction
  - lower tract
    - bladder
      - extraperitoneal rupture of bladder from pelvic fracture fragments
      - intraperitoneal rupture of bladder from trauma and full bladder
    - urethra
      - posterior urethral injuries: MVCs, falls, pelvic fractures
      - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  - external genitalia
- penetrating trauma
  - damage to: kidney, bladder, ureter (rare), external genitalia
- acceleration/deceleration injury
  - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
- iatrogenic
  - ureter and urethra (from instrumentation)

History
- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension

Physical Exam
- abdominal pain, flank pain, CVA tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, blood at penile/urethral meatus, high riding prostate, pelvic fractures

Investigations
- urethra: retrograde urethrography
- bladder: U/A, CT scan, urethrogram ± retrograde cystoscopy ± cystogram (distended bladder + post-void)
- ureter: retrograde urethrogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram



Gross hematuria suggests bladder injury

Management
- urology consult
- renal
  - minor injuries: conservative management
    - bed rest, hydration, analgesia, antibiotics
  - major injuries: admit
    - conservative management with frequent reassessments, serial U/A ± re-imaging
    - surgical repair (exploration, nephrectomy): hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis



In the case of gross hematuria, the genitourinary system is investigated from distal to proximal (i.e. urethrogram, cystogram, etc.)

- ureter
  - ureteroureterostomy
- bladder
  - extraperitoneal
    - minor rupture: Foley drainage x 10-14 d
    - major rupture: surgical repair
  - intraperitoneal: surgical repair
- urethra
  - anterior: conservative, if cannot void, Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

Orthopedic Injuries

- see Orthopedic Surgery *(see Shoulder OR12, Knee OR34, Wrist OR23, Pelvis OR29, Ankle OR41)*

Goals of ED Treatment
- diagnose potentially life/limb-threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

History
- use SAMPLE, mechanism of injury may be very important

Physical Exam
- look (inspection): "SEADS" = swelling, erythema, atrophy, deformity, and skin changes (e.g. bruises)
- feel (palpation): all joints/bones for local tenderness, swelling, warmth, crepitus, joint effusions, and subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
- neurovascular status: distal to injury (before and after reduction)

LIFE- AND LIMB-THREATENING INJURIES

Table 10. Life- and Limb-Threatening Orthopedic Injuries

Life-Threatening Injuries (usually blood loss)	Limb-Threatening Injuries (usually interruption of blood supply)
Major pelvic fractures	Fracture/dislocation of ankle (talar AVN)
Traumatic amputations	Crush injuries
Massive long bone injuries and associated fat emboli syndrome	Compartment syndrome
Vascular injury proximal to knee/elbow	Open fractures
	Dislocations of knee/hip
	Fractures above knee/elbow

Open Fractures
- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- standard of care is to secure definitive surgical management within 6 h, time to surgery may vary from case-to-case

Vascular Injuries
- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome
- when the intracompartmental pressure within an anatomical area (e.g. forearm or lower leg) exceeds the capillary perfusion pressure, eventually leading to muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - tense compartment
  - look for "The 6 Ps" (note: radial pulse pressure is 120/80 mmHg while capillary perfusion pressure is 30 mmHg, seeing any of the 6 Ps indicates advanced compartment syndrome, therefore do not wait for these signs to diagnose and treat)
  - in the unconscious patient, a Stryker compartment pressure monitor can be used
- requires prompt decompression: remove constrictive casts, dressings; emergent fasciotomy may be needed



Description of Fractures

SOLARTAT
Site
Open vs. closed
Length
Articular
Rotation
Translation
Alignment/Angulation
Type e.g. Salter-Harris, etc.



Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the ED
JAMA 2017;318:1661-1667
Purpose: To compare the efficacy of 4 analgesics on acute extremity pain.
Methods: RCT including 416 patients with moderate to severe acute extremity pain. Participants received ibuprofen 400 mg and acetaminophen 1000 mg; oxycodone 5 mg and acetaminophen 325 mg; hydrocodone 5 mg and acetaminophen 300 mg; or codeine 30 mg and acetaminophen 300 mg. The primary outcome was the difference in decline in pain 2 h after ingestion. Pain was assessed using an 11-point numerical rating scale (NRS).
Results: At 2 h, the mean NRS pain score decreased by 4.3 in the ibuprofen and acetaminophen group; by 4.4 in the oxycodone and acetaminophen group; by 3.5 in the hydrocodone and acetaminophen group; and by 3.9 in the codeine and acetaminophen group (P=0.053).
Conclusions: For patients presenting to the ED with acute extremity pain, there were no statistically significant or clinically important differences in pain reduction at 2 h among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics.



When Dealing with an Open Fracture, Remember "STAND"

Splint
Tetanus prophylaxis
Antibiotics
Neurovascular status (before and after)
Dressings (to cover wound)



Vascular injury/compartment syndrome is suggested by "The 6 Ps" Injury Compartment Syndrome -

6 Ps
Pulse discrepancies
Pallor
Paresthesia/hypoesthesia
Paralysis
Pain (especially when refractory to usual analgesics)
Polar (cold)

UPPER EXTREMITY INJURIES

- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
  - many techniques for reduction (e.g. traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with orthopedics
  - with forceful injury, look for fracture
- Colles' fracture
  - distal radius fracture with dorsal displacement from "Fall on Outstretched Hand" (FOOSH)
  - anteroposterior film: radial shortening, radial deviation, radial displacement
  - lateral film: dorsal displacement, volar angulation
  - reduce, immobilize with splint, out-patient follow-up with orthopedics or immediate orthopedic referral if complicated fracture
  - if involvement of articular surface, consider outpatient fracture clinic or orthopedic referral if unsatisfactory reduction in ED
- scaphoid fracture
  - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
  - negative x-ray: thumb spica splint, repeat x-ray in 1 wk ± CT scan/bone scan
  - positive x-ray: thumb spica splint x 6-8 wk, repeat x-ray in 2 wk
  - treat based on clinical suspicion even in absence of radiological scaphoid fracture
  - risk of AVN of scaphoid if not immobilized
  - outpatient orthopedic follow-up

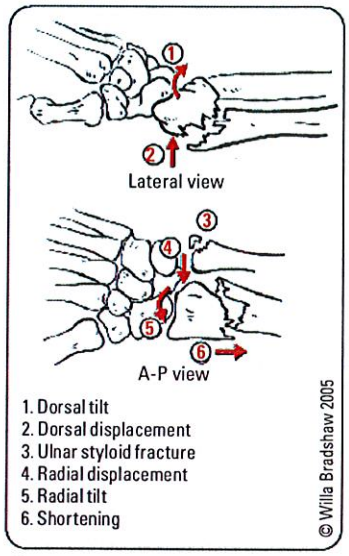


Figure 6. Colles' fracture

LOWER EXTREMITY INJURIES

- knee injuries
  - see *Ottawa Knee Rules*
- pelvic injuries (see Orthopedic Surgery, OR29)
- ankle and foot fractures
  - see *Ottawa Ankle and Foot Rules*
- avulsion of the base of 5th metatarsal
  - occurs with inversion injury
  - supportive tensor or below knee walking cast for 3 wk
- calcaneal fracture
  - associated with fall from height
  - associated with axial loading (other injuries may involve ankles, knees, hips, pelvis, lumbar spine)

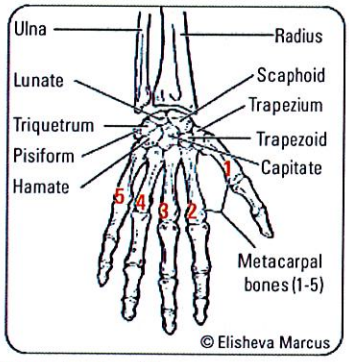


Figure 7. Carpal bones

A knee x-ray examination is required only for acute injury patients with one or more of:

- Age 55 yr or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90°
- Inability to bear weight both immediately and in the ED (four steps)

Figure 8. Ottawa knee rules
Adapted from: Stiell IG, Wells GA, Hoag RH, et al. JAMA 1997;278:2075-2079.

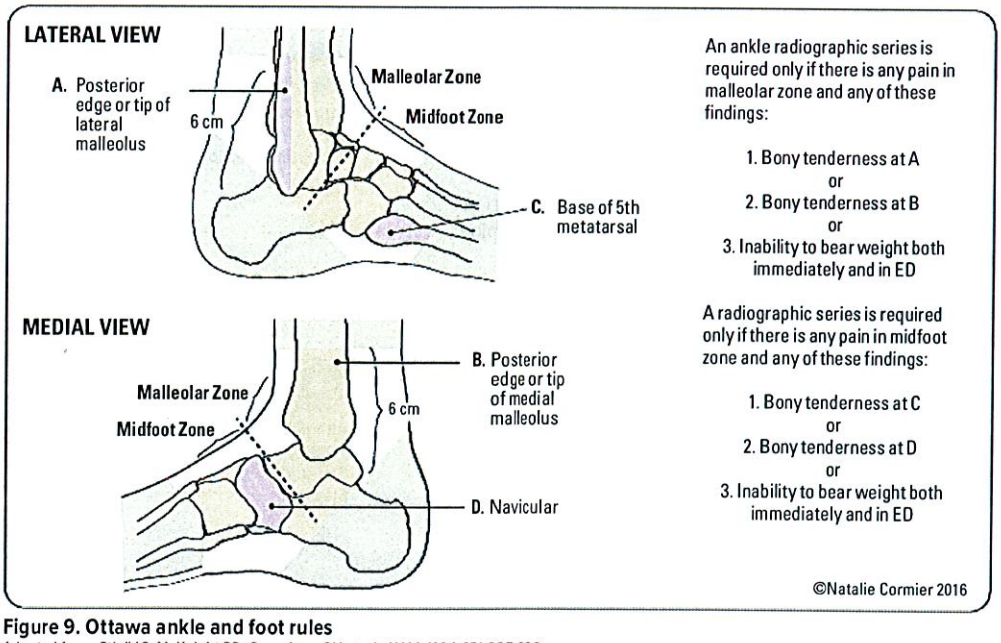


Figure 9. Ottawa ankle and foot rules
Adapted from: Stiell IG, McKnight RD, Greenberg GH, et al. JAMA 1994;271:827-832.

Wound Management

Goals of ED Treatment

- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration
- cleansing ± antibiotic and tetanus prophylaxis
- closure and dressing

Tetanus Prophylaxis

- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

Table 11. Guidelines for Tetanus Prophylaxis for Wounds

Vaccination History	Clean, Minor Wounds		All Other Wounds*	
	Tdap or Td†	TIG	Tdap or Td†	TIG
Unknown or fewer than 3 doses	Yes	No	Yes	Yes
3 or more doses	No§	No	No¶	No

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite
†Tdap is preferred to Td for adults who have never received Tdap. Single antigen tetanus toxoid (TT) is no longer available in the United States
§Yes, if more than ten years since the last tetanus toxoid-containing vaccine dose
¶Yes, if more than five years since the last tetanus toxoid-containing vaccine dose
Source: MMWR 1991;40(No. RR-10):1-28

Bruises

- non-palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use

Abrasions

- partial to full thickness break in skin
- management
  - clean thoroughly with brush to prevent foreign body impregnation ± local anesthetic antiseptic ointment (Polysporin® or Vaseline®) for 7 d ± tetanus prophylaxis

Lacerations

- see Plastic Surgery, PL8, sidebar PL24
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury
- physical exam
  - think about underlying anatomy
  - examine tendon function actively against resistance and neurovascular status distally
  - clean and explore under local anesthetic; look for partial tendon injuries
  - x-ray or U/S wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radiopaque), or if suspect intra-articular involvement
- management
  - disinfect skin/use sterile techniques
  - irrigate copiously with normal saline or tap water
  - analgesia ± anesthesia
  - maximum dose of lidocaine
    - 7 mg/kg with epinephrine
    - 5 mg/kg without epinephrine
- in children, topical anesthetics such as LET (lidocaine, epinephrine, and tetracaine), distraction provided by Child Life Specialist or parent; and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
- secure hemostasis
- evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
- ± prophylactic antibiotics (consider for animal/human bites, intra-oral lesion, or puncture wounds to the foot)
- suture unless: delayed presentation (>24 h), puncture wound, mammalian bite, crush injury, or retained foreign body
- take into account patient and wound factors when considering suturing
- advise patient when to have sutures removed
- cellulitis and necrotizing fasciitis (see Plastic Surgery, PL16)



Acute Treatment of Contusions

RICE
Rest
Ice
Compression
Elevation



High-Risk Factors for Infection

Wound Factors
- Puncture wounds
- Crush injuries
- Wounds >12 h old
- Hand or foot wounds

Patient Factors
- Age >50 yr
- Prosthetic joints or valves (risk of endocarditis)
- Immunocompromised



Suture Use and Duration

Suture to:	Close with Nylon or Other Non-absorbable Suture	Approx. Duration (d)
Face	6-0 or 5-0	5
Not Joint	4-0	7
Joint	3-0	10
Scalp	4-0	7
Mucous Membrane	Absorbable (vicryl)	N/A

N.B. Patients on steroid therapy may need sutures for longer periods of time



Early wound irrigation and debridement are the most important factors in decreasing infection risk



Alternatives to Sutures
Tissue glue
Steristrips®
Staples

Approach to Common ED Presentations

Abdominal Pain

Table 12. Selected Differential Diagnosis of Abdominal Pain

	Emergent	Usually Less Emergent
GI	Perforated viscus, bowel obstruction, ischaemic bowel, appendicitis, strangulated hernia, IBD flare, esophageal rupture, peptic ulcer disease	Diverticulitis, gastroenteritis, GERD, esophagitis, gastritis, IBS
Hepatobiliary	Hepatic/splenic injury, pancreatitis, cholangitis, spontaneous bacterial peritonitis	Biliary colic, cholecystitis, hepatitis
Genital	Female: Ovarian torsion, ectopic pregnancy, tubo-ovarian abscess Male: Testicular torsion	Female: PID, ovarian cyst, salpingitis, endometriosis Male: epididymitis, prostatitis, orchitis
Urinary	Pyelonephritis	Renal colic, cystitis
CVS	MI, aortic dissection, ruptured AAA	Pericarditis
Respirology	PE, empyema	Pneumonia
Metabolic	DKA, sickle cell crisis, toxin, Addisonian crisis	Toxic ingestions (e.g. acetaminophen, iron, NSAIDs, etc.), lead poisoning, porphyria
Other	Significant trauma	Abdominal wall injury, herpes zoster, psychiatric, abscess, hernia, mesenteric adenitis

- differential can be focused anatomically by location of pain: right upper quadrant, left upper quadrant, right lower quadrant, left lower quadrant, epigastric, periumbilical, diffuse

History
- pain: OPQRST
- review symptoms from genitourinary, gynecological, gastrointestinal, respiratory, and cardiovascular systems
- abdominal trauma/surgeries, most recent colonoscopy, most recent endoscopy, last FOBT/FIT test

Physical Exam
- vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and cardiac exams as indicated by history

Investigations
- ABCs, do not delay management and consultation if patient unstable
- labs: CBC, electrolytes, glucose, BUN/Cr, U/A ± liver enzymes, LFTs, lipase, β-hCG, ECG, troponins, ± VBG/lactate
- AXR: if suspicious of foreign body or SBO (small bowel obstruction) in low resource setting. Can also use if frequent SBOs and usual conservative management
- CXR upright: look for pneumoperitoneum (free air under diaphragm), lung disease
- U/S: all gynecologic structure, testicles, biliary tract, ectopic pregnancy, appendicitis in children and young adults, nephro-/urolithiasis in young patients, AAA, free fluid; in select cases, can proceed to CT if U/S is non-diagnostic but there is high clinical suspicion
- CT: SBO, trauma, AAA, pancreatitis, nephro-/urolithiasis, appendicitis, and diverticulitis



Ruptured AAA
Flank/back pain
Pulsatile abdominal mass
Hypotension

Management
- NPO, IV, NG tube (if SBO), analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: internal medicine, general surgery, vascular surgery, gynecology, etc.

Disposition
- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develops

Acute Pelvic Pain

Etiology
- gynecological
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass), mittelschmerz
  - fallopian tubes: salpingitis, tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in a pregnant patient (degeneration), PID, cervicitis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), endometriosis and dysmenorrhea, sexual or physical abuse, adrenal neoplasms
- non-gynecological (see causes of lower abdominal pain above)

History and Physical Exam
- pain: OPQRST
- associated symptoms: vaginal bleeding, discharge, dyspareunia, bowel and/or bladder symptoms
- pregnancy and sexual history, including oligo/amenorrhea, menorrhagia, and fibroids
- vitals
- gynecological exam: assess for cervical motion tenderness/"chandelier sign" (suggests PID)
- abdominal exam

Investigations
- β-hCG for all women of childbearing age
- CBC and differential, electrolytes, glucose, creatinine, BUN, culture and sensitivity, PTT/INR
- U/A to rule out urologic causes
- vaginal and cervical swabs for culture and sensitivity if performing a pelvic exam or urine NAAT for STI testing if no speculum exam is performed
- pelvic and abdominal U/S: evaluate adnexa, thickness of endometrium, pregnancy, free fluid or masses in the pelvis
- Doppler flow studies for ovarian torsion

Management
- general: analgesia, determine if admission and consults are needed
- specific:
  - ovarian cysts
    - unruptured or ruptured, and hemodynamically stable: analgesia and follow-up
    - ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis, and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: broad spectrum antibiotics (ceftriaxone 1 g IV q24 h, doxycycline 100 mg PO/IV q12 h, and metronidazole 500 mg PO/IV q12 h), recommend low threshold to treat empirically

Disposition
- referral: gynecological or obstetrical causes requiring surgical intervention, requiring admission, or oncological in nature
- admission: patients requiring surgery, IV antibiotics/pain management
- discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

Gynecological Causes of Pelvic Pain
- Ovarian cyst
- Dysmenorrhea
- Mittelschmerz
- Endometriosis
- Ovarian torsion
- Uterine fibroids/neoplasm
- Adnexal neoplasm
- PID + cervicitis

U/S is the preferred imaging modality in the assessment of acute pelvic pain

Possible Causes of Coma

AEIOU TIPS
Acidosis/**A**lcohol
Epilepsy
Infection
Oxygen (hypoxia)/**O**piates
Uremia
Temperature/**T**rauma (especially head)
Insulin (too little or too much)
Psychogenic/**P**oisoning
Structural or space-occupying lesion

Altered Level of Consciousness

Definitions
- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see Psychiatry, PS23)
  - dementia (see Psychiatry, PS24)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but rousable
  - coma: a sleep-like state, not rousable to consciousness

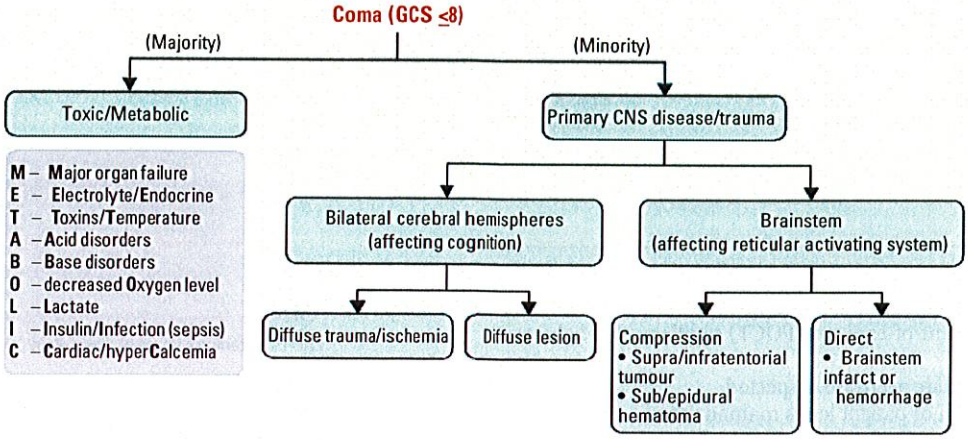


Figure 10. Etiology of coma

MANAGEMENT OF ALTERED LOC

History

- obtain collateral from family, friends, police, paramedics, patient record, MedicAlert® bracelet, etc.
- onset and progression
  - antecedent trauma, seizure activity, fever
  - abrupt onset suggests CNS hemorrhage/ischaemia, cardiac cause, or poisoning
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- determine patient's baseline LOC
- past medical history (e.g. similar episode(s), depression, overdose, changes to usual medications)

Physical Exam

- ABCs, vitals including temperature; cardiac, respiratory, abdominal exams
- complete neurological exam; in particular, examination of the eyes (pupils equal and reactive to light (PEARL))
- use the GCS to evaluate LOC (see *Patient Assessment/Management, ER2*)

Investigations

- blood work
  - serum glucose level, electrolytes, creatinine, BUN, LFTs, serum osmolality, CBC, VBG, lactate, PT/PTT/INR, troponins
  - serum acetaminophen, salicylate levels, ethanol (± toxic alcohols)
- imaging
  - CT head, CXR (if respiratory compromise or symptoms)
- other tests
  - ECG, U/A, urine toxicology

Diagnosis

- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extraocular movements, and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - respiratory depression with intact upper brainstem (e.g. equal and reactive pupils)
    - extraocular movements and motor findings are symmetric or absent
    - essential to re-examine frequently because status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")

Table 13. Toxic-Metabolic Causes of Fixed Pupils

Dilated	Dilated to Normal	Constricted
Anoxia Anticholinergic agents (e.g. atropine, tricyclic antidepressants) Methanol Cocaine Opioid withdrawal Amphetamines Hallucinogens Serotonin syndrome (MAOI, SSRI)	Hypothermia Barbiturates Antipsychotics	Cholinergic agents (e.g. organophosphates) Opioids (e.g. heroin/fentanyl), except meperidine

Management

- administer appropriate universal antidotes (mnemonic DONT)
  - D50W (50 mL) if hypoglycemic on point-of-care test (POCT) capillary blood glucose
  - oxygen if needed
  - naloxone 0.4 mg, up to 10 mg IV if opiate overdose suspected
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished

Disposition

- admission: if ongoing decreased LOC, admit to service based on tentative diagnosis, or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care

Chest Pain

Table 14. Differential Diagnosis for Chest Pain

	Emergent	Usually Less Emergent
CVS	MI, unstable angina, aortic dissection, cardiac tamponade, arrhythmia	Stable angina, pericarditis, myocarditis
Respirology	PE, tension pneumothorax	Pneumonia, pleural effusion, malignancy, non-tension pneumothorax
GI	Esophageal rupture, Mallory-Weiss tear, pneumomediastinum	Mallory-Weiss tear or esophageal rupture, pneumomediastinum, GERD, esophageal spasm
MSK		Rib fracture, costochondritis
Other		Herpes zoster, psychiatric/panic attack

History and Physical Exam

- OPQRST, previous episodes, and change in pattern
- cardiac risk factors (HTN, DM, dyslipidemia, smoking, FHx)
- inquire about any previous cardiac procedures, last stress test, last angiogram, and if they are currently followed by a cardiologist
- vitals, cardiac, respiratory, peripheral vascular, abdominal exams

Investigations

- ECG (most important): assess for STEMI (or those that may evolve to STEMI), always compare with previous; may be normal in up to 50% of PE and acute MI
- CBC, electrolytes, Cr, BUN, glucose, PTT/INR, cardiac biomarkers (troponin), D-Dimer if indicated
- CXR: compare with previous
- CT if indicated (e.g. aortic dissection, PE)

Management and Disposition

- ABCs, O2 (if needed), cardiac monitors, IV access
- treat underlying cause and involve consultants as necessary
- consider further observation/monitoring if unclear diagnosis or risk of dysrhythmia
- can refer to HEART score to risk stratify patients with chest pain
- discharge: patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; arrange follow-up (e.g. rapid/acute cardiac clinic) and instruct to return if SOB or increased chest pain develops



Life-Threatening Causes of Chest Pain

PET MAP
PE
Esophageal rupture
Tamponade
MI/angina
Aortic dissection
Pneumothorax



Imaging is necessary for all suspected aortic dissections, regardless of BP



Classic Angina Characteristics
1. Retrosternal location
2. Provoked by exertion
3. Relieved by rest or nitroglycerin

Risk for Coronary Artery Disease
3/3 = "typical angina" - high-risk
2/3 = intermediate risk for women >50 yr, all men
1/3 = intermediate risk in men >40 yr, women >60 yr



HEART Score	
H (History)	
Highly suspicious history	2 pts
Moderately suspicious history	1 pt
Slightly or non-suspicious history	0 pts
E (ECG)	
Acute ischaemia	2 pts
LBBB, RBBB, LVH, PM	1 pt
No signs of acute ischaemia	0 pts
A (Age)	
>65 yr	2 pts
ages 45-65	1 pt
<45 yr	0 pts
R (Risk factors)	
3 risk factors*, or history of atherosclerotic disease	2 pts
1 or 2 risk factors	1 pt
No risk factors known	0 pts
T (Troponin)	
troponin >42 ng/L	2 pts
troponin 15-42 ng/L	1 pt
troponin 14 ng/L	0 pts

* Risk factors: Diabetes mellitus, current or recent (<30 d) smoker, hypertension, hypercholesterolemia, and family history of coronary artery disease
0 to 3 points = low risk (0.6% to 1.7% risk of major adverse cardiac events); 4 to 6 points = intermediate risk (16.6% risk); 7 to 10 points = high risk (50.1% risk)

Table 15. Comparison of Chest Pain Diagnoses

	Classic History	Classic Findings	Diagnostic Investigations	Management and Disposition
Acute Coronary Syndrome	New or worsening pattern of retrosternal squeezing/ pressure pain, radiation to arm/neck, dyspnea, worsened by exercise, relieved by rest, N/V, syncope	New or worsened murmur, hypotension, diaphoresis, pulmonary edema	ECG: ischaemia (15-lead if hypotensive, AV node involvement, or inferior MI), serial troponin I (sensitive 6-8 h after onset), CXR	ABCs, Aspirin®, anticoagulation, and emergent cardiology consult to consider percutaneous intervention or thrombolytic
Pulmonary Embolism	Pleuritic chest pain (75%), dyspnea; risk factors for venous thromboembolism	Tachycardia, hypoxemia; evidence of DVT	Wells' criteria: D-dimer, CT pulmonary angiogram, ventilation-perfusion (V/Q) scan; leg Doppler, CXR	ABCs, anticoagulation; consider airway management and thrombolysis if massive PE (hypotension and cardiovascular collapse)
Acute Pericarditis	Viral prodrome, anterior precordial pain, pleuritic, relieved by sitting up and leaning forward	Friction rub	ECG: sinus tachycardia, diffuse ST elevation, PR depression in II, III, aVF, and V4-6; reciprocal PR elevation and ST depression in aVR ±V1; echocardiography	ABCs, rule out MI, high dose NSAIDs ± colchicine; consult if chronic/recurrent, large pericardial effusion, or non-viral cause (e.g. SLE, renal failure, requires surgery)
Pneumothorax	Trauma or spontaneous pleuritic chest pain often in tall, thin, young athlete	Hemithorax with decreased/absent breath sounds, hyper-resonance; deviated trachea and hemodynamic compromise (if tension pneumothorax)	Clinical diagnosis CXR: posteroanterior view, lateral, expiratory views – lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view POCUS: Loss of lung slide, lack of comet tails, barcode sign, ± transition point	ABCs, needle to 2nd ICS at mid-clavicular line or 5th ICS in mid-axillary line if unstable; urgent surgical consult/thoracostomy 4th intercostal space and chest tube
Aortic Dissection	Sudden severe tearing retrosternal or midscapular pain ± focal pain/neurologic loss in extremities in context of HTN	HTN; systolic BP difference >20 mmHg or pulse deficit between arms; aortic regurgitant murmur	CT angiogram; CXR: wide mediastinum, left pleural effusion, indistinct aortic knob, >4 mm separation of intimal calcification from aortic shadow, 20% normal	ABCs, reduce BP and HR; classify type A (ascending aorta, urgent surgery) vs. B (not ascending aorta, medical) on CT angiogram and urgent consult
Cardiac Tamponade	Dyspnea, cold extremities, ± chest pain; often a recent cardiac intervention or symptoms of malignancy, connective tissue disease	Beck's triad - hypotension, elevated JVP, muffled heart sounds; tachycardia, pulsus paradoxus >10 mmHg	Clinical diagnosis/ POCUS to look for pericardial effusion CXR: may show cardiomegaly, evidence of trauma, ECG may show electrical alternans	ABCs, cardiac surgery or cardiology consult, pericardiocentesis if unstable, treat underlying cause
Esophageal Rupture	Sudden onset severe pain after endoscopy, forceful vomiting, labour, or convulsion, or in context of corrosive injury or cancer	Subcutaneous emphysema, findings consistent with sepsis	CXR: pleural effusion (75%), pneumomediastinum; CT or water soluble contrast esophagogram	ABCs, early antibiotics, resuscitation, thoracics consult, NPO, consider chest tube
Esophagitis or GERD	Frequent heartburn, acid reflux, dysphagia, relief with antacids	Oral thrush or ulcers (rare)	None acutely	ABCs, PPI medication, avoid EtOH, tobacco, trigger foods
Herpes Zoster	Abnormal skin sensation – itching/tingling/pain – preceding rash by 1-5 d	None if early; maculopapular rash (with dermatomal distribution) developing into vesicles and pustules that crust	Clinical diagnosis; direct immunofluorescence assay	ABCs, anti-virals (if < <48 h onset), analgesia ± steroids, dressing; r/o ocular involvement/refer if necessary
MSK	History of injury	Reproduction of symptoms with movement or palpation (not specific – present in 25% of MI)	MSK injury or fracture on x-rays	ABCs, NSAIDs, rest, orthopedics consultation for fractures
Anxiety	Symptoms of anxiety, depression, history of psychiatric disorder; may coexist with physical disease	Tachycardia, diaphoresis, tremor	Diagnosis of exclusion	ABCs, arrange social supports, rule out suicidality and consider psychiatry consult

ACS more likely to be atypical in females, diabetics, and >80 yr. Anginal equivalents include dyspnea, diaphoresis, fatigue, non-retrosternal pain

It is important to look for reciprocal changes in STEMI in order to differentiate from pericarditis (diffuse elevations)

Tracheal deviation is away from tension or towards non-tension pneumothorax

Does this Patient with Chest Pain have Acute Coronary Syndrome?: The Rational Clinical Examination Systematic Review
JAMA 2015;314:1955-1965
Purpose: To review accuracy of the initial history, physical examination, ECG, and risk scores incorporating these elements with the first cardiac-specific troponin.
Methods: Systematic review of prospective studies among patients admitted to the ED with symptoms suggesting ACS.
Results: Prior abnormal stress test (specificity 96%; LR 3.1, 95% CI 2.0-4.7), peripheral artery disease (specificity 97%; LR 2.7, 95% CI 1.5-4.8), and pain radiating to both arms (specificity 96%; LR 2.6, 95% CI 1.8-3.7) were most suggestive of ACS. The most suggestive ECG findings were ST-segment depression and any evidence of ischaemia. The History, ECG, Age, Risk Factors, Troponin (HEART) (LR 13, 95% CI 7-24) and the Thrombolysis in MI (TIMI) risk scores (LR 6.8, 95% CI, 5.2-8.9) were both predictive of ACS in the high-risk scores.
Conclusions: Among patients with suspected ACS presenting to the ED, the initial history, physical examination, and ECG alone did not confirm or exclude the diagnosis of ACS. Instead, the HEART or TIMI risk scores, which incorporate the first cardiac troponin, provided more diagnostic information.

Conservative vs. Interventional Treatment for Spontaneous Pneumothorax
NEJM 2020;382:405-415
Purpose: Determine whether conservative management is an acceptable alternative to interventional management for uncomplicated, moderate-to-large primary spontaneous pneumothorax.
Methods: Open-label, multicenter, noninferiority trial. Patients 14-50 yr were recruited with a first-known, unilateral, moderate-to-large primary spontaneous pneumothorax. Patients (n=316) were randomly assigned to immediate interventional management of the pneumothorax or a conservative observational approach and were followed for 12 mo. The primary outcome was lung re-expansion within 8 wk.
Results: Re-expansion within 8 wk occurred in 129 of 131 patients with interventional management and in 118 of 125 with conservative management (P=0.02, for noninferiority). Conservative management resulted in a lower risk of serious adverse events or pneumothorax recurrence than interventional management.
Conclusions: The trial provides modest evidence that conservative management of primary spontaneous pneumothorax was noninferior to interventional management, with a lower risk of serious adverse events.

Table 16. Common Life-Threatening ECG Changes

Pathology	ECG Findings
Dysrhythmia	
Torsades de pointes	Ventricular complexes in upward-pointing and downward-pointing continuum (160-250 bpm)
Ventricular tachycardia	3 or more consecutive premature ventricular beats (>100 bpm, QRS >120 ms)
Ventricular flutter	Smooth sine wave pattern of similar amplitude (>200 bpm)
Ventricular fibrillation	Erratic ECG tracing, no identifiable waves
Conduction	
2nd degree heart block (Mobitz Type II)	Constant PR interval, intermittently dropped P wave
3rd degree heart block	Prolonged QRS complex (>0.12 s) RSR' in V5 or V6 Total AV dissociation, but stable P-P and R-R intervals
Ischaemia	
STEMI	ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)
Metabolic	
Hyperkalemia	Initially, tall T-waves Followed by PR prolongation, QRS widening, loss of P waves Finally, sinusoidal pattern and pulse electrical activity (PEA)/Vfib/Asystole
Hypokalemia	P wave flattening QRS complex widening and flattening U waves appear Flattened T waves
Digitalis Toxicity	Range of arrhythmias may present Supraventricular tachycardia Slow ventricular response Frequent premature ventricular contractions At risk for AV blocks and ventricular irritability
Syndromes	
Brugada	Three types of repolarization patterns in leads V1, V2, and V3 Type 1 ("Brugada sign"): coved ST segment elevation >2mm in >1 of V1-V3, followed by an inverted T wave; only type that is diagnostic Syndrome diagnosis if patient has Brugada sign and one of the following: family history of sudden cardiac death at age <45; arrhythmia related symptoms (e.g. syncope, seizures); or ventricular arrhythmias (VFib, polymorphic ventricular tachycardia) Susceptible to deadly dysrhythmias, including VFib
Wellens	Marked T wave inversion in V2 and V3 Left anterior descending coronary stenosis
Long QT syndrome	QT interval longer than ½ of cardiac cycle Predisposed to ventricular dysrhythmias

Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability
NEJM 2019;381:2125-2134
Purpose: Retrospective analyses suggest that PE is ruled out by a D-dimer level of <1000 ng/mL in patients with a low clinical pretest probability (C-PTP) and by a d-dimer level of <500 ng/mL in patients with a moderate C-PTP.
Methods: Prospective study in which PE was considered to be ruled out without further testing in 2017 outpatients with a low C-PTP and a d-dimer level of <1000 ng/mL or with a moderate C-PTP and a d-dimer level of <500 ng/mL. If PE was not diagnosed, patients did not receive anticoagulant therapy. Patients were followed for 3 mo for VTE.
Results: Of the 1325 patients who had a low C-PTP or moderate C-PTP and a negative d-dimer test, none had VTE during follow-up. This diagnostic strategy resulted in the use of chest imaging in 34.3% of patients. A strategy in which PE is considered to be ruled out with a low C-PTP and a d-dimer level of <500 ng/mL would result in the use of chest imaging in 51.9%.
Conclusion: A combination of a low C-PTP and a d-dimer level of <1000 ng/mL identified a group of patients at low-risk for PE during follow-up.

Headache

- see Neurology, N46

Etiology

- **common and less serious**
  - common migraine (without aura)/classic migraine (with aura)
    - common: unilateral, throbbing, aggravated by activity, moderate/severe intensity, N/V, photo-/phonophobia
    - classic: fully reversible aura symptoms that precede headache, e.g. flashing lights, pins and needles (paresthesia), loss of vision, dysarthria
    - treatment: simple analgesics (NSAIDs, acetaminophen, Aspirin®), antiemetics, triptans
    - family physician to consider prophylactic treatment
  - tension headache
    - bilateral, non-throbbing, not aggravated by routine physical activity, mild-moderate intensity
    - can last 30 min to 7 d
    - triggered with stress, sleep deprivation
    - treatment: modify stressor(s), simple analgesics (NSAIDs, acetaminophen, Aspirin®)
- **less common but potentially fatal**
  - subarachnoid hemorrhage (SAH) (see Neurosurgery, NS22)
    - sudden onset, "worst headache of life," maximum intensity within minutes, "thunderclap headache"
    - increased pain with exertion, N/V, meningeal signs
    - diagnosis
      - new generation CT 100% sensitive within 6 h of onset (hyperattenuating signal around Circle of Willis)
      - LP to look for xanthochromia if suspected SAH and normal CT after 6 h
    - management: urgent neurosurgery consult
  - increased ICP
    - worse in morning, when supine or bending down, with cough or Valsalva

Common Therapeutic Approach to Severe Migraine
1 L bolus of NS
Prochlorperazine/metoclopramide 10 mg IV
Ketorolac 30 mg IV
Dexamethasone 10 mg IV
Other options include haloperidol, metoclopramide, ergotamine, sumatriptan, analgesics

Ottawa SAH Rule
JAMA 2013;310(12):1248-1255
Use for alert patients older than 15 yr with new severe non-traumatic headache reaching maximum intensity within 1 h
Not for patients with new neurologic deficits, previous aneurysms, SAH, brain tumours, or history of recurrent headaches (≥3 episodes over the course of ≥6 mo)
Investigate if ≥1 high-risk variables present:
- Age ≥40 yr
- Neck pain or stiffness
- Witnessed loss of consciousness
- Onset during exertion
- Thunderclap headache (instantly peaking pain)
- Limited neck flexion on examination

Subarachnoid hemorrhage can be predicted with 100% sensitivity using this rule.

- physical exam: neurological deficits, cranial nerve palsies, papilledema
- diagnosis: CT head, LP if suspect idiopathic intracranial hypertension (risk of blindness if missed)
- management: consult neurosurgery

- meningitis (see Infectious Diseases, ID17)
  - at least two of the following features suggests that the headache could be due to meningitis: fever, neck stiffness, altered mental status
  - possible clinical/laboratory findings: nausea, focal neurologic signs, seizure, papilledema, petechial rash, high CSF WBC count, growth of organism in blood culture
  - investigations: rule out increased ICP (CT head, mental status normal, no neurological signs, no papilledema), if ruled out then perform diagnostic LP
  - treatment: early empiric antibiotics (high dose ceftriaxone + vancomycin ± ampicillin if >50 y/o or immunocompromised) ± acyclovir ± steroid therapy (administer based on clinical suspicion, DO NOT wait for LP)
- giant cell arteritis/temporal arteritis (causes significant morbidity, blindness) (see Ophthalmology, OP36)
  - vasculitis of large and mid-sized arteries, gender 3:1 F:M, most commonly ages >70
  - headache, scalp tenderness, jaw claudication, arthralgia, myalgia, fever, malaise, weight loss
  - temporal artery tender on palpation, RAPD, optic disc edema on fundoscopy
  - labs: elevated ESR, CRP
  - temporal artery biopsy is gold standard for diagnosis
  - associated with polymyalgia rheumatica
  - treatment: high-dose steroids immediately if suspected, no need to hold treatment until pathology results
- cerebral venous sinus thrombosis
  - physical symptoms depend heavily on location, size, and extent of the clot. They may include gradual or sudden onset headache, vomiting, papilledema, visual disturbances, focal neurological deficits, seizures, and acute mental status changes
  - investigations: neuroimaging (e.g. CT head, CT venography) to assess and r/o other acute processes (e.g. intracranial hemorrhage), CBC with coagulation studies and/or D-dimer, consider LP to r/o meningitis
  - treatment: anticoagulation (most commonly LMWH or heparin)

Disposition
- admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- discharge: assess for risk of narcotic misuse; most patients can be discharged with appropriate analgesia and follow-up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

Joint Pain

- see Rheumatology, RH3
- rule out life-threatening causes e.g. septic joint (see Orthopedic Surgery, OR11)

History and Physical Exam
- history: recent trauma, drug use (anticoagulants, glucocorticoids)
- associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
- patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
- inflammatory symptoms: morning stiffness ≥30 min, pain/stiffness that ease with activity, mid-day fatigue, soft tissue swelling
- non-inflammatory symptoms: morning stiffness <30 min, stiffness short-lived after inactivity, increasing pain with activity
- assess for pain with ROM, localized joint pain, effusion, erythema, warmth, swelling, inability to bear weight, fever; may indicate presence of septic joint

Investigations
- blood work: CBC, ESR, CRP, INR/PTT, blood cultures, urate
- joint x-ray ± contralateral joint for comparison
- bedside U/S to identify effusion ± joint aspiration
- test joint aspirate for: culture, WBC, polynuclear cells, glucose, Gram stain, crystals

Management
- septic joint: empiric IV antibiotics ± orthopedic consultation for joint decompression and drainage
- crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
  - do not use allopurinol for acute flares, as it may worsen acute attack
- acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
- osteoarthritis: NSAIDs, acetaminophen
- soft tissue pain:
  - non-pharmacologic treatment: local heat or cold, electrical stimulation, massage
  - pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

Validation of the Ottawa Subarachnoid Hemorrhage Rule in Patients with Acute Headache
CMAJ 2017;189:E1379-E1385
Purpose: Validate the Ottawa SAH Rule in emergency department patients.
Methods: Prospective cohort study at 6 university-affiliated tertiary-care hospital emergency departments in Canada from 2010-2014. Included alert, neurologically intact adult patients with headache peaking within 1 hour of onset. The rule was scored before investigations.
Results: 1153/1743 potentially eligible patients were enrolled, 67 had subarachnoid hemorrhage. Ottawa SAH rule had 100% sensitivity and 13.6% specificity with similar neuroimaging rates (87%).
Conclusions: The Ottawa SAH Rule was sensitive for identifying subarachnoid hemorrhage in otherwise alert and neurologically intact patients.

Meningitis
Do not delay IV antibiotics for LP
Deliver first dose of dexamethasone with or before first dose of antibiotic therapy

Parenteral Dexamethasone for Preventing Recurrence of Acute Severe Migraine Headache
BMJ 2008;336(7657):1359
Purpose: To examine effectiveness of parenteral corticosteroids for relief of acute severe migraine headache and prevention of recurrent headaches.
Methods: Meta-analysis of RCTs comparing corticosteroids (alone or in combination with standard abortive therapy) to placebo or any other standard treatment for acute migraine in adults.
Results: Seven RCTs met eligibility criteria, all of which used standard abortive therapy and subsequently compared single dose parenteral dexamethasone to placebo. All trials examined pain relief and recurrence of headache within 72 hr. While dexamethasone and placebo were comparable for acute pain reduction (mean difference 0.37, 95% CI -0.20 to 0.94) and side effect profiles, dexamethasone provided lower recurrence rates (relative risk 0.75, 0.60 to 0.90; number needed to treat 9).
Conclusion: Single dose parenteral dexamethasone with standard abortive therapy is associated with a 26% relative reduction in headache recurrence within 72 h.

Back Pain

- see Family Medicine, FM11
- use Clinically Organized Relevant Exam (CORE) Back Tool to screen for common mechanical back pain syndromes
- rule out extraspinal emergencies: aortic dissection, AAA, PE, MI, retroperitoneal bleed, pancreatitis
- rule out spinal emergencies: osteomyelitis, cauda equina syndrome, epidural abscess or hematoma, discitis, spinal fracture, or malignancy

History and Physical Exam

- evaluate risk for fracture (osteoporosis, age, trauma), infection (IV drug user, recent spinal intervention, immunosuppression), cancer, vascular causes (cardiac risk factors), neurological symptoms (e.g. saddle anesthesia)
- typical musculoskeletal back pain is moderate, worse with movement or cough with no visceral symptoms
- assess vital signs, perform precordial, abdominal, and neurologic examination of lower extremities



Red Flags for Back Pain

Bowel or bladder dysfunction
Anesthesia (saddle)
Constitutional symptoms
K - Chronic disease, Constant pain
Paresthesia
Age >50 and mild trauma
IV drug use/infection
Neuromotor deficits

Investigations

- U/A, post-void residual bladder scan
- reserve imaging for neurological deficits, metastases, and patients at high-risk of fracture, infection, cancer, or vascular cause
  - consider CT if trauma or fracture risk
  - urgent MRI if neurological findings

Management

- treat underlying cause
- lumbosacral strain and disc herniation: analgesia and continue daily activities as much as tolerated; discuss red flags and organize follow-up
- spinal infection: early IV antibiotics and infectious disease/spine surgery consultation
- cauda equina syndrome: dexamethasone, early spine surgery consultation

Seizures

- see Neurology, N18

Definition

- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons
- status epilepticus: continuous or intermittent seizure activity for greater than 5 min without regaining consciousness (life-threatening)



Minimum Workup in an Adult with 1st Time Seizure
CBC and differential
Electrolytes including Ca^{2+}, Mg^{2+}, PO_4^{3-}

Categories

- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hypo-/hyperglycemia, hypo-/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
- differential diagnosis: syncope, stroke/TIA, psychogenic non-epileptic seizure, migraines, movement disorders, narcolepsy/cataplexy



If administering phenytoin, patient must be on a cardiac monitor as dysrhythmias and/or hypotension may occur

History and Physical Exam

- history of seizures, identify potential precipitants (illness, alcohol withdrawal, sleep deprivation)
- preceding aura, rapid onset, brief duration, alterations in consciousness, tonic-clonic movements, and post-ictal symptoms would suggest a seizure
- common signs include tongue biting (high specificity), loss of bladder/bowel control, emesis, and aspiration
- perform vitals, complete neurologic examination, and look for injuries to head, spine, and shoulder (particularly posterior dislocations)



If IV access is not feasible, midazolam 0.2 mg/kg IM up to 10 mg can be used for initial control of seizure in adults

Table 17. Concurrent Investigation and Management of Status Epilepticus

Timing	Steps
Immediate	Protect airway with positioning; intubate if airway compromised or elevated ICP Monitor: vital signs, ECG, oximetry; POCT capillary blood glucose Establish IV/IO access Benzodiazepine - lorazepam 2 mg IV at 2 mg/min up to 10 mg or midazolam 5 mg IM up to 10 mg; repeat at 10 min if ineffective; intranasal if no IV/IO access Fluid resuscitation IV dextrose if glucose 33 mmol/L Give 50% glucose 50 mL (preceded by thiamine 100 mg IM if concerned about alcohol withdrawal) Obtain CBC, electrolytes, Ca^{2+}, Mg^{2+}, VBG, serum blood glucose, toxins, and antiepileptic drug levels; β-hCG Vasopressor support if sBP <90 or MAP <70 mmHg after aggressive fluid resuscitation
Urgent	Establish second IV line If status persists, phenytoin 20 mg/kg IV at 25-50 mg/min in adults; may give additional 10 mg/kg IV 10 min after loading infusion If seizure resolves, antiepileptic drug still required to prevent recurrence (levetiracetam: loading dose of 60 mg/kg IV in adults, maximum 4500 mg, infused over 5 to 15 min) EEG monitoring to evaluate for non-convulsive status epilepticus

Table 17. Concurrent Investigation and Management of Status Epilepticus

Timing	Steps
Refractory	If status persists after maximum doses above, consult ICU and start one or more of: Phenobarbital 20 mg/kg IV at 50 mg/min Midazolam 0.2 mg/kg IV loading dose and 0.1-0.4 mg/kg/h Propofol 2 mg/kg IV at 2-5 mg/kg/h then loading dose then 2-10 mg/kg/h Requires definitive airway management including rapid sequence intubation and assisted ventilation. Electroencephalography (EEG) for continuous monitoring
Post-Seizure	Investigate underlying cause: consider CT, LP, MRI, ICP monitoring

Note: All interventions should be done as soon as possible. Adapted from Brophy et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23

Disposition
- decision to admit or discharge should be based on the underlying disease process identified
  - if a patient had a brief generalized seizure and has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
- first-time seizure patients being discharged should be referred to a neurologist for follow-up
- admitted patients should generally have a neurology consult
- patient should not drive until medically cleared (local regulations vary)
  - complete notification form to appropriate authority regarding ability to drive (based on local legal requirements)
- warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)

Intramuscular vs. Intravenous Therapy for Prehospital Status Epilepticus
NEJM 2012;366:591-600
Purpose: To investigate the efficacy of intramuscular (IM) midazolam with that of IV lorazepam for children and adults in status epilepticus treated by paramedics.
Methods: Double-blind, randomized, non-inferiority trial. Subjects whose convulsions had persisted more than 5 min and were still convulsing after paramedics arrived were given the study medication by either IM or IV infusion. Primary outcome: absence of seizures at the time of arrival in the emergency department without the need for rescue therapy.
Results: Seizures were absent without rescue therapy in 73% of the IM-midazolam group and in 63.4% of the IV-lorazepam group (P<0.001 for noninferiority and superiority). The median times to active treatment were 1.2 min in the IM midazolam group and 4.8 min in the IV-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 min and 1.6 min. Adverse-event rates were similar.
Conclusions: For subjects in status epilepticus, IM midazolam is at least as safe and effective as IV lorazepam for prehospital seizure cessation.

Shortness of Breath

- see Respirology, R3 and Cardiology and Cardiac Surgery, C6

Table 18. Differential Diagnosis for Dyspnea

	High Mortality/Morbidity	Usually Less Emergent
Respiratory	Airway obstruction (foreign body, epiglottitis, abscess, anaphylaxis) Pneumo/hemothorax Gas exchange (pulmonary edema, PE, pneumonia, acute exacerbations of asthma, or COPD)	Chronic obstructive, interstitial or restrictive lung disease Pleural effusion
Cardiac	CHF, MI, valvular disease, tamponade, arrhythmia	Chronic CHF, angina
Metabolic	Metabolic acidosis NYD, toxin ingestion	Anemia, hemoglobinopathy
Neuromuscular	Myasthenia gravis, diaphragmatic paralysis	CNS lesion, primary muscle weakness
Other	Deconditioning, respiratory splinting due to unrelated pain	Anxiety

History and Physical Exam
- acute SOB is often due to a relatively limited number of conditions; associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischaemia
  - fever, cough, and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - environmental or occupational exposures
- dyspnea may be the sole complaint and the physical exam may reveal few abnormalities (e.g. PE, pneumothorax)
- vitals including pulse oximetry
  - wheeze and stridor (ventilatory) vs. crackles (parenchymal), JVP, and murmurs

Investigations
- blood work
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider ABG/VBG
  - serial cardiac enzymes and ECG if considering cardiac source
  - PERC or Wells scores to consider appropriateness of D-dimer
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection, or interstitial fluid)
  - CT chest may be indicated in acute dyspnea, specifically when suspicion for thromboembolic disease (i.e. PE)

Disposition
- history and physical exam lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified and its severity
  - non-invasive positive pressure ventilation (NIPPV) should be considered in patients with severe COPD or CHF, may reduce the need for intubation in this patient population
  - consider intubation in COPD and CHF if NIPPV will not be tolerated (e.g. decreased LOC, vomiting)
- if discharging, organize follow-up and educate regarding signs to return to hospital

Syncope

Definition
- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system (brainstem) hypoperfusion

Etiology
- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, orthostatic, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)

History
- gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features: prodrome and situation (setting, patient posture)
- distinguish between syncope and seizure (see Neurology, N18)
  - some patients may have myoclonic jerks with syncope – NOT a seizure
    - signs and symptoms during presyncope, syncope, and postsyncope (seizure has post-ictal period afterwards, syncope does not)
    - past medical history, drugs
    - think anatomically in differential: pump (heart), blood, vessels, brain
- syncope is cardiogenic until proven otherwise if
  - there is sudden loss of consciousness with no warning or prodrome
  - syncope is accompanied by chest pain

Physical Exam
- postural BP and HR
- cardiac, respiratory, and neurological exams
- examine for signs of secondary injury caused by syncopal episode (e.g. head injury)

Investigations
- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval, Brugada Syndrome, right ventricular strain, hypertrophic cardiomyopathy)
- POCT capillary blood glucose
- consider blood work: CBC, electrolytes, BUN/Cr, VBG, troponin, Ca^{2+}, Mg^{2+}, β-hCG, D-dimer
- consider toxicology screen

Management
- ABCs, IV, O_2, monitor
- cardiogenic syncope: admit to medicine/cardiology
- low-risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

Disposition
- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow up with family physician
  - educate about avoiding orthostatic or situational syncope
  - evaluate the patient for fitness to drive or work
  - patients with recurrent syncope should avoid high-risk activities (e.g. driving)

Sexual Assault

Epidemiology
- 1 in 5 women and 1 in 50 men will be sexually assaulted in their lifetime; only 7% are reported

General Approach
- ABCs, treat acute, serious injuries; physician priority is to treat medical issues and provide clearance
- ensure patient is not left alone and provide ongoing emotional support
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained); ideally by an experienced provider (generally a sexual assault nurse examiner)
- administer Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault; ideally by an experienced provider
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests or if <16 y/o (i.e. legally required)

Interprofessional teams are key; many centres or regions have sexual assault teams who specialize in the assessment and treatment of sexual assault victims, leaving emergency physicians responsible only for significant injuries and medical clearance

History
- ensure privacy for the patient – others should be asked to leave
- questions to ask: who, when, where did penetration occur, what happened, any weapons, or physical assault?

- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravidity, parity, last menstrual period
  - contraception use
  - last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

Physical Exam

- never re-traumatize a patient with the examination
- intimate exams and specimen collection should ideally be deferred to a sexual assault nurse if there is one available. This is to avoid re-traumatization and for medico-legal reasons (samples once collected must be secured, otherwise their validity will be questioned during legal proceedings)
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- pelvic exam and specimen collection
  - ideally before urination or defecation
  - examine for seminal stains, hymen, signs of trauma
  - collect moistened swabs of dried seminal stains
  - pubic hair combings and cuttings
  - speculum exam
    - lubricate with water only
    - vaginal lacerations, foreign bodies
    - Pap smear, oral/cervical/rectal culture for gonorrhea and chlamydia
    - posterior fornix secretions if present or aspiration of saline irrigation
    - immediate wet smear for motile sperm
    - air-dried slides for immotile sperm, acid phosphatase, ABO group
- fingernail scrapings and saliva sample from victim

Investigations

- Venereal Disease Research Lab (VDRL): repeat in 3 mo if negative
- serum β-hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

Management

- involve local/regional sexual assault team (sexual assault forensic examiner or sexual assault nurse examiner)
- medical
  - suture lacerations, tetanus prophylaxis
  - gynecology consult for foreign body, complex lacerations
  - assume positive for gonorrhea and chlamydia
    - management: ceftriaxone IM x 1 dose (500 mg <150 kg; 1g >150 kg) and doxycycline 100 mg PO BID x 7 d (alt: azithromycin 1 g PO x 1 dose)
  - may start post-exposure prophylaxis for hepatitis B, syphilis, HIV
  - pre and post counselling for HIV testing
  - pregnancy prophylaxis offered
    - levonorgestrel 1.5 g PO STAT (Plan B®)
- psychological
  - high incidence of psychological sequelae
  - have victim change and shower after exam completed

Disposition

- discharge if injuries/social situation permit
- follow-up with physician in rape crisis center within 24 h for repeat pregnancy and STI testing
- best if patient does not leave ED alone

INTIMATE PARTNER VIOLENCE

- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
  - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns, or other injuries; often inconsistent with history provided)
  - somatic symptoms (chronic and vague complaints)
  - psychosocial symptoms
  - clinician impression (your 'gut feeling' e.g. overbearing partner that won't leave patient's side)
- if disclosed, be supportive and assess danger
- patient must consent to follow-up investigation/reporting (unless patient is <16 y/o)

Management

- treat injuries and document findings
- ask about sexual assault and children at home (encourage notification of police)
- safety plan with good follow-up with family physician/social worker

Medical Emergencies

Anaphylaxis and Allergic Reactions

Etiology

- anaphylaxis is an exaggerated immune-mediated hypersensitivity reaction that leads to systemic histamine and vasoactive mediator release leading to increased vascular permeability and vasodilation
- regardless of the etiology, the presentation and management of anaphylactic reactions are the same
  - epinephrine (1:1000) 0.3-0.5 mg (IM in anterolateral thigh)
- allergic (e.g. re-exposure to allergen)
- non-allergic (e.g. exercise-induced)

Most Common Triggers for Anaphylaxis
Foods (nuts, shellfish, etc.)
Stings
Drugs (penicillin, NSAIDs, ACEI)
Radiographic contrast media
Blood products
Latex

Diagnostic Criteria

- diagnosis of anaphylaxis is highly likely with any of the following:
  1. acute onset of an illness (min to h) with involvement of the skin, mucosal tissue, and at least one of
     - respiratory compromise (e.g. dyspnea, wheeze, stridor, hypoxemia)
     - hypotension/end-organ dysfunction (e.g. hypotonia, collapse, syncope, incontinence)
  2. two or more of the following after exposure to a LIKELY allergen for that patient (min to h)
     - involvement of the skin-mucosal tissue
     - respiratory compromise
     - hypotension or associated symptoms
     - persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
  3. hypotension after exposure to a KNOWN allergen for that patient (min to h)
     - management is also appropriate in cases which do not fulfill criteria, but who have had previous episodes of anaphylaxis
     - life-threatening differentials for anaphylaxis include asthma and septic shock
     - angioedema may mimic anaphylaxis but tends not to improve with standard anaphylaxis treatment

Anaphylaxis should be suspected if airway, breathing, or especially circulation compromise is present after exposure to a known allergen

Hypotension is defined as sBP >30% decrease from baseline or
≥11 yr: <90 mmHg
1-10 yr: <70 mmHg + (2 x age)
1 mo-1 yr: <70 mmHg

Management

- moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
  - epinephrine (1:1000) 0.3-0.5 mg (IM in anterolateral thigh)
  - antihistamine: cetirizine 10 mg PO/IV
  - salbutamol (Ventolin®) 1 cc via MDI
- severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
  - ABCs, may need definitive airway (e.g. ETT) due to airway edema
  - epinephrine (1:1000) 1-10 µg/min IV (or via ETT if no IV access) titrated to desired effect
  - antihistamine: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg) or cetirizine (Reactine®) 10 mg IV
  - glucocorticoids: methylprednisolone 125-250 mg IV or prednisone/prednisolone 40-60 mg PO
  - large volumes of crystalloid may be required
  - try to remove trigger (e.g. search for insect stingers, decompress GI tract if possible)
- patients on β-blockers may not respond to epinephrine in an anaphylactic reaction and may benefit from glucagon for reversal

Early epinephrine is lifesaving and there are no absolute contraindications

Disposition

- all patients should be kept under observation until symptoms fully resolve, especially if severe anaphylaxis and/or those who needed >1 dose of epinephrine; arrange follow-up with family physician in 24-48 h
- can have second phase (biphasic) reaction up to 72 h later, patient may need to be supervised
- educate patient on avoidance of allergens
- instructions to seek immediate medical attention in ED during any future anaphylaxis reaction, even when self-treatment has been self-initiated
- medications
  - epinephrine auto-injector
  - H1 antagonist (cetirizine 10 mg PO once daily)
  - Second-generation H1 antagonists (e.g. cetirizine) are less sedating than first-generation H1 antagonists (e.g. Benadryl®)
  - glucocorticoids not recommended

Pediatric Dosing
Epinephrine: 0.01 mg/kg IM up to 0.5 mg q5-10 min
Initial crystalloid bolus: 20-30 mL/kg, reassess
Epinephrine infusion: 0.1-1.5 µg/kg/min
Diphenhydramine: 1 mg/kg PO/IV q4-6 h
Methylprednisolone: 1-2 mg/kg IV

Asthma

- see Respirology, R7 and Pediatrics, P91
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

Beware of the silent chest in asthma exacerbations. This is a medical emergency and requires aggressive treatment. Intubation of patients with severe asthma is extremely high risk and maximum medical therapy should be used to avoid it if possible

History and Physical

- find cause(s) of asthma exacerbation (e.g. viral, environmental, etc.)
- history of asthma control; severity of exacerbations (e.g. ICU, intubation history)
- signs of respiratory distress (e.g. accessory muscle use)
- vitals, specifically O_2 saturation

Investigations
- peak flow meter
- ± ABG if in severe respiratory distress
- CXR if diagnosis is uncertain to rule out pneumonia, pneumothorax, etc.

Table 19. Asthma Assessment and Management

Classifications	History and Physical Exam	Management
Respiratory Arrest Imminent	Exhausted, confused, diaphoretic, cyanotic Silent chest, ineffective respiratory effort Decreased HR, respiratory rate (RR) >30, pCO_2 >45 mmHg O_2 sat <90% despite supplemental O_2	Anticipate need for intubation (high risk for complications; ideally carried out by an experienced provider) 100% O_2, cardiac monitor, IV access Intubate (consider induction with ketamine) Short acting β-agonist (salbutamol): nebulizer 5 mg continually Short-acting anticholinergic (ipratropium): nebulizer 0.5 mg x 3 IV steroids: methylprednisolone 125 mg, salbutamol 1-2 mg/kg. IV epinephrine can be helpful, especially if associated hypotension
Severe Asthma	Agitated, diaphoretic, laboured respirations Speaking in words No relief from β-agonist O_2 sat <90%, FEV1 <50%	Magnesium sulphate 2 g IV (25-50 mg/kg) O_2 to achieve O_2 sat >92% Short acting β-agonist (salbutamol): nebulizer 5 mg continually Short-acting anticholinergic ilpratropium): nebulizer 0.5 mg x 3 if not already given IV steroids: methylprednisolone 125 mg or 1-2 mg/kg
Moderate Asthma	SOB at rest, cough, congestion, chest tightness Speaking in phrases Inadequate relief from β-agonist FEV_1 50-80%	O_2 to achieve O_2 sat >92% Short-acting β-agonist (salbutamol): MDI or nebulizer q5 min Short-acting Anticholinergic (ipratropium): MDI or nebulizer x 3 Steroids: prednisone 40-60 mg PO
Mild Asthma	Exertional SOB/cough with some nocturnal symptoms Difficulty finishing sentences FEV_1 >80%	β-agonist Monitor FEV_1 Consider steroids (MDI or PO)

Disposition
- discharge is safe in patients with FEV1 or peak expiratory flow (PEF) >60% predicted, and may be safe if FEV_1 or PEF 40-60% predicted based on the patient's risk factors for recurrence of severe attack
  - risk factors for recurrence: frequent ED visits, frequent hospitalizations, recent steroid use, recent exacerbation, poor medication compliance, prolonged use of high dose β-agonists
- β-agonist MDI with aerochamber 2-4 puffs q2-4 h until symptoms controlled, then PRN
- initiate inhaled corticosteroids with aerochamber if not already prescribed
- if moderate to severe attack, administer prednisone 30-60 mg/d for 5-10 d with no taper
- counsel on medication adherence and educate on use of aerochamber
  - follow up with primary care physician or asthma specialist

Cardiac Dysrhythmias

- see Cardiology and Cardiac Surgery, C19

Bradydysrhythmias and AV Conduction Blocks
- AV conduction blocks
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - atropine and transcutaneous/transvenous pacing (atropine with caution)
    - if transcutaneous/transvenous pacing fails consider IV dopamine, epinephrine
  - long-term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate <60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, MI/ischemia, increased ICP, sinus node dysfunction, hypothyroidism, drugs (e.g. β-blockers, calcium channel blockers)
  - look for up-right P waves in lead II and/or biphasic in lead V1 – confirms sinus P wave origin
  - treat if symptomatic (hypotension, chest pain)
    - acute: atropine ± transcutaneous/transvenous pacing
    - sick sinus: transcutaneous/transvenous pacing
    - drug induced: discontinue/reduce offending drug, consider antidotes, pacing often ineffective, use IV epinephrine to increase chronotropy

Supraventricular Tachydysrhythmias (narrow QRS)
- sinus tachycardia (rate >100 bpm)
  - causes: increased sympathetic tone, drugs, fever, shock, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause
- regular rhythm (i.e. not sinus tachycardia)
  - vagal maneuvers (e.g. carotid massage, Valsalva)
  - continuous 12-lead ECG helpful during maneuvers or cardioversion if 1st episode; will help to elicit underlying etiology
  - adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once; warn patients regarding side effects (e.g. chest pain, nausea)



Elements of Well-Controlled Asthma
Can Respir J 2010;17(1):15-24
- Daytime symptoms <4x/wk
- Nocturnal symptoms <1x/wk
- No limitation in activity
- No absence from work/school
- Rescue inhaler use <4x/wk
- FEV_1 <90% personal best
- PEF <10-15% diurnal variation
- Mild infrequent exacerbations



Combined Inhaled β-Agonist and Anticholinergic Agents for Emergency Management in Adults with Asthma
Cochrane DB Syst Rev 2017:CD001284
Purpose: Determine the effectiveness of combined short-acting β-agonist (SABA) + short-acting antichoinergic (SAAC) vs. SABA alone to reduce hospitalization in adult patients presenting to the ED with an exacerbation of asthma.
Methods: Systematic review of RCTs.
Results: 23 trials, 2724 patients. Combination inhaled therapy was associated with reduced likelihood of hospitalization (RR 0.72, 95% CI 0.59-0.87) for severe but not mild or moderate asthma exacerbations. Combination therapy was also associated with improved FEV (MD 0.25L, 95% CI 0.02-0.48) and PEF (MD 24.88, 95% CI 14.83-34.93) and patients were less likely to return to ED for additional care (RR 0.80, 95% CI 0.66-0.98). In contrast, patients receiving combination therapy were more likely to experience adverse events than those treated with SABA alone (OR 2.03, 95% CI 1.28-3.20).
Conclusions: Combination SAAC + SABA therapy reduces hospitalizations and improves pulmonary function in adults presenting to the ED with acute asthma. However, adults receiving combination therapy were more likely to experience adverse events, such as tremor, agitation, and palpitations, compared to patients receiving SABA alone.



Adenosine vs. Intravenous Calcium Channel Antagonists for Supraventricular Tachycardia
Cochrane DB Syst Rev 2017;CD005154
Purpose: Compare adenosine vs. calcium channel antagonists in terminating supraventricular tachycardia.
Methods: Systematic review of RCTs for any patient presenting with supraventricular tachycardia.
Results: 7 RCTs, 622 participants. Moderate-quality evidence shows no differences in the number or people reverting to sinus rhythm who were treated with adenosine or calcium channel antagonist (89.7% vs. 92.9%, OR 1.51). Low-quality evidence suggests no differences in major adverse event rates.
Conclusions: Moderate-quality evidence shows no differences in effects of adenosine and calcium channel antagonists for treatment of supraventricular tachycardia on reverting to sinus rhythm, and low-quality evidence suggests no differences in the incidence of hypotension.



In patients with a regular rhythm and a supraventricular tachydysrhythmia, a modified valsalva maneuver is effective in up to 43% of patients. Procedure: position the patient in a semi-recumbent position (45°). Instruct the patient to blow into the tip of a 10 cc syringe for 15 s. The patient should be targeting a pressure reading on the manometer of 40 mmHg, or blowing hard enough to move the plunger tip. Lower the patient flat, and passively raise their legs to a 45° angle for 15 s. Return the patient to a semi-recumbent position for an additional 45 s.

- electrical cardioversion if vagal maneuvers and adenosine unsuccessful
- rhythm converts: probable reentrant tachycardia (atrioventricular (AV) nodal reentrant tachycardia (AVNRT) more common than AV reentrant tachycardia (AVRT))
  - monitor for recurrence
  - treat recurrence with adenosine or longer acting medications
- rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
  - rate control (diltiazem, β-blockers) or rhythm control with cardioversion
  - consult cardiology if refractory

• irregular rhythm
- probable AFib, atrial flutter, or multifocal atrial tachycardia
- rate control (e.g. diltiazem, β-blockers), or rhythm control if AFib/flutter and at least <48 h from onset

Atrial Fibrillation

•most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
•etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sinus node dysfunction
•treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
•decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
• acute management
- consider whether AFib is primary cause of symptoms; if different underlying cause, treat underlying cause first
- if unstable: immediate synchronized cardioversion
- hemodynamically stable patients with AFib <48 h: rhythm or rate control ± electrical or chemical cardioversion
- do not cardiovert if any of the following are present: valvular AFib (any duration) or non-valvular AFib (duration <12 h and recent stroke/TIA; duration 12-48 h and CHADS2 ≥2; or duration >48 h). Instead, start patient on appropriate anticoagulation and/or arrange for transesophageal echocardiogram to exclude a thrombus in the left atrial appendage

•electrical cardioversion: synchronized cardioversion
•chemical cardioversion: procainamide, flecainide, propafenone
•long-term management: rate or rhythm control, consider anticoagulation (see Cardiology and Cardiac Surgery, *CHADS2 score*, C22)

Ventricular Tachydysrhythmias (wide QRS)

•VTach (rate usually 140-200 bpm)
- definition: 3 or more consecutive ventricular beats at >100 bpm
- etiology: CAD with MI is the most common cause
- treatment: sustained VTach (>30 s) is an emergency
  - hemodynamic compromise: synchronized DC cardioversion
  - no hemodynamic compromise: synchronized DC cardioversion, amiodarone, procainamide

•VFib: call a code blue, follow ACLS for pulseless arrest
•torsades de pointes
- looks like VTach but QRS 'rotates around baseline' with changing axis and amplitude (twisted ribbon)
- etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
- treatment
  - IV Mg^{2+}, temporary overdrive pacing, isoproterenol
  - correct cause of prolonged QT

Acute Exacerbation of COPD

• see Respirology, R8
•progressive development of irreversible airway obstruction, typically caused by smoking

History and Physical Exam

•cardinal symptoms of acute exacerbation of COPD (AECOPD): increased dyspnea, increased coughing frequency or severity, increased sputum volume or purulence
•triggers: virus, pneumonia, PE, CHF, MI, drugs
•characterize previous episodes and hospitalizations, smoking history
•vital signs, LOC, signs of respiratory distress, respiratory exam

Investigations

•CBC, electrolytes, CXR, ECG, consider VBG
•Pulmonary Function Tests are NOT useful in managing acute exacerbations

Management

•oxygen: keep O_2 saturation 88-92% (be aware of chronic hypercapnic/CO_2 retainers but do not withhold O_2 if hypoxic)
•bronchodilators: short-acting β-agonist (salbutamol 4-8 puffs via MDI with spacer q15 min x3 PRN) ± short-acting anticholinergic (ipratropium 0.5 mg via MDI q30 min x3 PRN)
•steroids: prednisone 40-60 mg PO for 7-14 d, or methylprednisolone 1-2 mg/kg IV if severe exacerbation, or unable to take PO
•antibiotics: trimethoprim/sulfamethoxazole, cephalosporins, respiratory quinolones (given if all 3 cardinal symptoms present or 2 cardinal symptoms with increased sputum purulence or mechanical



If a patient with tachydysrhythmia is unstable, perform immediate synchronized cardioversion



If patient has Wolff-Parkinson-White and is in AFib, use procainamide or cardiovert; avoid AV nodal blocking agents (adenosine, digoxin, diltiazem, verapamil, β-blockers), as these can increase conduction through bypass tract, leading to cardiac arrest



Causes of Atrial Fibrillation

C ("sea") PIRATES
CHF, **C**ardiomyopathy
Pulmonary embolism
Ischaemic heart disease
Rheumatic or valvular disease
Anemia
Thyroid (hyperthyroidism)
EtOH, **E**levated blood pressure
Sick **S**inus, **S**tress - surgery, sepsis



Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation
NEJM 2019;380:1499-1508
Purpose: Patients with recent-onset AFib commonly undergo immediate restoration of sinus rhythm by cardioversion. Whether this is necessary is not known, since AFib often terminates spontaneously.
Methods: Randomly assigned patients with stable, recent-onset (<36 h), symptomatic AFib in the ED to be treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion. The wait-and-see approach involved initial treatment with rate-control medication only and delayed cardioversion if the AFib did not resolve within 48 h.
Primary endpoint: presence of sinus rhythm at 4 wk.
Results: The presence of sinus rhythm at 4 wk occurred in 91% of patients in the delayed-cardioversion group and in 94% in the early-cardioversion group (P=0.005 for noninferiority). Among the patients who completed remote monitoring during 4 wk of follow-up, a recurrence of AFib occurred in 30% of the delayed-cardioversion group and in 29% of the early-cardioversion group.
Conclusions: Wait-and-see approach was non-inferior to early cardioversion in stable AFib patients.



Physical Exam Findings in COPD
- Wheeze
- Maximum laryngeal height ≤4 cm
- Forced expiratory time ≥6 s
- Decreased breath sounds
- Decreased cardiac dullness



Need to Rule Out with COPD
- Exacerbation
- Pneumothorax
- CHF exacerbation
- Acute MI
- Pneumonia and other infectious causes
- PE

ventilation); no antibiotics for mild exacerbation (only 1 of 3 cardinal symptoms)
- ventilation: apply noninvasive positive-pressure ventilation (CPAP or Bi-PAP) if severe distress or signs of fatigue, arterial pH <7.35, or hypercapnic
- if life-threatening, intubate in ED and refer to ICU admission for ventilation (chance of ventilation dependency)

Disposition
- no specific guidelines for admission consider admission if: inadequate response to management, onset of new signs (cyanosis, altered LOC, peripheral edema, respiratory distress), marked increase in symptom intensity with increased oxygen requirement, hemodynamic instability
- lower threshold to admit if comorbid illness (e.g. diabetes, CHF, CAD, alcohol use disorder)
- if discharging, use antibiotics, taper steroids, up to 4-6 puffs QID of ipratropium and salbutamol, and organize follow-up

Heart Failure

- see Cardiology and Cardiac Surgery, C40

Etiology
- causes of chronic heart failure: decreased myocardial contractility (ischaemia, infarction, cardiomyopathy, myocarditis), pressure overload states (HTN, valve abnormalities, congenital heart disease), restricted cardiac output (myocardial infiltrative disease, cardiac tamponade)
- precipitants of acute decompensated heart failure (ADHF)
  - cardiac (ischaemia, infarction, arrhythmia, e.g. AFib)
  - medications (β-blockers, calcium channel blockers, NSAIDs, steroids, non-compliance)
  - dietary (increased sodium and/or water intake)
  - high output (anemia, infection, pregnancy, hyperthyroid)
  - other (renal failure, hypertensive crisis, iatrogenic fluid overload - blood transfusions or IV fluids)

Presentation
- left-sided heart failure
  - dyspnea, SOB on exertion, orthopnea, paroxysmal nocturnal dyspnea, nocturia, fatigue, altered mental status, presyncope/syncope, angina, systemic hypotension
  - hypoxia, decreased air entry to lungs, crackles, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right-sided)
- right-sided heart failure
  - dependent bilateral pitting edema, JVP elevation and positive abdominojugular test, ascites, hepatomegaly
- patients often present with a combination of right-sided and left-sided symptoms

Investigations
- blood work: CBC, electrolytes, AST, ALT, bilirubin, Cr, BUN, cardiac enzymes, brain natriuretic peptide
- CXR: most useful test (see sidebar)
- ECG: look for MI, ischaemia (ST elevation/depression, T-wave inversion), LVH, atrial enlargement, conduction abnormalities
- bedside ultrasound: Kerley B lines, pleural effusion, rule out cardiac tamponade
- echocardiogram: left ventricular function, structural heart disease
- rule out other serious diagnoses: PE, pneumothorax, pneumonia/empyema
- can be difficult to differentiate ADHF and AECOPD in patients who have both Kerley B lines, pleural effusion, elevated BNP

Management
- ABCs, may require intubation (rare with non-invasive ventilation, but consider if severe hypoxia)
- sit upright, cardiac monitoring, and continuous pulse oximetry
- saline lock IV, Foley catheter or an in out catheter
- 100% O_2 by mask
  - if poor response, may require Bi-PAP (preferred) or intubation (rare)
- medical
  - diuretic (if volume overloaded): furosemide 0.5-1 mg/kg IV, titrate to response
  - vasodilators (if sBP >100 mmHg): nitroglycerin 0.4 mg SL q5 min PRN
  - inotropes/vasopressors (if sBP <90 mmHg): first-line agent is norepinephrine; add dobutamine or epinephrine; milrinone helpful in refractory cases, but rarely available
- treat precipitating factor - e.g. rate control (β-blocker, calcium channel blockers) or rhythm-control (electrical or chemical cardioversion) if new AFib
- cardiology or medicine consult

Venous Thromboembolism

- see Respirology, R20

Risk Factors
- Virchow's triad: alterations in blood flow (venous stasis), injury to endothelium (smoking, HTN, surgery, catheter, trauma), hypercoagulable state (including pregnancy, use of oral contraceptive pills, malignancy)
- clinical risk factors (see *sidebar, Risk Factors for VTE, ER33*)



Precipitants of CHF Exacerbation

FAILURE
Forgot medication
Arrhythmia (Dysrhythmia)/Anemia
Ischaemia/Infarction/Infection
Lifestyle (e.g. high salt intake)
Upregulation of cardiac output (e.g. pregnancy, hyperthyroidism)
Renal failure
Embolism (pulmonary)



CHF on CXR
- Pulmonary vascular redistribution
- Perihilar infiltrates
- Interstitial edema, Kerley B lines
- Alveolar edema, bilateral infiltrates
- May see cardiomegaly, pleural effusions
- Peribronchial cuffing
- Fissural thickening (fluid in fissure)



Acute Treatment of CHF

LMNOP
Lasix® (furosemide)
Morphine
Nitroglycerin
Oxygen
Position (sit upright), Pressure (Bi-PAP)



Hospital Management Required if
- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring interventions
- Clinically significant dysrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen (walk test with SpO_2 monitor can identify patients with occult hypoxia)



YEARS Criteria for Pulmonary Embolism Evaluation
Use in hemodynamically stable patients ≥18 y/o with clinically suspected acute PE, and pregnant patients if DVT excluded. Criteria: clinical signs of deep vein thrombosis (DVT), hemoptysis, and whether PE is the most likely diagnosis. In patients with no YEARS items and D-dimer <1,000 ng/mL, or with 1+ YEARS items and D-dimer <500 ng/mL, PE is excluded. All other patients should have a CT pulmonary angiogram (CTPA)

DEEP VEIN THROMBOSIS

Presentation

- calf pain, unilateral leg swelling/erythema/edema, palpable cord along the deep venous system on exam
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT (may be asymptomatic; bilateral leg presentation unlikely but does not rule out diagnosis; think inferior vena cava (IVC) occlusion if bilateral DVT)
  - further investigation is often needed

Investigations

- use Wells' criteria for DVT to guide investigations (see *Figure 11, ER34*)
- D-dimer is only useful for ruling out DVT, and a D-dimer test result should only be considered in cases where a low-moderate risk patient has a negative test (high sensitivity)
  - high-risk of false positives in: elderly, infection, recent surgery, trauma, hemorrhage, late in pregnancy, liver disease, cancer
- U/S has high sensitivity & specificity for proximal clot but only 73% sensitivity for calf DVT (may need to repeat in 1 wk)
  - if positive – treat for DVT unless anticoagulation is contraindicated
  - if negative and low-risk – rule out DVT
  - if negative and moderate to high-risk – repeat U/S in 5-7 d to rule out DVT

Management

- direct oral anticoagulants (DOAC) can be used in acute management of symptomatic DVT
  - rivaroxaban: 15 mg PO BID for first 21 d; 20 mg PO once daily for remaining treatment (taken with food at the same time each day)
  - apixaban: 10 mg PO BID for first 7 d; 5 mg PO BID for remaining treatment
- low molecular weight heparin (LMWH) unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24 h or enoxaparin 1 mg/kg SC q24 h
  - use of DOAC vs. LMWH for cancer induced VTE; local practice vary
- consider thrombolysis if extensive DVT threatening limb compromise
- IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
- duration of anticoagulation: 3 mo if transient coagulopathy; 6 mo if unprovoked DVT; life-long if ongoing coagulopathy
- calf/distal DVT: local practices vary, no consensus on best treatment; options include a (i) serial venous doppler, start anticoagulation close to proximal system or large clot burden; or (ii) oral anticoagulation, with follow-up in thrombosis clinic

PULMONARY EMBOLISM

Presentation

- dyspnea, pleuritic chest pain, hemoptysis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of PE; investigation often needed

Investigations

- use Wells' criteria for PE to guide investigations (see *Figure 12, ER34*)
- pulmonary embolism rule-out criteria (PERC) score (see EBM on sidebar, Respirology, R21) alone can rule out PE in low-risk patients unless pregnant
- ECG and CXR are useful to rule out other causes (e.g. ACS, pneumonia, pericarditis) or to support diagnosis of PE
  - ECG changes in PE: sinus tachycardia, right ventricular strain (S1Q3T3, see Cardiology and Cardiac Surgery, C10), T wave inversions in anterior and inferior leads (more common sign of RV strain), AFib
  - CXR findings in PE (rarely seen): Hampton's hump (triangular density extending from pleura, sign of pulmonary infarct) or Westermark's sign (dilatation of vessels proximal to an obstruction, with collapse of vessels distal to obstruction, often with a sharp cutoff)
- D-dimer is only useful at ruling out a PE if it is negative in low-moderate risk patients (highly sensitive)
  - if positive D-dimer or high-probability patient, then pursue CT pulmonary angiography or V/Q scan
- CT pulmonary angiography has high sensitivity and specificity for PE, may also indicate an alternative diagnosis
- V/Q scan useful in pregnancy, when CT pulmonary angiography not available, or IV contrast contraindicated

Management

- treatment of PE with anticoagulation and duration of treatment is the same as for DVT (see above)
- thrombolysis indicated in massive PE, which is defined as acute PE with sustained hypotension (sBP <90 mmHg for at least 15 min or requiring inotropic support, not due to a cause other than PE)
- catheter-directed thrombolysis or surgical thrombectomy may be considered in massive PE or if anticoagulation is contraindicated
- often can be treated as an outpatient, may require analgesia for chest pain (narcotic or NSAID)
- admit if hemodynamically unstable, require supplemental O_2, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy, or clinical signs of RV strain on echocardiography
  - referral to medicine for coagulopathy and malignancy workup



Effect of a Diagnostic Strategy Using an Elevated and Age-Adjusted D-Dimer Threshold on Thromboembolic Events in Emergency Department Patients With Suspected Pulmonary Embolism: A Randomized Clinical Trial
JAMA 2021;326:2141-2149.
Purpose: To prospectively validate the safety of a strategy that combines the YEARS rule with the pulmonary embolism rule-out criteria (PERC) rule and an age-adjusted D-dimer threshold.
Methods: Multi-center (n=18), cluster-randomized, crossover, non-inferiority trial in France and Spain. Patients (n=1414) with low clinical risk of PE (<15%) who could not be excluded with PERC or a subjective clinical intermediate risk of PE were included from October 2019 to June 2020, and followed up until October 2020. In intervention period (n=726): PE was excluded without chest imaging in patients with no YEARS criteria and a D-dimer <1000 ng/mL, or in patients with 1+ YEARS criteria and D-dimer level less than age-adjusted threshold. In controls (n=688): PE was excluded without chest imaging if D-dimer level was less than age-adjusted threshold. The primary endpoint was the presence of VTE at 3 mo.
Results: At 3 mo, VTE was diagnosed in 1 patient in the intervention group (0.15% [95% CI, 0.0% to 0.86%]) vs 5 patients in the control group (0.80% [95% CI, 0.26% to 1.86%]). The adjusted difference was -0.64% [1-sided 97.5% CI, -∞ to 0.21%], within the non-inferiority margin).
Conclusions: In ED patients with a suspected PE, the YEARS rule, combined with the age-adjusted D-dimer threshold in PERC-positive patients, did not result in an inferior rate of thromboembolic events, when compared to a conventional diagnostic strategy.



Diagnostic Accuracy of POCUS and CXR in Adults With Symptoms Suggestive of ADHF
JAMA 2019;2:e190703
Purpose: To compare the accuracy of Point-of-Care Lung Ultrasonography (LUS) with the accuracy of CXR in the diagnosis of cardiogenic pulmonary edema.
Methods: Systematic review with inclusion criteria of patients presenting with dyspnea who underwent both LUS and CXR on initial assessment. Imaging results were compared by a clinical expert after either a medical record review or a combination of echocardiography findings and B-type natriuretic peptide (BNP) criteria. Primary outcome was the comparative accuracy of LUS and CXR in diagnosing ADHF as measured by the differences between the 2 modalities in pooled sensitivity and specificity.
Results: 6 studies met the inclusion criteria; a total of 1827 patients. Pooled estimates for LUS were 0.88 for sensitivity and 0.90 for specificity. Pooled estimates for CXR were 0.73 for sensitivity and 0.90 for specificity. The relative sensitivity ratio of LUS, compared with CXR, was 1.2. No difference was found in specificity between tests.
Conclusions: The findings suggest that LUS is more sensitive than CXR in detecting pulmonary edema in ADHF; LUS should be considered as an adjunct imaging modality in the evaluation of patients with dyspnea at risk for ADHF.



Risk Factors for VTE

THROMBOSIS
Trauma, travel
Hypercoagulable, hormone replacement therapy (HRT)
Recreational drugs (IV drug use)
Old (age >60 yr)
Malignancy
Birth control pill
Obesity, obstetrics
Surgery, smoking
Immobilization
Sickness (CHF, MI, nephrotic syndrome, vasculitis)

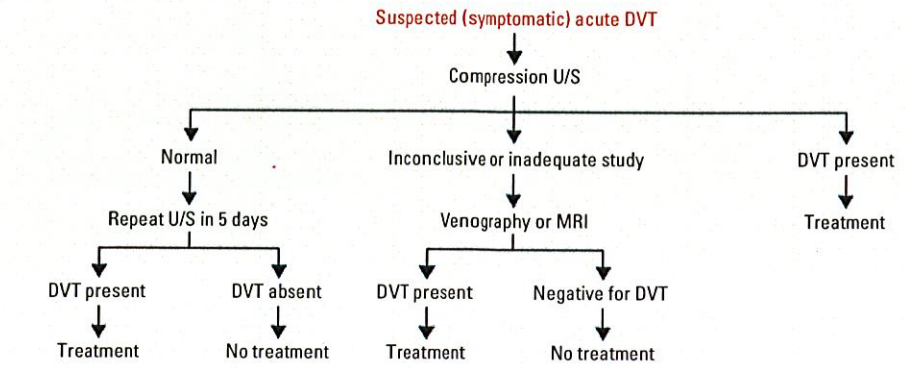


Figure 11. Approach to suspected DVT (with high clinical suspicion and no other cause)

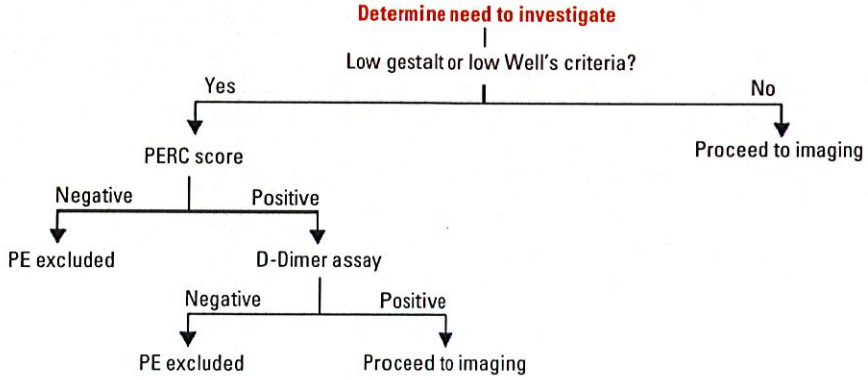


Figure 12. Approach to PE in patients with low clinical suspicion of a PE
Adapted with permission from Dr. Salim R. Rezaie from REBELEM [online]. Original figure can be found at https://rebelem.com/is-it-proper-to-perc-it-up/

Diabetic Emergencies

- see Endocrinology, E13

Diabetic Ketoacidosis

- triad of hyperglycemia, ketosis, and acidosis due to severe insulin deficiency and counter-regulatory hormone excess
- precipitating factors: infection, cardiac or mesenteric ischaemia, MI, intoxication, insulin omission, or SGLT2i (euglycemic DKA)
- clinical features
  - often young, T1DM patients (may rarely be first presentation of undiagnosed T2DM), with symptoms evolving within a day
  - early signs and symptoms: polyuria, polydipsia, malaise, nocturia, weight loss, abdominal pain
  - late signs and symptoms
    - GI: anorexia, nausea, vomiting, increasing abdominal pain
    - neurological: fatigue, drowsiness, stupor, coma
    - respiratory: Kussmaul's respiration, dyspnea (often due to acidosis), fruity ketotic breath
- investigations
  - blood work: CBC, electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, Cr, BUN, glucose, ketones, osmolality, AST/ALT/ALP, amylase, troponin
  - urine: glucose and ketones
  - ABG or VBG
  - ECG (electrolyte disturbances may predispose to dysrhythmia, MI is rarely a precipitant)
- management
  - rehydration
    - bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema in pediatric patients (see Pediatrics, P32))
    - beware of a pseudohyponatremia due to hyperglycemia (add 3 Na^+ per 10 glucose over 5.5 mmol/L)
  - potassium
    - essential to avoid hypokalemia: replace KCl 20 mEq/L (only if patient is voiding, adequate renal function, and initial K^+ <5.5 mmol/L)
    - use cardiac monitoring if potassium levels normal or low

Wells' Criteria for DVT

Active cancer	+1
Paralysis, paresis or recent immobilization of leg	+1
Recently bedridden x3 d or major surgery within 4 wk	+1
Local tenderness	+1
Entire leg swollen	+1
Calf swelling 3 cm > asymptomatic leg	+1
Unilateral pitting edema	+1
Collateral superficial veins	+1
Alternative Dx more likely	-2

0: Low probability
1-2: Moderate probability
>3: High probability

Wells' Criteria for PE

Previous Hx of DVT/PE	+1.5
HR >100	+1.5
Recent immobility or surgery	+1.5
Clinical signs of DVT	+3
Alternate Dx less likely than PE	+3
Hemoptysis	+1
Cancer	+1

<2: Low probability
2-6: Intermediate probability
>6: High probability

Signs of PE on CXR
Westermark's sign: abrupt tapering of a vessel on chest film
Hampton's hump: a wedge-shaped infiltrate that abuts the pleura
Effusion, atelectasis, or infiltrates 50%
normal
Both signs are specific but not sensitive
A normal CXR in the hypoxic patient warrants a work-up for PE

PERC Score
- Age >50
- HR >100 bpm
- O_2 saturation on room air <95%
- Prior Hx of DVT/PE
- Recent trauma or surgery
- Hemoptysis
- Exogenous estrogen
- Clinical signs suggesting DVT

Score 1 for each question; a score 0/8 means the patient has <1.6% chance of having a PE and avoids further investigation. Caution against using the PERC score in patients with concurrent beta-blocker use, and in pregnant women as the original study excluded both.

D-dimer is only useful if it is negative; negative predictive value >99%

50% of patients with symptomatic proximal DVT will develop PE, often within days to weeks of the event

- insulin
  - critical, as this is the only way to inhibit gluconeogenesis/ketosis
  - do not give insulin if K^+<3.3 mmol/L as insulin will exacerbate hypokalemia
  - continuous infusion at 0.1 U/kg/h
  - once the blood glucose <14 mmol/L, dextrose should be added to the patient's IV fluids
- bicarbonate is not given unless patient is at risk of shock or death (typically pH <7.0)

Hyperosmolar Hyperglycemic State

- hyperosmolar hyperglycemic state (HHS) is characterized by extreme hyperglycemia (33.3 mmol/L) due to relative insulin deficiency, counter-regulatory hormones excess, gluconeogenesis, and dehydration (due to osmotic diuresis)
- clinical features
  - often older, T2DM patients with more comorbid illnesses and larger fluid losses with symptoms evolving over days to weeks, fewer GI symptoms and more neurological deficits than DKA including: mental disturbances, coma, delirium, seizures
  - polyuria, N/V
- investigations
  - blood work: CBC, electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, Cr, BUN, glucose, ketones, osmolality
  - urine: glucose and ketones
  - VBG
  - find underlying cause: ECG, CXR, blood and urine C&S
  - monitor pH (expected: pH >7.3) and bicarbonate (>18 mEq/L)
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O_2, cardiac monitoring, frequent electrolyte, and glucose monitoring
  - insulin management as per DKA
  - identify and treat precipitating factors, similar to DKA but HHS has also been noted following cardiac surgery and with the use of certain drugs (e.g. diuretics, glucocorticoids, lithium, atypical antipsychotics)
  - admission to medicine

Hypoglycemia

- characterized by Whipple's triad: low plasma glucose, symptoms suggestive of hypoglycemia, prompt resolution of symptoms when glucose administered
- clinical features
  - neuroglycopenic symptoms: headaches, confusion, seizures, loss of consciousness, coma
  - autonomic symptoms: diaphoresis, nausea, tremor, hunger, tachycardia, palpitations
- history and physical exam
  - last meal, known DM, prior similar episodes, drug therapy, and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
- management
  - check a bedside capillary blood glucose
  - oral sugar if possible (juice, sugar tablets)
  - IV access if oral route not possible
  - D50W 50 mL IV push
    - use lower concentration dextrose solutions in children (rule of 50's: 1 mL/kg of D50W, 2 mL/kg of D25W, 5 mL/kg of D10W, 10 mL/kg of D5W)
  - if IV access and oral replacement not possible, glucagon 1-2 mg IM, repeat in 10-20 min
  - O_2, cardiac, frequent blood glucose monitoring
  - thiamine 300 mg IM (if alcohol use disorder is suspected)
  - full meal as soon as mental status permits
  - if due to long-acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long half-life (may require admission for monitoring)
  - search for cause (common causes include exogenous insulin, alcohol, or sulfonylureas)



Oral Direct Thrombin Inhibitors or Oral Factor Xa Inhibitors for the Treatment of Pulmonary Embolism
Cochrane DB Syst Rev 2023:CD010957
Purpose: Assess effectiveness of oral direct thrombin inhibitors and oral factor Xa inhibitors for long-term treatment of PE as compared to conventional anticoagulants.
Methods: Systematic review of RCTs in patients with confirmed PE receiving oral direct thrombin inhibitors or factor Xa inhibitors for minimum 3 mo.
Results: Ten RCTs (n=13,073). No difference in the effectiveness of oral factor Xa inhibitors vs. standard anticoagulation in preventing recurrent PE (OR 0.95; 95% CI, 0.66-1.03), recurrent VTE (OR 0.83; 95% CI, 0.66-1.25), DVT (OR 0.77; 95% CI, 0.48-1.25), all-cause mortality (OR 1.16; 95% CI, 0.79-1.70), or major bleeding (OR 0.71; 95% CI, 0.36-1.41).
Conclusions: Moderate-low evidence suggests there is little to no difference between DOACs compared to conventional anticoagulation in the treatment of PE.



Criteria for DKA Dx
Hyperglycemia
Metabolic acidosis
Hyperketonemia or Ketonuria



Signs and Symptoms of DKA

Diuresis, dehydration, drowsy, delirium, dizziness
Kussmaul's breathing, ketotic breath
Abdominal pain, anorexia



Precipitating Factors in DKA

The 5 Is
Infection
Ischaemia
Infarction
Intoxication
Insulin missed



Causes of Hypoglycemia
Most common: excessive insulin use in setting of poor PO intake
Common: alcohol intoxication, sepsis, liver disease, oral anti-hyperglycemics
Rare: insulinomas, hypopituitarism, adrenal insufficiency, medication side effects



Cerebral edema may occur if hyperosmolality is treated too aggressively

Electrolyte Disturbances

- see Nephrology, NP8

Table 20. Electrolyte Disturbances

Electrolyte Disturbance	Common Causes	Symptoms	Tréatment	Special Considerations
Hypernatremia	Inadequate H_2O intake (elderly/disabled) or inappropriate excretion of H_2O (diuretics, Li, and diabetes insipidus)	Lethargy, weakness, irritability, and edema; seizures and coma occur with severe elevations of Na^+ levels (>158 mmol/L)	Salt restrict and give normal saline until hemodynamically stable. Use half-normal saline once vitals are stable	No more than 12 mmol/L in 24 h drop in Na^+ (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death
Hyponatremia	Hypovolemic (GI, renal, skin, blood fluid loss), euvolemic (syndrome of inappropriate antidiuretic hormone secretion (SIADH)/ stress, adrenal insufficiency, hypothyroid, diet/intake), hypervolemic (CHF, cirrhosis, nephrotic syndrome)	Neurologic symptoms secondary to cerebral edema, headache, seizure, decreased LOC, depressed reflexes; chronic milder than acute	Hypovolemic: normal saline Euvolemic: restrict water, eliminate underlying cause Hypervolemic: restrict fluid and sodium, loop diuretic if severe 3% hypertonic saline if seizure or coma	Limit total rise to 8 mmol/L in 24 h (0.25 mmol/L/h maximum) as patients are at risk of osmotic demyelinating syndrome (ODS)
Hyperkalemia	Rhabdomyolysis, insulin deficiency, metabolic acidosis (e.g. acute renal failure, missed dialysis), medications (e.g. K^+ sparing diuretics, ACEI, NSAIDs)	Nausea, palpitations, dysrhythmias, muscle stiffness, areflexia	Protect heart: calcium gluconate Shift K^+ into cells: D50W + insulin, $NaHCO_3$, salbutamol Remove K^+: fluids + furosemide, dialysis	High-risk of dysrhythmia - ECG: peaked/ narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, sine wave, AV block, VFib, bradycardia
Hypokalemia	Metabolic alkalosis (e.g. diarrhea), insulin, diuretics (except K^+ sparing), anorexia, salbutamol	N/V, fatigue, muscle cramps, constipation, dysrhythmias	K-Dur®, K^+ sparing diuretics, IV solutions with 20-40 mEq/L KCl over 3-4 h	ECG: U waves most important, flattened/ inverted T waves, prolonged QT, depressed ST May need to restore Mg^{2+}
Hypercalcemia	Hyperparathyroidism and malignancy account for ~90% of cases, medications (e.g. thiazide diuretics, lithium)	Multisystem including CVS, GI (groans), renal (stones), rheumatological, MSK (bones), psychiatric (moans)	Isotonic saline (+ furosemide if hypervolemic) Bisphosphonates, dialysis, chelation (Ethylenediaminetetraacetic acid (EDTA) or oral PO_4^{3-})	Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy
Hypocalcemia	Iatrogenic, hypoalbuminemia, liver dysfunction, primary hypo-parathyroid hormone, recent thyroid surgery	Laryngospasm, hyperreflexia, paresthesia, tetany, Chvostek's and Trousseau's sign	Acute (ionized Ca^{2+}<0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion	Prolonged QT interval can arise (leading to dysrhythmia as can upper airway obstruction)

Hypertensive Emergencies

Hypertensive Emergency (Hypertensive Crisis)

- definition: severe elevation of BP with evidence of end-organ damage (CNS, retinal, CVS, renal, GI)
- etiology
  - essential HTN, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy
- clinical features

Table 21. Signs and Symptoms of Hypertensive Emergencies

	CNS	Retinal	Renal	Cardiovascular	Gastrointestinal
Complication	Stroke/TIA, headache, altered mental status, seizures, hemorrhage	Vision change, hemorrhage, exudates, papilledema	Nocturia, elevated Cr, proteinuria, hematuria, oliguria	Ischaemia/angina, infarction, dissection (back pain), CHF	N/V, abdominal pain, elevated liver enzymes

- investigations
  - blood work: CBC, electrolytes, BUN, Cr
  - urinalysis
  - peripheral blood smear: to detect microangiopathic hemolytic anemia
  - CXR: if SOB or chest pain
  - ECG, troponins, creatine kinase (CK): if chest pain
  - CT head: if neurological findings or severe headache
    - toxicology screen if sympathomimetic overdose suspected (not needed if patient admits to taking it)
- management
  - in general, strategy is to gradually and progressively reduce BP in 24-48 h
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually labetalol)
  - if preeclampsia, immediately consult obstetrician-gynecologist (OB/GYN) (see Obstetrics, OB26) and give magnesium
  - establish arterial line; transfer to ICU for further reduction in BP under monitored setting
  - in case of ischaemic stroke: do not rapidly reduce BP, maintain BP >150/100 for 5 d
  - in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
  - in case of excessive catecholamines: avoid β-blockers (except labetalol)
  - in case of ACS: address ischaemia initially, then BP



HELLP Syndrome (seen only in preeclampsia/eclampsia)

Hemolytic anemia
Elevated Liver enzymes
Low Platelet count



Catecholamine-Induced Hypertensive Emergencies
Avoid use of non-selective β-blockers as they inhibit β-mediated vasodilation and leave α-adrenergic vasoconstriction unopposed

Hypertensive Urgency (Severe Asymptomatic Hypertension)

- elevated BP (sBP > 180, dPB > 120), but no evidence of end organ injury
- most will have a mild headache, non-specific vision changes, and/or nausea
- search carefully for end organ injury; measure BP properly (measure in a quiet room and bilaterally)
- modify or initiate anti-hypertensives and follow up with primary care team
- no proven benefit from rapid reduction of blood pressure (rapid reduction can lead to MI, AKI, and/or CVA)

Table 22. Commonly Used Agents for the Treatment of Hypertensive Crisis

Drug	Dosage	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
VASODILATORS					
Sodium Nitroprusside (vascular smooth muscle dilator)	0.25-10 µg/kg/min	Immediate	3-5 min	N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome	Use in combination with β-blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia
Nicardipine (calcium channel blocker)	5 mg/h IV, then increase by 2.5 mg/h q5-10 min (max 15 mg/h)	15-30 min	40 min	Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, renal failure, eclampsia, sympathetic crisis)	Most hypertensive emergencies (note: IV form not available in Canada; oral form does not have a reliable response for acute settings) Caution with acute CHF
Nitroglycerin	5-20 µg/min IV	1-2 min	3-5 min	Hypotension, bradycardia, headache, lightheadedness, dizziness	MI, pulmonary edema
Hydralazine	5-10 mg IV/IM q20 min (max 20 mg)	5-20 min	2-6 h	Dizziness, drowsiness, headache, tachycardia, Na^+ retention	Eclampsia
ADRENERGIC INHIBITORS					
Labetalol	20 mg IV bolus q10 min or 0.5-2 mg/min	5-10 min	3-6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Usually first choice Most hypertensive emergencies (especially eclampsia) Avoid in acute CHF, heart block >1st degree
Esmolol	250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat	1-2 min	10-20 min	Hypotension, nausea, bronchospasm	Aortic dissection, acute MI supraventricular tachycardia (SVT) dysrhythmias, perioperative HTN Avoid in acute CHF, heart block >1st degree
Phentolamine	5-15 mg q5-15 min	1-2 min	3-10 min	Tachycardia, headache, flushing	Catecholamine excess (e.g. pheochromocytoma, unopposed α - e.g. cocaine)

*Hypotension may occur when using any of these agents



With CNS manifestations of severe HTN, it is often difficult to differentiate causal relationships (i.e. HTN could be secondary to a cerebral event with an associated Cushing reflex)

Acute Coronary Syndrome

- see Cardiology and Cardiac Surgery, C36
- definition: new onset of chest pain, or acute worsening of previous chest pain, or chest pain at rest with:
  - negative cardiac biomarkers and no ECG changes = unstable angina (UA)
  - positive cardiac biomarkers (elevated troponin), NSTEMI on ECG, ± other changes (NSTEMI)
  - positive cardiac biomarkers (elevated troponin) and STEMI on ECG
- occlusion myocardial infarction: new paradigm, supports ECG findings suggesting acute coronary artery occlusion without a ST elevation on ECG; examples include Wellens Syndrome, De Winter T waves and hyperacute T waves
- investigations
  - ECG STAT (as soon as history suggests possible ACS), serial troponins (2-6 h after symptom onset), CXR (to rule out other causes of the patient's presentation)
  - serial ECGs improve sensitivity; consider in patients who have pain highlight suggestive of ACS
- management
  - stabilize: ABCs, oxygen, IV access, cardiac monitors, oximetry
  - ASA 162-325 mg chewed and swallowed
  - nitroglycerin 0.3 mg SL q5 min x 3; IV only if persistent pain, CHF, or hypertensive
    - contraindications: hypotension, phosphodiesterase inhibitor use, right ventricular infarctions (1/3 of all inferior MIs, as these MIs are preload-dependent)
    - symptom relief only, no mortality benefit
  - anticoagulation: choice of anticoagulation (unfractionated heparin, LMWH, or fondaparinux) and additional antiplatelet therapy (clopidogrel, ticagrelor, or prasugrel) depends on STEMI vs. NSTEMI and reperfusion strategy
  - early cardiology consult for reperfusion therapy
    - UA/NSTEMI: early coronary angiography recommended if high thrombolysis in MI (TIMI) risk score
    - STEMI: primary percutaneous coronary intervention (PCI) (within 90 min) preferred; thrombolytics if PCI unavailable within 120 min of medical contact, symptoms <12 h and no contraindications

Sepsis

- see Infectious Diseases, ID20 and Respirology, R32
- definitions
  - overall, sepsis can be thought of as a life-threatening organ dysfunction caused by a dysregulated host response to infection; however, definitions exist on a spectrum, as outlined below
  - systemic inflammatory response syndrome (SIRS): two or more of T >38°C or <36°C, HR >90, RR >20, WBC >12
  - sepsis: SIRS and suspected or present source of infection
  - septic shock: sepsis and either initial lactate >4 or hypotension
  - qSOFA score ≥2: high risk for in-hospital mortality (see Infectious Diseases, ID20)
  - although the presence of a positive qSOFA should alert clinicians to the possibility of sepsis in all resource settings, it should not be used as a single screening tool given its poor sensitivity.
- management
  - early recognition of sepsis and investigations to locate source of infection
  - identify severe sepsis with lactate or evidence of tissue hypoperfusion (evaluate tissue perfusion at bedside with cap refill, mental status, or urine output)
  - sepsis standard operating procedures, initially specified as Early Goal Directed Therapy have evolved to "usual care" which includes a standard approach with components of the sepsis bundle, early identification, lactate, cultures, antibiotics, and fluids
  - treatment priorities:
    - ABCs, monitors, lines
    - aggressive fluid resuscitation; consider ventilatory and early inotropic support
    - cultures, then early empiric appropriate antibiotics - consider broad spectrum and atypical coverage
    - source control (e.g. remove infected Foley or surgery for ischaemic gut)
    - monitor adequate resuscitation with vital signs, inferior vena cava on U/S (if patient is mechanically ventilated), urine output, and serial measurement of serum lactate
    - in patients presenting with septic shock, goal-directed therapy and aggressive management should not be delayed while waiting for lab values
    - patients failing initial therapy should be resuscitated more aggressively (e.g. use of vasopressors, inotropic therapy, blood transfusion)
      - consider glucocorticoids if treatment refractory hypotension for relative adrenal insufficiency
      - look for other causes of shock if not responding to treatment (use protocols, such as PoCUS RUSH, to assess for free fluid, ectopic pregnancy, pneumothorax, AAA, tamponade)

Surviving Sepsis Campaign 1 Hour Bundle
J Intensive Care Med 2018;44:925-928
Update sepsis bundle from 3 h to 1 h time frame with time zero being time of triage in the ED
Actions include:
- Measure lactate level. Remeasure if initial lactate is >2 mmol/L
- Obtain blood cultures prior to administration of antibiotics
- Administer broad spectrum antibiotics
- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate >4 mmol/L
- Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP >65 mmHg

Stroke and Transient Ischaemic Attack

- see Neurology, N51
- definitions
  - stroke: sudden loss of brain function due to ischaemia (87%) or hemorrhage (13%) with persistence of symptoms >24 h or neuroimaging evidence
  - TIA: transient episode of neurologic dysfunction from focal ischaemia without acute infarction or neuroimaging evidence
- clinical features

Table 23. Signs and Symptoms of Stroke

	General	Language/ Throat	Vision	Coordination	Motor	Sensation	Reflex
Signs/ Symptoms	Decreased LOC (rare), changed mental status, confusion, neglect	Dysarthria, aphasia, swallowing difficulty	Diplopia, eye deviation, asymmetric pupils, visual field defect	Ataxia, intention tremor, lack of coordination	Increased tone, loss of power, spasticity	Loss of sensation	Hyper-reflexia, clonus

- patients with hemorrhagic stroke resulting in subarachnoid hemorrhage can present with sudden onset thunderclap headache that is usually described as "worst headache of life" and can often recall the exact moment their headache started
- stroke mimickers: seizure, Todd's paresis (period of partial or complete paralysis following a seizure), migraine, hypoglycemia, peripheral nerve injury, Bell's palsy, tumour, syncope, somatic symptom disorder

Table 24. Stroke Syndromes

Region of Stroke	Stroke Syndrome
Anterior Cerebral Artery	Contralateral hemianesthesia and hemiparesis (legs > arms/face), gait apraxia, altered mental status, impaired judgement
Middle Cerebral Artery	Contralateral hemianesthesia and hemiparesis (arms/face > legs), contralateral homonymous hemianopsia, ipsilateral gaze
Posterior Cerebral Artery	Contralateral homonymous hemianopsia, cortical blindness, impaired memory
Vertebrobasilar Artery	Wide variety of cranial nerve, cerebellar, and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoesthesia, syncope, ataxia Loss of pain and temperature sensation in ipsilateral face and contralateral body

Seven Causes of Emboli from the Heart
- AFib
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves

Differentiation of Upper Motor Neuron (UMN) Disease vs. Lower Motor Neuron (LMN) Disease

Category	UMN Disease	LMN Disease
Muscular deficit	Muscle groups	Individual muscles
Reflexes	Increased	Decreased/ absent
Tone	Increased	Decreased
Fasciculations	Absent	Present
Atrophy	Absent/ minimal	Present
Plantar Response	Upgoing	Downgoing

Investigations
- CBC, electrolytes, blood glucose, coagulation studies ± cardiac biomarkers ± toxicology screen
- CT angiography and perfusion of the head and neck
- ECG: rule out AFib, acute MI as source of emboli
- other imaging: if you are suspicious of a TIA a plain CT followed by carotid Doppler, outpatient CT angiography neck and/or head, magnetic resonance angiography (MRA) can be arranged based on local resources

Management
- ABCs; intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protective reflexes
- for ischaemic CVA thrombolysis (rt-PA, e.g. alteplase): immediate assessment for eligibility; need acute onset, <4.5 h from last seen normal AND compatible physical findings AND no evidence of hemorrhage on CT scan
  - thrombectomy: may be an option in some centres as an alternative to thrombolysis in the first 4.5 to 6 h, and in some instances up to 24 h after symptom onset or last seen normal
- dual antiplatelet therapy for 21 d
  - this should be initiated for high risk TIA in the ED
- elevating head of bed if suspicious of increased ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
  - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischaemic penumbra)
- BP control: only treat severe HTN (sBP >200 mmHg, dBP >120 mmHg, MAP >140 mmHg) or HTN associated with hemorrhagic stroke transformation, cardiac ischaemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
- glycemic control serum glucose of 7.8-10 mmol/L
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology, medicine as indicated
- following acute ischaemic event:
  - antiplatelet agents to: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st line); clopidogrel, Aggrenox® (2nd line)
  - consider anticoagulation: if Afib present or if immobile for DVT prophylaxis
  - follow-up for consideration of carotid endarterectomy, cardiovascular risk optimization



If a patient presents within 4.5 h of onset of disabling neurological deficits >60 min with no signs of resolution, they may be a candidate for thrombolysis. Do brief assessment and order CT head STAT

Use the NIH Stroke Scale/Score (NIHSS) to assess stroke severity in an acute setting and predict clinical outcomes.

Absolute Exclusion Criteria for Tissue Plasminogen Activator (tPA)
- Suspected subarachnoid hemorrhage
- Previous intracranial hemorrhage
- Cerebral infarct or severe HI within the past 3 mo
- sBP >185 mmHg, or dBP >110 mmHg
- Bleeding diathesis
- Prolonged PT >15 s or INR >1.7
- Platelet count <100000
- Heparin received within last 48 h
- Current use of thrombin inhibitors or direct factor Xa inhibitors
- Blood glucose <2.8 mmol/L (<50 mg/dL)
- Intracranial hemorrhage on CT or large volume infarct

Relative Exclusion Criteria for tPA
- Only minor or rapidly improving symptoms
- Pregnancy
- GI or urinary hemorrhage within the past 21 d
- Seizure at onset causing postictal impairments

Otolaryngological Presentations and Emergencies

- ear symptoms: otalgia, aural fullness, otorrhea, hearing loss, tinnitus, vertigo, pruritus, fever
- risk factors for hearing loss: Q-tip use, hearing aids, headphones, occupational noise exposure

Dizziness and Vertigo
- distinguish four types of dizziness: vertigo ("room spinning"), lightheadedness ("disconnected from environment"), presyncope ("almost blacking out"), dysequilibrium ("unstable," "off-balance")
- broad differential and diverse management (see Family Medicine, FM28 and Otolaryngology, OT6)
- rule out stroke
- consider adverse drug events

Otalgia (see Otolaryngology, OT6)
- differential diagnosis
  - infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis externa in patients with diabetes, herpes simplex/zoster, auricular cellulitis, external canal abscess, dental disease, referred pain from neck and/or jaw
  - others: trauma, temporomandibular joint dysfunction, neoplasm, foreign body, cerumen impactions, trigeminal neuralgia, granulomatosis with polyangiitis
- inspect for otorrhea, palpate outer ear/mastoid, otoscopic examination to look for bulging erythematous tympanic membrane, perforation, membrane retraction, infiltration, vesicles, ulcers, masses, lesions
- C&S of ear canal discharge, if present
- CT head if suspicion of mastoiditis, malignant otitis externa
- antibiotics/antifungals/antivirals for respective infections

Hearing Loss (see Otolaryngology, OT7)
- differentiate conductive vs. sensorineural hearing loss
- rule out sudden sensorineural hearing loss (SSNHL), a medical emergency requiring high dose steroids and urgent referral
- an elderly patient presenting with unilateral tinnitus or SSNHL must be presumed to have an acoustic neuroma (vestibular schwannoma) until proven otherwise
- consider audiogram and referral to or follow-up with family physician

Epistaxis

- see Otolaryngology, OT27
- 90% of nosebleeds stem from the anterior nasal septum (Kiesselbach's plexus located in Little's area)
- can be life-threatening

Etiology
- most cases of epistaxis are caused by trauma (e.g. digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (e.g. cocaine, Otrivin®), or systemic disease (e.g. coagulopathies, HTN)

Investigations
- blood work: CBC, PT/PTT/INR/platelet function assay (if suspicious of bleeding disorder) as needed
- imaging: x-ray, CT as needed (e.g. trauma)

Treatment
- goals of treatment: localize bleeding and achieve haemostasis
- first-aid: ABCs, clear clots by blowing nose or suctioning, lean forward, pinch cartilaginous portion of nose for 20 min twice (note: best to use a compression device and not the patient's fingers)
- assess blood loss: vitals; if severe bleeding or unstable patient IV NS, cross match 2 units pRBC
- if first aid measures fail twice, proceed to packing
- apply an anterior pack
  - clear nose of any clots
  - apply topical anesthesia/vasoconstrictors (lidocaine with epinephrine, cocaine, or soaked pledgets)
  - insert either a traditional Vaseline® gauze pack or a commercial nasal tampon or balloon
  - N.B. if the site of bleeding is identified, cautery with silver nitrate can be performed as an alternative to packing (only cauterize one side of the septum because if both are cauterized this can lead to septal perforation)
  - if bleeding stops, arrange follow-up in 48-72 h for reassessment and pack removal
  - if packing both nares, prophylactic anti-staphylococcal antibiotics to prevent sinusitis or TSS
- if suspect posterior bleed or anterior packing does not provide haemostasis, consult ENT for posterior packing and further evaluation
  - though posterior packing may be placed by an ED physician, it requires monitoring; can cause significant vagal response and posterior bleeding source can lead to significant blood loss, therefore usually requires admission

Disposition
- discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. topical vaseline, humidifiers, saline spray, avoiding irritants, managing HTN)
- admission: severe cases of refractory bleeding, and most cases of posterior packing

Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

Complications of Nasal Packing
- Hypoxemia
- TSS
- Aspiration
- Pharyngeal fibrosis/stenosis
- Alar/septal necrosis

Tranexamic Acid For Patients with Nasal Haemorrhage (Epistaxis)
Cochrane DB Syst Rev 2018:CD004328
Purpose: Determine the effects of tranexamic acid compared to placebo, no additional intervention or any other haemostatic agent in the management of patients with epistaxis.
Methods: Systematic review of RCTs comparing tranexamic acid, in addition to standard care, compared to usual care plus placebo in adults and children.
Results: 6 RCTs, 692 participants. Oral (RR 0.73, 95% CI 0.55-0.96) and topical (RR 0.66, 95% CI 0.41-1.05) reduced risk of re-bleeding compared to placebo. There was no difference in time to stop initial bleeding. The proportion of patients whose bleeding stopped within 10 min was higher with topical tranexamic acid than other haemostatic agents (RR 2.35, 95% CI 1.90-2.92).
Conclusions: Moderate-quality evidence that risk of re-bleeding with oral or topical tranexamic acid, in addition to usual care, is lower in adult patients with epistaxis, compared to placebo with usual care. Further, topical tranexamic acid is probably better than other topical agents in stopping bleeding in the first 10 min.

Gynecologic/Urologic Emergencies

Vaginal Bleeding

- see Gynecology, GY20 and Obstetrics, OB14

Etiology
- pregnant patient (note: unless proven otherwise, all female patients of possible childbearing age should be assumed to be pregnant and to have an ectopic pregnancy)
  - 1st/2nd trimester: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause), subchorionic hemorrhage
  - 2nd/3rd trimester: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  - other: trauma, bleeding cervical polyp, passing of mucous plug, incompetent cervix, cervicitis, endometritis
- postpartum
  - causes of postpartum hemorrhage (Four T's): tone (uterine atony), tissue (retained placenta), trauma (laceration, uterine inversion), and thrombin (coagulopathy)
- non-pregnant patients
  - structural (PALM- polyps, adenomyosis, leiomyoma, malignancies/hyperplasia)
  - non-structural (COEIN - coagulopathy, ovulatory, endometrial, iatrogenic, not yet diagnosed)

History
- characterize bleeding (frequency, duration, number of pads/tampons, types of pads used, cyclicity)
- pain, if present (OPQRSTUV)
- menstrual history, sexual history, STI history, syncope/presyncope, malignancy history, family history, hematological history, cardiac history, abdominal history, history of previous ectopic pregnancy, smoking history, IUD or OCP use
- details of pregnancy, including gush of fluid and fetal movement (>20 wk)

Physical Exam
- ABCs (especially noting postural BP/HR)
- abdominal examination (signs of peritoneal pathology, tenderness, distension, mass)
- speculum examination (NOT if 2nd/3rd trimester bleeding as may worsen bleeding; perform only if placenta previa has been ruled out with U/S)
  - look for active bleeding, trauma/anomaly, and cervical dilatation
  - in 1st trimester, removing a clot at cervical os can help slow bleeding
  - a dilated os is highly suggestive of incomplete abortion
- bimanual examination (NOT if 2nd/3rd trimester bleeding as may worsen bleeding; perform only if placenta previa has been ruled out with U/S)
  - cervical motion tenderness, size of uterus, cervical length/dilatation
- sterile gloves and speculum if pregnant and beyond the first trimester
- POCUS: rule in intra-uterine pregnancy, check for free fluid in pelvis/right upper quadrant (RUQ)/left upper quadrant (LUQ), consider assessment of fluid responsiveness (intra-hepatic IVC collapsibility, carotid flow measurement)



Vaginal bleeding can be life-threatening. Always start with ABCs and ensure your patient is stable



An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using *in vitro* fertilization (IVF) due to the associated high-risk of heterotopic pregnancy



Vaginal bleeding (and its underlying causes) can be a very distressing event for patients; ensure appropriate support is provided

Investigations
- β-hCG test for all patients with childbearing potential
- CBC, blood and Rh type, quantitative β-hCG, PTT, INR
- type & cross if significant blood loss
- transvaginal U/S (rule out ectopic pregnancy and spontaneous abortion)
- abdominal U/S (rule out placenta previa, fetal demise, or retained products postpartum)

Management
- ABCs
- cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or β-hCG >1000-2000 IU: further workup and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, consult gynecology
- 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type & cross 4 units of blood, consult OB/GYN immediately
  - uterine atony: oxytocin 10 units IM or 40 units in 1L wide open until the uterus is firm, then 200 cc/hr
  - genital tract trauma: visual inspection and repair
  - retained products of conception: bimanual or speculum
  - coagulopathy: TXA may be helpful
  - tamponade: use Bakri tube or foley catheter to tamponade, if other measures not successful
- non-pregnant
  - if unstable admit to gynecology for IV hormonal therapy, possible dilation and curettage
  - non-structural abnormalities
    - tranexamic acid to stabilize clots
    - medroxyprogesterone acetate 10 mg PO once daily x10 d, warn patient of a withdrawal bleed
  - stable structural abnormalities (fibroids, polyps, endometrial thickening, adenomyosis), outpatient gynecology referral once stable

Disposition
- decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult OB/GYN for patients requiring admission
- if patient can be safely discharged, ensure follow-up with family physician or OB/GYN
- instruct patient to return to ED for increased bleeding or presyncope

Pregnant Patient in the ED

Table 25. Complications of Pregnancy

Trimester	Fetal	Maternal
First 1-12 wk	Pregnancy failure Spontaneous abortion Fetal demise Gestational trophoblastic disease	Ectopic pregnancy Anemia Hyperemesis gravidarum UTI/pyelonephritis
Second 13-27 wk	Disorders of fetal growth Intrauterine growth restriction Oligo/polyhydramnios	Gestational DM Rh incompatibility UTI/pyelonephritis Cervical incompetence
Third 28-41 wk	Vasa previa	Preterm labour/preterm premature rupture of the membranes Preeclampsia (hypertension in pregnancy)/eclampsia Placenta previa Placental abruption Uterine rupture DVT/PE

Nephrolithiasis (Renal Colic)

• see Urology, U19

Epidemiology and Risk Factors
•10% of population (twice as common in males)
•recurrence 50% at 5 yr
•peak incidence 30-50 yr
•75% of stones <4 mm pass spontaneously within 2 wk, larger stones may require consultation

Kidney Stones
80% calcium oxalate
10% struvite
10% uric acid

Clinical Features
•urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
•may complain of pain at flank, groin, testes, or tip of penis
•writhing, N/V, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
•occasionally symptoms of trigonal irritation (frequency, urgency)
•fever, chills, rigors in secondary pyelonephritis
•peritoneal findings/anterior abdominal tenderness usually absent (if present, consider renal pelvis rupture or other cause)

Obstruction + Infection
= Urological Emergency
Urgent urology consult + IV fluids + broad spectrum antibiotics

Differential Diagnosis of Renal Colic
•acute ureteric obstruction
•acute abdomen: biliary, bowel, pancreas, AAA, diverticulitis
•urogynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, testicular torsion
•pyelonephritis (fever, chills, pyuria, vomiting)
•radiculitis (L1): herpes zoster, nerve root compression

Investigations
•CBC: elevated WBC in presence of fever may support an infectious cause
•electrolytes, Cr, BUN to assess renal function
•U/A: routine and microscopy (WBCs, RBCs, crystals), C&S
•non-contrast CT is the study of choice (better specificity and sensitivity)
•consider abdominal U/S in females of childbearing age, children, or if patient has another contraindication to CT scanning: may demonstrate stone(s), hydronephrosis, debris in the collecting system, reduced cortical vascularity, abnormal renal parenchyma
•AXR will identify large radiopaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones, or stones overlying bony structures; consider as an initial investigation in patients who have a history of radiopaque stones and similar episodes of acute flank pain, carry out with U/S (CT necessary if film is negative).

Indications for Admission to Hospital
- Intractable pain
- Fever (suggests infection) or other evidence of pyelonephritis
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function

Management
•analgesics: NSAIDs (usually ketorolac (Toradol®), preferable over opioids), antiemetics, IV fluids if indicated
•urology consult indicated, especially if stone >5 mm, or if patient has signs of obstruction leading to renal dysfunction or infection
•α-blocker (e.g. tamsulosin) may be helpful to increase stone passage in select cases

Disposition
•most patients can be discharged
•ensure patient is stable, has adequate analgesia, and able to tolerate oral medications
•may advise hydration and limitation of protein, sodium, oxalate, and alcohol intake

Ophthalmologic Emergencies

• see Ophthalmology, OP5

History and Physical Exam
• patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
• mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital x-rays, U/S, or CT scan to exclude presence of intraocular metallic foreign body
• ask about sexual partners and exposure of eye(s) to bodily fluids (semen, urine, blood, vaginal fluids, saliva, etc.)
• visual acuity in both eyes, pupils, extraocular structures, extraocular movements, fundoscopy, tonometry, slit lamp exam, visual fields

Contraindications to Pupil Dilation
- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia

Management of Ophthalmologic Foreign Body
• for a chemical injury: copious irrigation with saline for any foreign body
• remove foreign body under slit lamp exam with cotton swab, sterile needle, or electric burr tool
• antibiotic drops if indicated (e.g. organic foreign body)
• patching may not improve healing or comfort – do not patch contact lens wearers
• limit use of topical anesthetic to examination only

- tetanus prophylaxis
- ophthalmology should see in follow-up or ED consult if globe penetration suspected

Table 26. Differential Diagnosis of Red Eye in the Emergency Department

Symptom	Possible Serious Etiology
Light Sensitivity	Iritis, keratitis, abrasion, ulcer
Unilateral	Above + herpes simplex, acute angle closure glaucoma
Significant Pain	Above + scleritis
White Spot on Cornea	Corneal ulcer
Non-Reactive Pupil	Acute glaucoma, iritis
Copious Discharge	Gonococcal conjunctivitis
Blurred Vision	All of the above

Table 27. Select Ophthalmologic Emergencies

Condition	Signs and Symptoms	Management
Acute Angle Closure Glaucoma	Unilateral red, painful eye Decreased visual acuity, halos around lights Fixed, mid-dilated pupil N/V Marked increase in intraocular pressure (IOP) (>40 mmHg) Shallow anterior chamber ± cells	Ophthalmology consult for laser iridotomy Medications: AABCDE/EAT PAL α-agonist: epinephrine α2-agonist: apraclonidine β-blocker: timolol Cholinomimetic: pilocarpine Diuretic: acetazolamide, mannitol Eicosanoid: latanoprost
Corneal Abrasion	Pain, redness, tearing, photophobia, foreign body sensation De-epithelialized area stains with fluorescein dye	Most clear spontaneously within 24-48 h If due to foreign body, remove under magnification using local anesthetic and sterile needle, or consult ophthalmology for removal under magnification Topical antibiotic (drops or ointment)
Chemical Burn	Known exposure to acids or alkali (worse) Pain, decreased visual acuity Vascularization or defects of cornea Iris and lens damage	Irrigate site of accident with NS with eyelid retracted until neutral pH achieved Sweep fornices Cycloplegic drops and topical antibiotics
Orbital Cellulitis	Red, painful eye, decreased visual acuity Headache, fever Lid erythema, edema, and difficulty opening eye Conjunctival injection and chemosis Proptosis, opthalmoplegia ± RAPD	Admission, ophthalmology consult Blood cultures, orbital CT IV antibiotics (ceftriaxone + vancomycin) Drainage of abscess
Retinal Artery Occlusion	Sudden, painless, monocular vision loss RAPD Cherry red spot and retinal pallor on fundoscopy if central retinal artery occlusion	Restore blood flow <2 h Massage globe Decrease IOP (topical β-blockers, inhaled O_2/CO_2 mix, IV Diamox®, IV mannitol, drain aqueous fluid)
Retinal Vein Occlusion	Painless, monocular, gradual, or sudden vision loss ±RAPD On fundoscopy: "blood and thunder" appearance, diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema	Ophthalmology consult for retinal laser photocoagulation, anti-VEGF, and/or corticosteroid injection
Retinal Detachment	Flashes of light, floaters, and curtains of blackness/peripheral vision loss Painless Loss of red reflex, decreased IOP Detached areas are grey Visible detachment orbital POCUS ± RAPD	Ophthalmology consult for scleral buckle/pneumatic retinopexy

Other Ophthalmologic Emergencies
Infectious: Red eye, endophthalmitis, hypopyon
Trauma: Globe rupture, orbital blow-out fractures, corneal injuries, eyelid laceration, hyphema, lens dislocation, retrobulbar hemorrhage
Painful vision loss: Acute iritis, corneal abrasion, globe rupture, lens dislocation, retrobulbar hemorrhage, optic neuritis, temporal arteritis, endophthalmitis, keratitis
Painless vision loss: Central retinal vein occlusion, amaurosis fugax, occipital stroke

POCUS for the Diagnosis of Retinal Detachment: A Systematic Review and Meta-Analysis
Acad Emerg Med 2019;26:931-939
Purpose: POCUS has been suggested to identify retinal detachment rapidly. The primary outcome for this review was to determine the test characteristics of POCUS for the diagnosis of retinal detachment.
Methods: Systematic review and meta-analysis looking for all prospective trials and RCTs assessing the accuracy of POCUS for identifying retinal detachment.
Results: 11 studies (n = 844) were identified. Overall, ultrasound was 94.2% (95% CI 78.4% to 98.6%) sensitive and 96.3% (95% CI 89.2% to 98.8%) specific for the diagnosis of retinal detachment with a positive likelihood ratio of 25.2 (95% CI 8.1 to 78.0) and a negative likelihood ratio of 0.06 (95% CI = 0.01 to 0.25).
Conclusions: POCUS is sensitive and specific for the diagnosis of retinal detachment.

Visual acuity is the "vital sign" of the eyes and should ALWAYS be assessed and documented in both eyes when a patient presents to the ED with an ophthalmologic complaint

Dilating pupils for examination

1st drop	2nd drop	Notes
cyclopentolate 1%	phenylephrine 2.5%	can add 2nd trop of phenylephrine if not adequare diation
tropcamide 1%	phenylephrine 2.5%	

Dermatologic Emergencies

Rash Characteristics

A. Diffuse Rashes

- Staphylococcal Scalded Skin Syndrome (SSSS)
  - caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
  - mostly occurs in children
  - prodrome: fever, irritability, malaise, and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
- Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
  - see Dermatology, D26
  - caused by drugs (e.g. phenytoin, sulfas, penicillins, and NSAIDs), bone marrow transplantation, and blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
  - see Dermatology, D25
  - presents 1-6 weeks after first exposure to drug; persists wk after withdrawal of drug
  - morbilliform rash involving face, trunk, arms
  - systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- Toxic Shock Syndrome (TSS)
  - see Infectious Diseases, ID22
  - caused by superantigen from *S. aureus* or Group A *Streptococcus* (GAS) activating T-cells and cytokines
  - patient often presents with onset of shock and multi-organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, and skin (necrotizing fasciitis, gangrene)
  - vesiculobullous lesions
- Erythema Multiforme (EM)
  - commonly caused by herpes simplex; less common: *Mycoplasma pneumoniae*, drug-induced
  - viral prodrome 1-14 d before rash
  - target lesion: central grey bulla or wheal surrounded by concentric rings of erythema and normal skin
  - if mucous membrane involvement, then may have difficulty with oral intake

B. Discrete Lesions

- Pyoderma Gangrenosum
  - unclear pathogenesis: may be due to neutrophil dysfunction, genetic predisposition, or immune dysregulation
  - often associated with IBD, rheumatoid conditions, leukemia, and monoclonal gammopathies
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule/vesicle/pustule/bulla on red/blue base sloughing, leaving a gangrenous ulcer
- Disseminated Gonococcal Infection (DGI)
  - see Dermatology, D38
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), and septic arthritis (in larger joints, such as knees, ankles, and elbows)
  - most commonly in gonococcus-positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- Meningococcemia
  - Gram-negative bacterium *Neisseria meningitidis* causes flu-like symptoms of headache, myalgia, N/V
  - petechial, macular, or maculopapular lesions with grey vesicular centres
  - usually a few millimeters in size, but may become confluent and hemorrhagic
  - usually appear in extremities, but may appear anywhere
  - look for signs of meningeal irritation: positive jolt accentuation test, Brudzinski, Kernig

History and Physical Exam

- determine onset, course, and location of skin lesions
- fever, joint pain
- associated symptoms: CNS, respiratory, GU, GI, renal, liver, mucous membranes
- medications, sexual encounters, living environment, occupational exposures
- vitals, physical exam based on relevant history

Investigations

- case-dependent, consider: CBC, electrolytes, Cr, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)



Thorough dermatologic examinations are required; examination of asymptomatic skin may identify more lesions; ensure adequate draping during dermatologic examinations

Management

- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevent infection
- if patient unstable, immediately consult for admission: dermatology, or infectious diseases, allergy/immunology, plastic surgery
- specific management is determined by etiology
  - SSSS, TSS, DGI, and meningococcemia
    - IV antibiotics
  - EM, SJS, TEN, and DRESS syndrome
    - stop precipitating medication
    - fluids
    - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IV immunoglobulin (IVIG), plasmapheresis
    - TEN: debride necrotic tissue
    - EM: treat underlying cause, provide supportive care, and manage symptoms; may need admission for hydration, diffuse lesions, or ocular involvement



SJS = <10% of BSA
SJS/TEN = 10-30% BSA
TEN = >30% BSA

Disposition

- most cases will require urgent care and hospitalization
- SJS & TEN: early transfer to burn centre improves outcome

For an approach to describing a rash and common skin lesions that are seen in the emergency department, refer to Dermatology

Environmental Injuries

Heat Exhaustion and Heat Stroke

HEAT EXHAUSTION

- clinical features relate to loss of circulating volume caused by exposure to heat stress
- "water depletion": heat exhaustion occurs if lost fluid not adequately replaced
- "salt depletion": heat exhaustion occurs when losses replaced with hypotonic fluid

Heat exhaustion may closely resemble heat stroke; heat exhaustion may eventually progress to heat stroke, so if diagnosis is uncertain treat as heat stroke

HEAT STROKE

- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, infections), adverse drug events (including drug interactions)

Table 28. Heat Exhaustion vs. Heat Stroke

	Heat Exhaustion	Classical Heat Stroke	Exertional Heat Stroke
Clinical Features	Non-specific malaise, nausea, headache, fatigue Body temperature <40.5°C (usually normal) No coma or seizures Dehydration (HR, orthostatic hypotension)	Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation) Often patients are older and sedentary or immobile Dry, hot skin Temp usually >40.5°C Altered mental status, seizures, delirium, or coma May have elevated AST, ALT	Occurs with high endogenous heat production (e.g. exercise) that overwhelms homeostatic mechanisms Patients often younger, more active Skin often diaphoretic Other features as for classical heat stroke, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis
Treatment	Rest in a cool environment IV NS if orthostatic hypotension; otherwise replace losses slowly PO with salt and electrolyte solutions	Cool body temperature with water mist (e.g. spray bottle) and standing fans Ice water immersion also effective; monitor body temperature closely using rectal thermometer to avoid hypothermic overshoot Secure airway because of seizure and aspiration risk Give fluid resuscitation if still hypotensive after above therapy Avoid β-agonists (e.g. epinephrine), peripheral vasoconstriction, and antipyretics (e.g. ASA)	

Hypothermia and Cold Injuries

HYPOTHERMIA

- hypothermia is defined as a core temperature below 35°C, in which the body's heat loss is greater than heat production
- etiology: increased heat loss (e.g. environmental exposure), decreased heat production (e.g. endocrine disease), impaired regulation (e.g. CNS failure)
- predisposing risk factors: ethanol use, homelessness, psychiatric disease, and older age (older adults have increased risk due to decreased physiological reserve, chronic diseases, medication side effects, and social isolation)
- treatment based on re-warming and supporting cardiorespiratory function
- complications: coagulopathy, acidosis, dysrhythmias (AFib, VFib, profound bradycardia, asystole), and volume/electrolyte depletion
- labs: CBC, electrolytes, VBG, serum glucose, Cr/BUN, Mg^{2+}, Ca^{2+}, amylase, coagulation profile, troponin, lactate ± β-hCG
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, initial rectal thermometer followed by transesophageal temperature probe for ongoing monitoring, Foley catheter, NG tube, monitor metabolic status frequently

Table 29. Classification of Hypothermia

Class	Temp	Symptoms/Signs
Mild	32-34.9°C	Tachypnea, tachycardia, ataxia, dysarthria, shivering
Moderate	28-31.9°C	Loss of shivering, dysrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behaviour, muscle rigidity, dilated pupils
Severe	<28°C	Unresponsive, hypotension, acidemia, VFib, AFib, asystole, flaccidity, apnea

Re-warming Options

- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- passive external re-warming
  - suitable for most stable patients with core temperature >32.2°C
  - remove all wet clothes, then cover patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
- active external re-warming
  - involves use of warming blankets
  - beware of "afterdrop" phenomenon
  - safer when done in conjunction with active core re-warming

Afterdrop Phenomenon
Warming of extremities causes vasodilation and movement of cool pooled blood from extremities to core, resulting in a drop in core temperature leading to cardiac arrest

- active core re-warming
  - generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
  - avoids "afterdrop" seen with active external re-warming alone
  - re-warm core by using
    - warmed humidified oxygen, IV fluids
    - peritoneal dialysis with warm fluids
    - gastric/colonic/pleural/bladder irrigation with warm fluids
    - external circulation (ECMO) is most effective and fastest

Approach to Cardiac Arrest in the Hypothermic Patient

- treatment focus: active core re-warming (preferably with extracorporeal membrane oxygenation, ECMO, over cardiopulmonary bypass)
- intubate if required, ventilate with warmed, humidified O_2
- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
- if in VFib try to defibrillate up to maximum 3 shocks if core temperature <30°C
- intubate if required, ventilate with warmed, humidified O_2
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures (controversial); may try one dose
- focus of treatment is re-warming

FROSTBITE

Classification

- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
- 1st degree
  - symptoms: initial paresthesia, pruritus
  - signs: erythema, edema, hyperemia, no blisters
- 2nd degree
  - symptoms: numbness
  - signs: blistering (clear), erythema, edema
- 3rd degree
  - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
  - signs: hemorrhagic blisters, skin necrosis, edema, no movement
- 4th degree
  - extension into subcuticular, osseous, and muscle tissues

Management

- treat for hypothermia: O_2, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in 40-42°C agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area and leave it open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider antibiotics as frostbite injury has high-risk of infection
- surgical intervention may be required to release restrictive eschars (compartment syndrome)
- never allow a thawed area to re-chill/freeze
- consider using tPA and/or iloprost for severe burns, in conjunction with specialist advice

Burns

- see Plastic Surgery, PL18

Clinical Features/Physical Exam Findings

- burn size
  - rule of nines; does not include 1st degree (superficial) burns
- burn depth
  - superficial (1st degree): epidermis only (e.g. sunburn), painful and tender to palpation
  - superficial partial thickness (2nd degree): extends to epidermis and superficial dermis, blister formation occurs, very painful
  - deep partial thickness (2nd degree): involves hair follicles, sebaceous glands; skin is blistered, exposed dermis is white to yellow, absent sensation
  - full thickness (3rd degree): epidermis and all dermal layers; skin is pale, insensate, and charred or leathery
  - deep (4th degree): involvement of fat, muscle, even bone

Management

- remove noxious agent/stop burning process and consider appropriate PPE usage
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury or signs of significant upper airway burns)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
- fluid boluses if unstable
  - Parkland Formula: Ringer's lactate 4 cc/kg/% BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
  - urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics

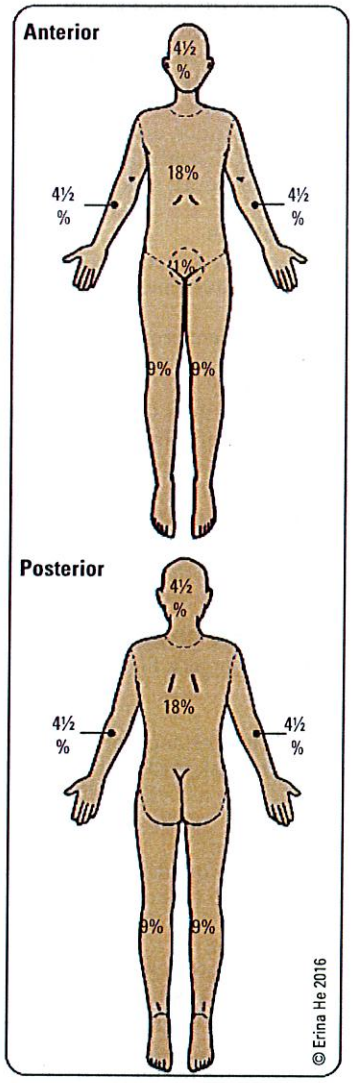


Figure 13. Rule of 9s for total BSA

BSA percentages differ in pediatric patients (e.g., infants have proportionately larger heads).

- pain relief: continuous opioid (e.g. hydromorphone, fentanyl, morphine) infusion for pain with breakthrough doses PRN
- investigations: CBC, electrolytes, U/A, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, burn victims are highly susceptible to infection (portal of entry with reduced immune function) – systemic antibiotics are often required
- tetanus prophylaxis if burn is deeper than superficial dermis



Use palm of the patient's hand to estimate 1% of BSA affected

Disposition

- admit
  - 2nd degree burns >10% BSA, or any significant 3rd degree burns
  - 2nd degree burns on face, hands, feet, perineum, or across major joints
  - electrical, chemical burns, and inhalation injury
  - burn victims with chronic medical conditions or immunosuppressed patients



Burn Causes
- Thermal (flame, scald)
- Chemical
- Radiation (UV, medical/therapeutic)
- Electrical

Inhalation Injury

Etiology

- carbon monoxide (CO) or cyanide (poisoning through dermal contact or inhalation)
- direct thermal injury: limited to upper airway (above the vocal cords)
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

History and Physical Exam

- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin and bitter almond odour are classic findings of cyanide toxicity but are often not present clinically
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO_2 normal but O_2 saturation low suggests CO poisoning



Always look for inhalational injury in patients with burns. Intubate early (prior to fluid boluses) if you suspect inhalation injury, as airway can become obstructed due to edema

Investigations

- CBC, electrolytes, lactate (if high, cyanide toxicity should be assumed)
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± outpatient bronchoscopy

Management

- CO poisoning: 100% O_2 ± hyperbaric O_2 (controversial, specific scenarios where it can be considered)
- cyanide poisoning: hydroxocobalamin 70 mg/kg IV over 15 min (max 5 g), up to two doses, hemodynamic support; obtain labs immediately as hydroxocobalamin will alter lab test results
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators, and mucolytics (N-acetylcysteine)

Bites

MAMMALIAN BITES

- see Plastic Surgery, PL11

History

- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, risk of rabies exposure/transmission, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, "fight bites"

Physical Exam

- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status, joints (if applicable)

Investigations

- if bony injury or infection suspected, check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds ± CT to rule out cranial perforation
- ultrasound may be helpful for identifying abscess formation as well as locating radiolucent foreign bodies in infected wounds

Initial Management

- wound cleaning and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
- culture wound if signs of infection (erythema, necrosis, or pus); obtain anaerobic cultures if wound is foul smelling, necrotizing, or if abscess is present; notify lab that sample is from bite wound

- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - consider suturing uncomplicated wounds that have been well irrigated/debrided and are vascular
  - provide antibiotics if suturing, and in the case of hand injuries (even if not suturing)
- tetanus immunization if >5 yr or incomplete primary series (see *Table 11, ER17*)

Prophylactic Antibiotics

- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present
- dog and cat bites (pathogens: *Pasteurella multocida, S. aureus, S. viridans*)
  - 10-50% of cat bites, and 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid (not cefalexin as it does not cover *Pasteurella* spp. or *Eikenella corrodens*)
- human bites (pathogens: *Eikenella corrodens, S. aureus, S. viridans*, oral anaerobes)
  - carry out a risk assessment for blood borne infections
  - if hand injury, always consider the associated metacarpophalangeal joint
  - 1st line: amoxicillin + clavulanic acid
- rabies (see Infectious Diseases, ID19)
  - reservoirs: warm-blooded animals except rodents (primarily bats and raccoons in Canada), lagomorphs (e.g. rabbits); incidence in domestic animals is low, higher risk if animal bite outside of Canada
  - post-exposure vaccine is effective; treatment depends on local prevalence, solicit guidance from local public health unit

Non-Fatal Drowning

- most common in children <4 yr and teenagers
- causes lung damage, hypoxemia, and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, and scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

Physical Exam

- ABCs, vitals: watch closely for hypotension
- respiratory: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- neurological: GCS or AVPU, pupils, focal deficits

Investigations

- labs: CBC, electrolytes, ABGs, Cr, BUN
- imaging: CXR (pulmonary edema, pneumothorax) ± C-spine imaging
- ECG

Management

- ABCs, treat for trauma, shock, hypothermia
- cardiac and O_2 monitors, IV access
- intensive respiratory care
  - ventilator assistance if decreased respirations, pCO_2 >50 mmHg, or pO_2 <60 mmHg on maximum FiO_2
  - may require intubation for airway protection, ventilation, pulmonary toilet
  - high flow O_2/CPAP/Bi-PAP may be adequate but some may need mechanical ventilation with positive end-expiratory pressure
- dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, and acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to O_2; if not, lorazepam 4 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: prophylactic antibiotics not necessary unless contaminated water or hot tub (*Pseudomonas*)
- always provide rescue ventilation and initiate CPR in drowning-induced cardiac arrest even if patient is hypothermic; continue CPR until patient is fully rewarmed

Disposition

- if asymptomatic, may discharge if no respiratory impairment, normal vitals, and normal mentation
- if symptomatic but never hypoxemic, may be discharged after 6-8 h observation period if resolving symptoms, normal vitals, and normal mentation
- CXR should only be considered for an abnormal lung examination or oxygen saturation
- CNS symptoms or hypoxemia: admit
- severe hypoxemia, decreased LOC: ICU

Toxicology

Approach to the Overdose Patient



Indications to Suspect Overdose

Altered LOC/coma

Young patient with life-threatening dysrhythmia

Trauma patient

Bizarre or puzzling clinical feature

History

- age, weight, underlying medical problems, medications
- substance, route, and quantity
- time and symptoms since exposure determines prognosis and need for decontamination
- route
- intention, suicidality

Physical Exam

- focus on: ABCs, LOC/GCS, vitals, pupils

"ABCD3EFG" of Toxicology



- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable



Principles of Toxicology

4 principles to consider with all ingestions:

- Resuscitation (ABCD3EFG)
- Screening (toxidrome, clinical clues)
- Decrease absorption of drug
- Increase elimination of drug

A	**A**irway (consider stabilizing C-spine)
B	**B**reathing
C	**C**irculation
D1	**D**rugs – ACLS as necessary to resuscitate the patient – universal antidotes (DONT)
D2	**D**raw bloods
D3	**D**econtamination (decrease absorption)
E	**E**xpose (look for specific toxidromes)/examine the patient
F	**F**ull vitals, ECG monitor, foley, x-rays
G	**G**ive specific antidotes and treatments

Further Steps following ABCD3EFG

- reassess
- call Poison Information Centre
- obtain corroborative history from family and bystanders

D1 – Universal Antidotes



- treatments that will not harm patients and may be essential



Universal Antidotes

DONT
Dextrose
Oxygen
Naloxone
Thiamine (must give BEFORE dextrose)

Dextrose (glucose)

- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: D50W 0.5-1.0 g/kg (1-2 mL/kg) IV
- children: D25W 0.25 g/kg (2-4 mL/kg) IV

Oxygen

- do not deprive a hypoxic patient of oxygen regardless of the antecedent medical history (i.e. even COPD with CO_2 retention)
- if depression of hypoxic drive, intubate and ventilate



Although doses in the ED are generally small, administration of naloxone can cause acute opioid withdrawal in people who are chronic opioid users (Ultrarapid Opioid Detoxification, UROD):

Minor withdrawal may present as lacrimation, restlessness, rhinorrhea, diaphoresis, yawning, piloerection, HTN, myalgia, N/V, tachycardia

Severe withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps

Naloxone (central μ-receptor competitive antagonist, shorter half-life than naltrexone)

- antidote for opioids: administration is both diagnostic and therapeutic (<1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - response to naloxone can be drastic, so stepwise delivery is recommended
    - 0.05 or 0.1 mg IV with escalation of doses PRN
    - naloxone administration during cardiac arrest:
      - begin ACLS protocol and administer 2 mg IV/IM every 3 min, may increase dose by doubling up to maximum of 12 mg
  - child
    - 0.01 mg/kg initial bolus IV/IO/ETT (max 2 mg per dose)
    - children over 20 kg can receive naloxone 2 mg IV
  - maintenance dose
    - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
    - hourly infusion rate at 2/3 of initial dose that allowed patient to be roused

Thiamine (Vitamin B1)

- 200 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine is unavailable
- must assume all undifferentiated comatose patients are at risk



Thiamine is deficient in the malnourished. Consider in patients with alcohol use disorder, anorexia, or malnutrition states

D2 – Draw Bloods

- essential tests
  - CBC, electrolytes, BUN/Cr, glucose, INR/PTT, osmolality
  - ABGs, O_2 sat
  - ASA, acetaminophen, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen (e.g. digoxin, iron)
  - Ca^{2+}, Mg^{2+}, PO_4^{3-}
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical features



Urine drug screen is costly and generally not helpful in the ED management of the poisoned patient unless suspicion of ASA, acetaminophen, or toxic EtOH ingestion

Serum Drug Levels

- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only; not often thought to change management)

Table 30. Toxic Gaps (see Nephrology, NP18)

METABOLIC ACIDOSIS

Increased AG: "GOLDMARK" (* = toxic)
Glycols* (ethylene glycol, propylene glycol)
Oxoproline (metabolite of acetaminophen)*
L-lactate
D-lactate (acetaminophen, short bowel syndrome, propylene glycol infusions for lorazepam & phenobarbital)
Methanol*
ASA*
Renal failure
Ketoacidosis (DKA, EtOH*, starvation)

Increased osmolar gap: "MAE DIE" (if it ends in "-ol", it will likely increase the osmolar gap)
Methanol
Acetone
Ethanol
Diuretics (glycerol, mannitol, sorbitol)
Isopropanol
Ethylene glycol

Note: normal osmolar gap does not rule out toxic alcohol; only an elevated gap is helpful

Decreased AG
Electrolyte imbalance (increased Na^+/K^+/Mg^{2+})
Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)
Lithium, bromine elevation
Paraproteins (multiple myeloma)

Increased O_2 saturation gap
Carboxyhemoglobin
Methemoglobin
Sulfmethemoglobin

Normal AG
Renal HCO_3 loss: renal tubular acidosis, hyperparathyroidism
GI HCO_3 loss: diarrhea, fistula
Other: NS infusion, acetazolamide, hyperkalemia, hypoaldosteronism

Table 31. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

Test	Finding	Selected Causes
ABG	Hypoventilation (high pCO_2)	CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH)
	Hyperventilation (low pCO_2)	Salicylates, CO, other asphyxiants
Electrolytes	AG metabolic acidosis	"GOLDMARK": see Table 30
	Hyperkalemia	Digitalis glycosides, fluoride, potassium
	Hypokalemia	Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin
Glucose	Hypoglycemia	Oral hypoglycemic agents, insulin, EtOH, ASA
Osmolality and Osmolar Gap	Elevated osmolar gap	"MAE DIE": see Table 30
ECG	Wide QRS complex	TCAs, quinidine, other class Ia and Ic antidysrhythmic agents
	Prolonged QT interval	Terfenadine, astemizole, antipsychotics, hydroxychloroquine
	Atrioventricular block	Ca^{2+} antagonists, digitalis glycosides, phenylpropanolamine, hydroxychloroquine
Abdominal X-Ray	Radiopaque pills or objects	"CHIPES": Calcium, Chloral hydrate, CCl_4, Heavy metals, Iron, Potassium, Enteric coated Salicylates, and some foreign bodies
Serum Acetaminophen	Elevated level (1000 µmol/L 4 h after ingestion) Consult Rumack-Matthew nomogram in single ingestion cases	May be only sign of acetaminophen poisoning



Anion Gap
= $Na^+ - Cl^- - HCO_3^-$
Normal AG ≤12 mM/L



Osmolar Gap
= [(2 x Na^+) + Glu + Urea] - Measured Osmolality
Normal <10

D3 – Decontamination and Enhanced Elimination

Ocular Decontamination

- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

Dermal Decontamination

- wear protective gear
- remove clothing, brush off toxic agents, irrigate all external surfaces

Gastrointestinal Decontamination

- single dose activated charcoal
  - use of activated charcoal is a source of much debate amongst toxicologists, evidence of effectiveness is not strong and risk of aspiration is high
  - consider if recent ingestion, delayed absorption medication, can consult poison control PRN
  - adsorption of drug/toxin to activated charcoal decreases toxin bioavailability
  - contraindications: unprotected airway, late presentation after ingestion (1-2 h post ingestion), small bowel obstruction, poor toxin adsorption
  - dose: 10 g/g drug ingested or 1 g/kg body weight (may vary depending on ingestion)
  - odourless, tasteless, prepared as slurry with H_2O
- whole bowel irrigation (occasionally used)
  - 500 mL/h (child) to 2000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
    - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
  - indications
    - awake, alert, can be nursed upright, with an NG tube who cannot tolerate drinking it, or intubated and airway protected
    - delayed release product
    - drug/toxin not bound to charcoal
    - drug packages (if any evidence of breakage emergency surgery)
    - recent toxin ingestion
  - contraindications
    - evidence of ileus, perforation, or obstruction
- multidose activated charcoal
  - may be used for: carbamazepine, phenobarbital, quinine, theophylline, for toxins which undergo enterohepatic recirculation
  - removes drug that has already been absorbed by drawing it back into GI tract
  - various regimens: 12.5 g (1/4 bottle) PO q1 h or 25 g (1/2 bottle) PO q2 h until non-toxic
- surgical removal in extreme cases
  - surgical indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
- use of cathartics (i.e. ipecac) and gastric lavage in the ED is generally not recommended

Lipid Emulsification

- new therapy used in cardiogenic shock due to toxins
- may be used for: anesthetics (e.g. lidocaine), β-blocker/calcium channel blocker, atypical antidepressant overdose
- initial bolus lipid solution 20% 1.5 mL/kg over 3 min then infusion of 0.25 mL/kg/min

Urine Alkalinization

- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkaline urine (pH >7.5) to increase elimination

Hemodialysis

- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution, or rapid plasma equilibration
  - clinical deterioration despite maximal medical support
- useful for the following toxins
  - methanol
  - ethylene glycol
  - salicylates
  - lithium
  - phenobarbital
  - chloral hydrate (trichloroethanol)
- others include theophylline, carbamazepine, valproate, methotrexate

E – Expose and Examine the Patient

- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours, and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, "tongue biting," etc.), infection (meningismus), or chronic alcohol/drug misuse (track marks, nasal septum erosion)
  - feel the patient's axillae; in the average patient, should be somewhat moist (if dry, may indicate anticholinergic toxicity)
- mental status

Table 32. Specific Toxidromes

Toxidrome	Overdose Signs and Symptoms		Examples of Drugs
Anticholinergic	Hyperthermia Dilated pupils Dry skin Vasodilation Agitation/hallucinations Ileus Urinary retention Tachycardia	"Hot as a hare" "Blind as a bat" "Dry as a bone" "Red as a beet" "Mad as a hatter" "The bowel and bladder lose their tone and the heart goes on alone"	Antidepressants (e.g. TCAs) Cyclobenzaprine (Flexeril®) Carbamazepine Antihistamines (e.g. diphenhydramine) Antiparkinsonians Antipsychotics Antispasmodics Belladonna alkaloids (e.g. atropine)
Cholinergic	"DUMBELS" Diaphoresis, Diarrhea, Decreased BP Urination Miosis Bronchospasm, Bronchorrhea, Bradycardia Emesis, Excitation of skeletal muscle Lacrimation Salivation, Seizures		Natural plants: mushrooms, trumpet flower Anticholinesterases: physostigmine Insecticides (organophosphates, carbamates) Nerve gases
Extrapyramidal	Dysphonia, dysphagia Rigidity and tremor Motor restlessness, crawling sensation (akathisia) Constant movements (dyskinesia) Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)		Major tranquilizers Antipsychotics
Hemoglobin Derangements	Increased respiratory rate Decreased LOC Seizures Cyanosis unresponsive to O_2 Lactic acidosis		CO poisoning (carboxyhemoglobin) Drug ingestion (methemoglobin, sulfmethemoglobin)
Opioid, Sedative/ Hypnotic, EtOH	Hypothermia Hypotension Respiratory depression (opioid) Dilated or constricted pupils (pinpoint in opioid) CNS depression		EtOH Benzodiazepines Opioids (morphine, heroin, fentanyl, etc.) Barbiturates GHB ("G," "liquid gold")
Sympathomimetic	Increased temperature CNS excitation (including seizures) Tachycardia, HTN N/V Diaphoresis Dilated pupils		Amphetamines, caffeine, cocaine, LSD, phencyclidine Ephedrine and other decongestants Thyroid hormone Sedative or EtOH withdrawal
Serotonin Syndrome	Mental status changes, autonomic hyperactivity, neuromuscular hyperactivity, hyperthermia, diarrhea, HTN		MAOI, TCA, SSRI, opiate analgesics Cough medicine, weight reduction medications

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

F – Full Vitals, ECG Monitor, Foley, X-Rays

G – Give Specific Antidotes and Treatments

Urine Alkalinization Treatment for ASA Overdose

- urine pH >7.5
- fluid resuscitate first, then 3 amps $NaHCO_3$/L of D5W at 1.5x maintenance
- add 20-40 mEq/L KCl if patient is able to urinate

Table 33. Protocol for Warfarin Overdose

INR	Management: Consider Prothrombin Complex Concentrate (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding, or a plan for the patient to undergo a surgical procedure within the next 6 h (vitamin K takes 4-6 h post IV administration to work)
<5.0	Cessation of warfarin administration, observation, serial INR/PT
5.1–9.0	If no risk factors for bleeding, hold warfarin x1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding
9.1–20.0	Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary
>20.0	Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4 h) if needed

Table 34. Specific Antidotes and Treatments for Common Toxins*

Toxin	Treatment	Considerations
Acetaminophen	Decontaminate (activated charcoal) N-acetylcysteine	Often clinically silent; evidence of liver/renal damage delayed >24 h Toxic dose >200 mg/kg (>7.5 g adult) Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PTT, BUN, Cr Hypoglycemia, metabolic acidosis, encephalopathy poor prognosis Dialysis may be required to manage in very high overdoses
Acute Dystonic Reaction	Benztropine: 1-2 mg IM/IV then 2 mg PO 3 d OR Diphenhydramine 1-2 mg/kg IV, then 25 mg PO QID x3 d	Benztropine (Cogentin®) has euphoric effect and the potential for misuse
Anticholinergics	Consider decontamination (activated charcoal) Supportive care	Special antidotes available; consult Poison Information Centre
ASA	Consider decontamination (activated charcoal) Alkalinize urine; want urine pH >7.5	Monitor serum pH and drug levels closely Monitor K^+ level; may require supplement for urine alkalinization Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese)
Benzodiazepines	Consider decontamination (activated charcoal) Flumazenil (only use in iatrogenic overdose (operative oversedation) due to extensive contraindications (mixed overdose, Hx of EtOH, seizures)) Supportive care	
β-blockers	Consider decontamination (activated charcoal, consider whole bowel irrigation for extended-release ingestion) IV glucagon, IV calcium chloride, IV high-dose insulin (with dextrose), IV lipid emulsification	
Calcium Channel Blockers	Consider decontamination (activated charcoal, consider whole bowel irrigation for extended-release ingestion) IV glucagon, IV calcium chloride, IV high-dose insulin (with dextrose), IV intralipid	Order ECG, electrolytes (especially Ca^{2+}, Mg^{2+}, Na^+, K^+)
Cocaine	Decontaminate (activated charcoal) if oral Aggressive supportive care	β-blockers are contraindicated in acute cocaine toxicity Intralipid for life-threatening symptoms Consider benzodiazepines for any major side effect of cocaine overdose (agitation, hypertension, tachycardia, etc.)
CO Poisoning	See *Inhalation Injury, ER47* Supportive care 100% O_2; may require hyperbaric O_2	Order ECG, VBG. Consider lactate and troponin depending on specific presentation
Cyanide	Hydroxocobalamin 5 g IV (Cyanokit™)	Consider in all patients found in a fire
Digoxin	Consider decontamination (activated charcoal) Digoxin-specific antibody fragments 10-20 vials IV if acute; 3-6 if chronic 1 vial (40 mg) neutralizes 0.5 mg of toxin	Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin >12 nmol/L, initial K^+>5 mmol/L, ingestion >10 mg (adult)/>4 mg (child) Common dysrhythmias include VFib, VTach, and conduction blocks
Ethanol	Thiamine 100 mg IM/IV Manage airway and circulatory support	Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH Order serum EtOH level and glucose level; treat glucose level appropriately
Ethylene Glycol/ Methanol	Fomepizole (4-methylpyrazole) 15 mg/kg IV load over 30 min, then 10 mg/kg q12 h OR Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h	CBC, electrolytes, glucose, ethanol level Consider hemodialysis
Heparin	Protamine sulfate 25-50 mg IV	For unfractionated heparin overdose only
Insulin IM/SC/ Oral Hypoglycemic	Glucose IV/PO/NG tube Glucagon: 1-2 mg IM (if no access to glucose)	Glyburide carries highest risk of hypoglycemia among oral agents Consider octreotide for oral hypoglycemics (50-100 µg SC q6 h) in these cases; consult local Poison Information Centre
MDMA	Consider decontamination (activated charcoal) Supportive care	Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia Review medical history if possible for serotonergic use
Opioids	See *Universal Antidotes, ER49*	
TCAs	Consider decontamination (activated charcoal) Aggressive supportive care $NaHCO_3$ bolus for wide QRS/seizures	Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose Also consider cardiac and hypotension support, seizure control Intralipid therapy
Organophosphate	100% O_2 + endotracheal intubation Atropine Pralidoxime (2-PAM)	Succinylcholine

* Call local Poison Information Centre for reporting of cases, specific doses, and treatment recommendations. Most toxicology cases should involve communication with your local Poison Information Centre

Alcohol Related Emergencies

• see Psychiatry, PS28

Acute Intoxication

•slurred speech, CNS depression, disinhibition, lack of coordination
•nystagmus, diplopia, dysarthria, ataxia, may progress to coma
•hypotension (peripheral vasodilation)
•if obtunded, rule out
  ▪ head trauma/intracranial hemorrhage
  ▪ associated depressants, toxic alcohols
•may also contribute to respiratory/cardiac depression
  ▪ hypoglycemia (screen with bedside glucometer)
  ▪ hepatic encephalopathy: confusion, altered LOC, coma

Alcohol levels correlate poorly with intoxication

Alcohol intoxication may invalidate informed consent

Withdrawal

•beware of withdrawal signs
• treatment
  ▪ diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1 h (if known liver dysfunction) until two CIWA scores <10
•frequency of dosing may have to be increased depending on clinical response
  ▪ may use CIWA protocol and give benzodiazepines as above until CIWA <10
  ▪ thiamine 200 mg IM/IV then 50-100 mg/d
    ◆ naltrexone & gabapentin if no improvement
  ▪ magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  ▪ admit patients with delirium tremens or multiple seizures or persistently high CIWA (symptoms) despite high doses of benzodiazepines

CIWA Withdrawal Symptoms
- N/V
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Visual disturbances
- Tactile disturbances
- Auditory disturbances
- Headache
- Disorientation
- 10 symptoms each scored out of 7 except orientation, which is scored out of 4

Table 35. Alcohol Withdrawal Signs

Time Since Last Drink	Syndrome	Description
6-8 h	Mild withdrawal	Generalized tremor, anxiety, agitation, but no delirium Autonomic hyperactivity (sinus tachycardia), insomnia, N/V
1-2 d	Alcoholic hallucinations	Visual (most common), auditory, and tactile hallucinations Vitals often normal
8 h-2 d	Withdrawal seizures	Typically brief generalized tonic-clonic seizures May have several within a few hours CT head if focal seizures have occurred
3-5 d	DT	5% of untreated withdrawal patients Severely confused state, fluctuating LOC Agitation, insomnia, hallucinations/delusions, tremor Tachycardia, hyperpyrexia, diaphoresis High mortality rate

Cardiovascular Complications

• HTN
• cardiomyopathy: SOB, edema
• dysrhythmias: AFib (most common), atrial flutter, SVT, VTach (especially Torsades if hypomagnesemic/hypokalemic)

Metabolic Abnormalities

• alcoholic ketoacidosis
  ▪ metabolic acidosis, urine ketones, low glucose, and normal osmolality
  ▪ history of chronic alcohol intake with abrupt decrease/cessation
  ▪ malnourished, abdominal pain with N/V
  ▪ treatment: thiamine (250-500 mg IM/IV prior to dextrose), dextrose, volume repletion (with NS or LR)
  ▪ generally resolves in 12-24 h
• toxic alcohols
  ▪ ethylene glycol: CNS, CVS, renal findings
  ▪ methanol
    ◆ early: lethargy, confusion
    ◆ late: headache, visual changes, N/V, abdominal pain, tachypnea
  ▪ toxic alcohols initially produce a high osmolar gap, as the toxic alcohol is metabolized the osmolar gap drops and an anion gap develops leading to a severe metabolic acidosis, the goal of treatment is to block this pathway
  ▪ EtOH co-ingestion is protective

- treatment
  - urgent hemodialysis required
  - fomepizole 15 mg/kg IV bolus (treatment of choice) or 10% EtOH IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
  - consider folic acid for methanol, and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites

- other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

Gastrointestinal Abnormalities

- gastritis
  - common cause of abdominal pain and GI bleed in chronic alcohol users
- pancreatitis
  - Elevated serum lipase is diagnostic
  - hemorrhagic form (15%) associated with increased mortality
  - fluid resuscitation very important
- hepatitis
  - AST/ALT ratio >2 suggests alcohol as the cause
- peritonitis/spontaneous bacterial peritonitis
  - leukocytosis, fever, generalized abdominal pain/tenderness
  - occasionally accompanies cirrhosis
  - paracentesis for diagnosis (common pathogens: *E. coli, Klebsiella, Streptococcus*)
  - albumin shown to improve outcomes in sBP patients
- GI bleeds
  - most commonly gastritis or ulcers, even if patient known to have varices
  - consider Mallory-Weiss tear secondary to retching
  - often complicated by underlying coagulopathies
  - minor: treat with antacids
  - severe or recurrent: endoscopy
  - variceal bleeds: octreotide

Disposition from the Emergency Department

- alcohol
  - before patient leaves ED ensure stable vital signs, can walk unassisted, and fully oriented
  - explore need for social services, housing, addictions services, or detox program
  - ensure patient can obtain any medications prescribed and can complete any necessary follow-up
- methanol, ethylene glycol
  - admit for dialysis
- TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored ICU bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of overdose warrants observation in ED and consultation with poison centre
- hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA, must have at least 2 measurements showing decreasing toxin serum concentration before discharge (3 levels minimum)
- oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h
- opioids
  - administer naloxone, a short-acting opioid antagonist, preferably IV in incremental doses (0.2-1 mg)
  - patients in cardiorespiratory arrest following possible opioid overdose should be given 2 mg of naloxone minimum
  - if a naloxone infusion is needed: admit to ICU; start infusion at 2/3rds of the minimum effective bolus dose (e.g. if the minimum effective dose was 0.3 mg, then the infusion dose should start at 0.2 mg/h)
  - admit and observe for 24 h
  - referral to rapid access clinic and offer a naloxone kit

Psychiatric Consultation

- once patient medically cleared, arrange psychiatric intervention if required
- in the setting of an intentional overdose, patients should be certified using the local mental health legislation
- beware – suicidal ideation may not be expressed

Psychiatric Emergencies

Approach to Common Psychiatric Presentations

- see Psychiatry, PS2
- before seeing patient, ensure your own safety; have security/police available if necessary

History

- safety
  - assess suicidality: suicidal ideation (SI; passive/active), intent, plan, lethal means, past history and family history of attempts, protective factors
    - Use scales, like SAD PERSONS (Scale and Columbia–Suicide Severity Rating Scale), to assess suicide risk
  - assess homicidality: homicidal ideation (HI), access to weapons, intended victim, and history of violence
  - driving and children
  - command hallucinations
- identify current stressors, mood (in patient's own words), and coping strategies
- psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
- substance use history: substance(s), most recent use, amount, previous withdrawal reactions
- past psychiatric history, medications, adherence with medications, admissions
- medical history: obtain collateral if available (patients are unable to provide collateral if experiencing acute psychosis, catatonia, or intoxication)

Key Functions of Emergency Psychiatric Assessment

- Is the patient medically stable?
- Rule out medical cause
- Is psychiatric consult needed?
- Are there safety issues (SI, HI)?
- Is patient certifiable? (must demonstrate risk (present/past test) and apparent mental illness (future test))

Physical Exam

- emphasis on mental status exam: general appearance, behaviour, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability
- complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder; which could be contributing or causing psychiatric presentation

Psychiatric Review of Systems

MOAPS
Mood
Organic
Anxiety
Psychosis
Safety

Investigations

- investigations vary with age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
- as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum Cr, BUN, and osmolality
- blood levels of psychiatric medications
- CT head if suspect neurological etiology
- LP if indicated (anti-NMDA receptor encephalitis)

Acute Psychosis

Differential Diagnosis

- primary psychotic disorder (e.g. schizophrenia)
- secondary to medical condition (e.g. delirium)
- drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
- infectious (CNS)
- metabolic (hypoglycemic, hepatic, renal, thyroid)
- structural (hemorrhage, neoplasm)
  - autoimmune (anti-NMDA receptor encephalitis)

Management

- violence prevention
  - remain calm, empathic, and reassuring
  - ensure safety of staff and patients, have extra staff and/or security on hand
  - patients demonstrating escalating agitation or overt violent behaviour may require physical restraint and chemical restraint
- treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  - benzodiazepines: lorazepam 2 mg PO/IM/SL
  - antipsychotics: olanzapine 5-10 mg PO/IM, haloperidol 5 mg PO/IM
- treat underlying medical condition
- psychiatry or Crisis Intervention Team consult

Suicidal Patient

Epidemiology

- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr
- significantly increased incidence among marginalized communities, particularly Indigenous peoples and 2SLGBTQQIA+ Canadians

See Psychiatry, *Common Forms*, PS61 for certification (involuntary assessment/admission) considerations

Management

- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), past history and family history of attempts, protective factors
- admit if there is evidence of: active intent and organized plan, access to lethal means, psychiatric disorder, intoxication (in rare circumstances, active suicidal ideation may resolve with few days of abstinence)
- patient may require certification based on local mental health legislation if unwilling to stay voluntarily
- do not start long-term medications in the ED
- psychiatry or Crisis Intervention Team consult



High-Risk Patients

SAD PERSONS
Sex = male
Age >45 yr
Depression
Previous attempts
Ethanol use
Rational thinking loss
Suicide in family
Organized plan
No spouse, no support system
Serious illness

Common Pediatric ED Presentations

Modified Glasgow Coma Score

Table 36. Modified GCS

Modified GCS for Infants		
Eye Opening	**Verbal Response**	**Motor Response**
4 – spontaneously	5 – coos, babbles	6 – normal, spontaneous movement
3 – to speech	4 – irritable cry	5 – withdraws to touch
2 – to pain	3 – cries to pain	4 – withdraws to pain
1 – no response	2 – moans to pain	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response
Modified GCS for Infant (<2 years)1 or Non-verbal Patients		
Eye Opening	**Verbal Response**	**Motor Response**
4 – spontaneously	5 – oriented, social, speaks, interacts	6 – normal, spontaneous movement
3 – to speech	4 – confused speech, disoriented, consolable	5 – localizes to pain
2 – to pain	3 – inappropriate words, not consolable/aware	4 – withdraws to pain
1 – no response	2 – incomprehensible, agitated, restless, not aware	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response

1Consider Alert, Pain, Verbal, Unconscious (AVPU) scale



Any trauma or suspected trauma patient <1 yr with a large, boggy scalp hematoma requires U/S or CT

Respiratory Distress

- see Pediatrics, P80, P93

History and Physical Exam

- see Pediatrics, P4 for how to obtain a standard pediatric history
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see Pediatrics, P3 for age specific vital signs
- pulsus paradoxus (rarely used clinically)
- wheezing, grunting, vomiting

Table 37. Stridorous Upper Airway Diseases: Differential Diagnosis

Feature	Croup	Bacterial Tracheitis[1]	Epiglottitis[1]
Age Range (yr)	0.5-4	5-10	2-8
Prodrome	Mild for days then acutely severe	Hours to days	Minutes to hours
Temperature	Low grade	High	High
Radiography	Steeple sign[2]	Exudates in trachea[3]	Thumb sign
Etiology	Parainfluenza	*S. aureus*/GAS	*H. influenzae* type b
Barky Cough	Yes	Yes	No
Drooling	Occasionally	No	Yes
Appear Toxic	No	Yes	Yes
Intubation/ICU4	No but yes if severe (rare)	Yes	Yes
Antibiotics	No	Yes	Yes
NOTE	Oral exam	Oral exam	No oral exam, consult ENT

[1]Now rare with Hib vaccine in common use
[2]Rarely perform x-ray unless unresponsive to therapy
[3]Found as diffuse haziness and irregularity of the anterior wall of trachea; consider imaging only after ruling out epiglottitis
[4]Should only be performed by experienced providers; ideally in the OR

Management
- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - dexamethasone x 1 dose
  - assess croup severity (can use Westley score): in moderate croup, child may have stridor and sternal/intercostal indrawing at rest, and moderate difficulty breathing; in severe croup, child has stridor and sternal/intercostal indrawing at rest, and worsening cyanosis over time
  - if moderate-severe, add nebulized or MDI epinephrine (racemic has limited availability)
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
  - humidified O_2 has no evidence for efficacy
- bacterial tracheitis
  - airway maintenance - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S
- epiglottitis
  - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesia/ENT call – intubate
  - then IV fluids, antibiotics, blood cultures

Febrile Infant and Febrile Seizures

FEBRILE INFANT
- for fever >38°C without obvious focus
  - <28 d
    - admit
    - full septic workup (CBC and differential, CRP, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
    - treat empirically with broad spectrum IV antibiotics (ampicillin, and ceftazidime or cefepime or cefotaxime (if available) or gentamicin (add acyclovir or vancomycin when indicated))
  - 28-90 d
    - as above unless infant meets Rochester criteria, if so, complete a partial septic workup (CBC and differential, blood C&S, urine C&S, CXR if indicated)
    - antibiotics (ceftriaxone or cefotaxime (if available), add acyclovir or vancomycin when indicated)
  - >90 d
    - toxic: admit, treat, full septic workup
    - non-toxic and no focus: investigate as indicated by history and physical
    - if bacterial: antibiotics (ceftriaxone or cefotaxime (if available, add acyclovir or vancomycin when indicated)

Rochester Criteria for Febrile Infants Ages 28-90 Days Old
- Helps identify SBI (serious bacterial infection) and guide testing/work-up for well-looking febrile neonates
- Non-toxic looking
- Previously well (>37 wk gestational age, home with mother, no hyperbilirubinemia, no prior antibiotics or hospitalizations, no chronic/underlying illness)
- No skin, soft tissue, bone, joint, or ear infection on physical exam
- WBC 5000-15000, bands <1500, urine <10 WBC/HPF, stool <5 WBC/HPF

FEBRILE SEIZURES
- see Pediatrics, P88

Etiology
- children age 6 mo-6 yr with fever or history of recent fever
- typical vs. atypical febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- well-looking after seizure

Investigations and Management
- if confirmed febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
  - note: may also have fever but may not meet criteria for febrile seizure
- ± EEG (especially if first seizure), head U/S (if fontanelle open)

Table 38. Typical vs. Atypical Febrile Seizures

Characteristic	Typical	Atypical
Duration	<5 min	>5 min
Type of Seizure	Generalized	Focal features
Frequency	1 in 24 h	>1 in 24 h

Abdominal Pain

• see Pediatrics, P47

History
•neuro, infections, autoimmune, hematology, trauma, abuse Hx questions
•nature of pain, associated fever
•associated GI, GU symptoms
•anorexia, decreased fluid intake
- stress and/or social issues (most common in middle aged children)

Physical Exam
•HEENT, respiratory, abdominal exam, testicular exam

Red Flags for Abdominal Pain
- Significant weight loss or growth retardation (need growth chart)
- Fever
- Joint pain with objective physical findings
- Rash
- Rectal bleeding
- Rebound tenderness and radiation of pain to back, shoulders, or legs
- Pain wakes from sleep
- Severe diarrhea and encopresis

Table 39. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

Medical	Surgical
Colic	Malrotation with volvulus
UTI	Hirschsprung's disease
Constipation	Necrotizing enterocolitis
Gastroenteritis	Incarcerated hernia
Sepsis	Intussusception
Henoch-Schönlein purpura	Duodenal atresia
IBD	Appendicitis
Hemolytic uremic syndrome	Cholecystitis
Pneumonia	Pancreatitis
Strep throat	Adnexal torsion (testicular or ovarian)
Sickle cell disease crisis	Ectopic pregnancy
DKA	Trauma
Functional	Pyloric stenosis

*Remember to keep an index of suspicion for child abuse

Common Infections

• see Pediatrics, P58

Table 40. Antibiotic Treatment of Pediatric Bacterial Infections

Infection	Pathogens	Treatment
MENINGITIS SEPSIS		
Neonatal	Group B *Streptococcus* (GBS), *E. coli*, *Listeria*, Gram-negative bacilli	ampicillin + cefotaxime
1-3 mo	Same pathogens as above and below	ceftriaxone/cefotaxime + vancomycin + ampicillin (if immunocompromised)
>3 mo	*S. pneumoniae*, *H. influenzae* type B (>5 yr), meningococcus	ceftriaxone + vancomycin
OTITIS MEDIA		
1st Line	*S. pneumoniae*, *H. influenzae* type B, *M. catarrhalis*	amoxicillin 75-90 mg/kg/d BID
1st Line with Penicillin Allergy		1. cefprozil or cefuroxime-axetil 30 mg/kg/d BID/TID OR ceftriaxone 50 mg/kg/dayIM x 3 d (if minor allergy) 2. clarithromycin 15 mg/kg/d BID (for severe allergy); known to have inferior bacterial killing capabilities
Treatment Failure		7:1 amoxicillin to clavulanate ratio ≤35 kg: 45-60 mg/kg/d TID >35 kg: 50 mg PO TID
STREP PHARYNGITIS		
	Group A β-hemolytic *Streptococcus*	penicillin/amoxicillin, cefalexin, or erythromycin (can cause GI upset)
UTI		
	E. coli, *Proteus*, *H. influenzae*, *Pseudomonas*, *S. saprophyticus*, *Enterococcus*, GBS	Oral: cefixime IV: aminoglycoside (gentamicin) ± ampicillin; or use cefotaxime or ceftriaxone
PNEUMONIA		
1-3 mo	Viral, *S. pneumoniae*, *C. trachomatis*, *B. pertussis*, *S. aureus*, *H. influenzae*	IV: ceftriaxone
3 mo-5 yr	Viral, *S. pneumoniae*, *S. aureus*, *H. influenzae*, *Mycoplasma pneumoniae*	if discharged: amoxicillin or cefprozil if admitted: ceftriaxone
>5 yr	As above	ampicillin/amoxicillin OR cefuroxime

Child Abuse and Neglect

- see Pediatrics, P18
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - HI: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken baby syndrome: diffuse brain injury, subdural/SAH, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures <1 yr, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - GU/GI injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea

Association of 2 Social Needs Interventions with Child Emergency Department Use and Hospitalizations
JAMA Pediatr 2022;176:716-717
Purpose: To link social needs interventions to healthcare outcomes among pediatric populations.
Methods: 604 child-caregiver pairs were randomized to groups in which they are given a social resources handout (SRH) with and without the help of a patient navigator (PN) support.
Results: During the 90 d of follow-up, pairs that navigated the SRH alone were associated with increased probability of hospitalization when compared to those given professional help (HR 5.69; 95% CI, 1.07-30.10; p = 0.04).
Conclusion: Social interventions, such as SRH plus PN guidance, can lead to improved pediatric health care outcomes in the ED.

Presentation of Neglect
Failure to thrive, developmental delay
Inadequate or dirty clothing, poor hygiene
Child exhibits poor attachment to parents

Procedures that may Require Sedation
- Setting fractures
- Reducing dislocations
- Draining abscesses
- Exploring wounds/ulcers/superficial infections
- Endoscopic examination
- Reduce patient anxiety/agitation for imaging/procedures

Common Medications

Table 41. Commonly Used Medications

Drug	Dosing Schedule	Indications	Comments
Acetaminophen	325-650 mg PO q4-6h PRN	Pain control	Max 4 g daily
Activated charcoal	30-100 g PO in 250 mL H_2O	Poisoning/overdose	Efficacy and safety are case-dependent and are a source of debate
ASA	325-650 mg PO q4 h max 4 g/d stroke/MI risk: 81-325 mg PO once daily 160 mg chewed	Pain control Prevention of adverse cardiac events ACS	
β-blockers (metoprolol)	5 mg slow IV q5 min x3 if no contraindications Or 25 mg PO BID up to 100 mg PO BID	Rate control in AFib	
Diazepam	anxiety: 2-10 mg PO TID/QID alcohol withdrawal: 10-20 mg PO/IV q1 h titrated to signs/symptoms	Anxiety Alcohol withdrawal	
Enoxaparin	1 mg/kg SC BID	Acute MI DVT Prophylaxis/treatment PE or DVT in patients who cannot take DOACs	
Epinephrine	anaphylaxis: 0.3-0.5 mg IM; ACLS cardiac arrest: 1 mg IV q3-5 min ACLS bradycardia: 2-10 µg/min IV infusion	Anaphylaxis, ACLS cardiac arrest, ACLS bradycardia Hypotension	Max 1 mg/dose
Fentanyl	0.5-1.0 µg/kg IV	Procedural sedation Pain control	Very short acting narcotic (complication=apnea)
Furosemide (Lasix®)	CHF: 40-80 mg IV HTN: 10-40 mg PO BID	CHF HTN	Monitor for electrolyte imbalances; also risk of ototoxicity with high dose
Glucose	0.5-1.0 g/kg (1-2 mL/kg) IV of D50W	Hypoglycemia/DKA	In conjunction with Insulin for hyperkalemia
Haloperidol	2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d	Psychosis Cannabis Hyperemesis Syndrome (any N/V) Sedation	Monitor for side effects if prescribing to a patient with Parkinson's disease (extrapyramidal side effects); results in CNS depression
Ibuprofen	200-800 mg PO TID PRN max 1200 mg/d	Mild to moderate acute pain Analgesic and anti-inflammatory properties	
Insulin	bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per h	Hyperglycemia CCB/BB overdose	Monitor blood glucose levels Consider K+ replacement, also measure blood glucose levels before administration
Ipratropium bromide	2-3 puffs inhaled TID-QID, max 12 puffs/d	Asthma COPD	Contraindications include: peanut/soy allergy Caution with narrow-angle glaucoma
Lidocaine with epi	max 7 mg/kg SC	Local anesthetic	
Lidocaine w/o epi	max 5 mg/kg SC	Local anesthetic	
Lorazepam	anxiety: 0.5-2 mg PO/IM/IV q6-8 h status epilepticus: 4 mg IV repeat up to q5 min	Anxiety Status epilepticus Alcohol withdrawal	

Table 41. Commonly Used Medications

Drug	Dosing Schedule	Indications	Comments
Midazolam	50 µg/kg IV	Procedural sedation Sedation for agitation	Short acting benzodiazepine (complication = apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation
Morphine	0.05-0.1 mg/kg	Mild to moderate acute/chronic pain Prescribed in combination with NSAIDs or acetaminophen	GI and constipation side effects DO NOT CRUSH, CUT, or CHEW (increases risk of overdose) Risk of tolerance
Naloxone	0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg	Comatose patient Opioid overdose Reversal in procedural sedation	If patient is a chronic opioid user begin with very small doses, and go up with small increments as needed
Nitroglycerin	acute angina: 0.3-0.6 mg SL q5 min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5 min	Angina Acute MI (for symptomatic control only) Heart failure	Not to be used with other antihypertensives Not in right ventricular MI
Percocet 10/325®	1-2 tabs PO q6 h PRN	Moderate pain control	Oxycodone + acetaminophen Max 4 g acetaminophen daily
Phenytoin	Status epilepticus: *see Table 17, ER26*	Status epilepticus Epilepsy	Begin maintenance dose 12 h after loading dose Continuous ECG, BP monitoring mandatory
Polysporin®	Apply to affected area BID/TID	Superficial infections	
Propofol	0.25-1 mg/kg IV	Procedural sedation, also refractory status epilepticus Rapid sequence intubation	Short acting Anesthetic/sedative (complication = apnea, decreased BP)
Salbutamol	2 puffs inhaled q4-6 h max 12 puffs/d	Asthma Reactive airways COPD	Caution with cardiac abnormalities
Thiamine	100 mg IV/IM initially, then 50-100 mg IM/IV/PO once daily x3 d	To treat/prevent Wernicke's encephalopathy	Caution use in pregnancy

Landmark Emergency Medicine Trials

Trial Name	Reference	Clinical Trial Details
DIVERTICULITIS		
DINAMO	Ann Surg. 2021;274:e435	**Title:** Efficacy and Safety of Nonantibiotic Outpatient Treatment in Mild Acute Diverticulitis **Purpose:** To support that uncomplicated acute diverticulitis can be treated using outpatient care without antibiotics. **Methods:** A Prospective, multicentre, open-label, RCT trial was conducted with 480 patients diagnosed with uncomplicated mild diverticulitis using CT. Patients were randomized to the classical treatment with antibiotics and without antibiotics. The outcome of interest was hospital admission. **Results:** 14/238 patients treated with antibiotics were admitted to hospital and 8/242 patients treated without antibiotics were admitted to hospital. **Conclusion:** The results show that treatment of uncomplicated mild diverticulitis can be effectively conducted as an outpatient without use of antibiotics.
CONCUSSION		
NCT03564210	JAMA Pediatr. 2021;175:1124-1131	**Title Title:** Effect of Screen Time on Recovery from Concussion **Purpose:** To determine if screen time during the first 48 h after injury has an impact on the duration of concussive symptoms. **Methods:** RCT consisting of 125 patients who were permitted to engage in unrestricted screen time or advised to abstain from screen time for 48 h after injury. The primary outcome of concern was days needed for resolution of concussive symptoms (<3 on post-concussive symptom scale). **Results:** The treatment group with unrestricted screen time had a significantly longer recovery time when compared to the group advised to abstain from screen time - 8 d and 3.5 d, respectively. **Conclusion:** The results of this study show that abstention from screen time during the first 48 h may reduce the duration of concussive symptoms.
SHOCK		
CLASSIC	NEJM 2022;386:2459-2470	Title: Restriction of Intravenous Fluid in ICU Patients with Septic Shock **Purpose:** To determine the effect of standard intravenous (IV) fluids or restricted IV fluids on mortality in patients with septic shock. **Methods:** RCT of 1554 patients with septic shock (≤12 h) who received at least 1L of IV fluid were assigned to either restricted IV fluid or standard IV fluid therapy. Primary outcome was death within 90 d. **Results:** Death resulted in 42.3% of the fluid-restricted group (median 1798 mL IV fluids), whereas death resulted in 42.1% of patients in the standard-fluid group (median 3811 mL IV fluids). Serious adverse events in restricted and standard-fluid groups occurred in 29.4% and 30.8% of patients, respectively. **Conclusion:** In patients with septic shock, IV fluid restriction does not result in fewer deaths within 90 d as compared to standard IV fluid therapy.
STROKE		
SELECT2	NEJM 2023;388:1259-1271	**Title:** Trial of Endovascular Thrombectomy for Large Ischemic Strokes **Purpose:** To evaluate efficacy and safety of endovascular thrombectomy in patients with large ischemic strokes (within 24 h of onset). **Methods:** A prospective Phase 3, randomized, open-label, international Phase 3 RCT involving patients assigned in a 1:1 ratio to endovascular thrombectomy plus medical care, or medical care alone. **Results:** Thrombectomy resulted in better functional outcomes using a Modified Rankin Scale (OR 1.51 [(95% CI, 1.20-1.89]); P<0.001) than medical care but was associated with vascular complications. **Conclusion:** Endovascular thrombectomy improves functional outcomes in patients with large ischemic strokes but carries a risk of vascular complications.

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Endocrinology

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Acronyms

A1c	hemoglobin A1c
AAA	abdominal aortic aneurysm
Ab	antibodies
ABCA1	Adenosine triphosphate-binding cassette transporter A1
ACEI	angiotensin converting enzyme inhibitor
ACR	albumin-creatinine ratio
ADH	antidiuretic hormone
AG	anion gap
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ApoC2	apolipoprotein C2
ApoE4	apolipoprotein E4
ARB	angiotensin receptor blockers
ARR	absolute risk reduction
AVP	arginine vasopressin
BG	blood glucose
BMD	bone mineral density
BMI	body-mass index
CAH	congenital adrenal hyperplasia
CHO	carbohydrates
CK	creatine kinase
CKD	chronic kidney disease
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CVD	cardiovascular disease
DDAVP	desmopressin (1-deamino-8-D-arginine vasopressin)
DHEA	dehydroepiandrosterone
DI	diabetes insipidus
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DXM	dexamethasone
DVT	deep vein thrombosis
ECF	extracellular fluid
ECFV	extracellular fluid volume
FFA	free fatty acids
FNA	fine needle aspiration
FPG	fasting plasma glucose
GFR	glomerular filtration rate
GHRH	growth hormone releasing hormone
GLP-1	glucagon-like peptide 1
GnRH	gonadotropin releasing hormone
Hb	hemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HHS	hyperosmolar hyperglycemic state
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPA	hypothalamic pituitary adrenal
Hs-CRP	highly-sensitive C-reactive protein
HVA	homovanillic acid
ICF	intracellular fluid
IDL	intermediate density lipoprotein
IFG	impaired fasting glucose
IGF2	insulin-like growth factor 2
IGT	impaired glucose tolerance
JGA	juxtaglomerular apparatus
LCAT	lecithin-cholesterol acyltransferase
LDL	low density lipoprotein
LDL-C	low density lipoprotein-cholesterol
LDL-R	low density lipoprotein receptor
LP	lipoprotein
LP(a)	lipoprotein (a)
LPL	lipoprotein lipase
MEN	multiple endocrine neoplasia
MMI	methimazole
MTC	medullary thyroid cancer
NS	normal saline
OSA	obstructive sleep apnea
OGTT	oral glucose tolerance test
PA	primary aldosteronism
PAD	peripheral arterial disease
PCOS	polycystic ovary syndrome
PCSK9	proprotein convertase subtilisin/kexin type 9
POMC	pro-opiomelanocorticotropin
PRL	prolactin
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
PTU	propylthiouracil
RAAS	renin-angiotensin-aldosterone system
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RANKL	receptor activator of nuclear factor-κB ligand
RH	releasing hormone
RRR	relative risk reduction
SA	secondary aldosteronism
SGLT2i	sodium-glucose cotransporter-2 inhibitor
SHBG	sex hormone-binding globulin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TBG	thyroid-binding globulin
TC	total cholesterol
TG	triglycerides
TgAb	thyroglobulin antibodies
TPOAb	anti-thyroid peroxidase antibodies
TRAb	Thyroid stimulating hormone receptor antibodies
TRH	thyrotropin-releasing hormone
TSI	thyroid stimulating immunoglobulin
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
WC	waist circumference

Basic Anatomy Review

Major Endocrine Organs

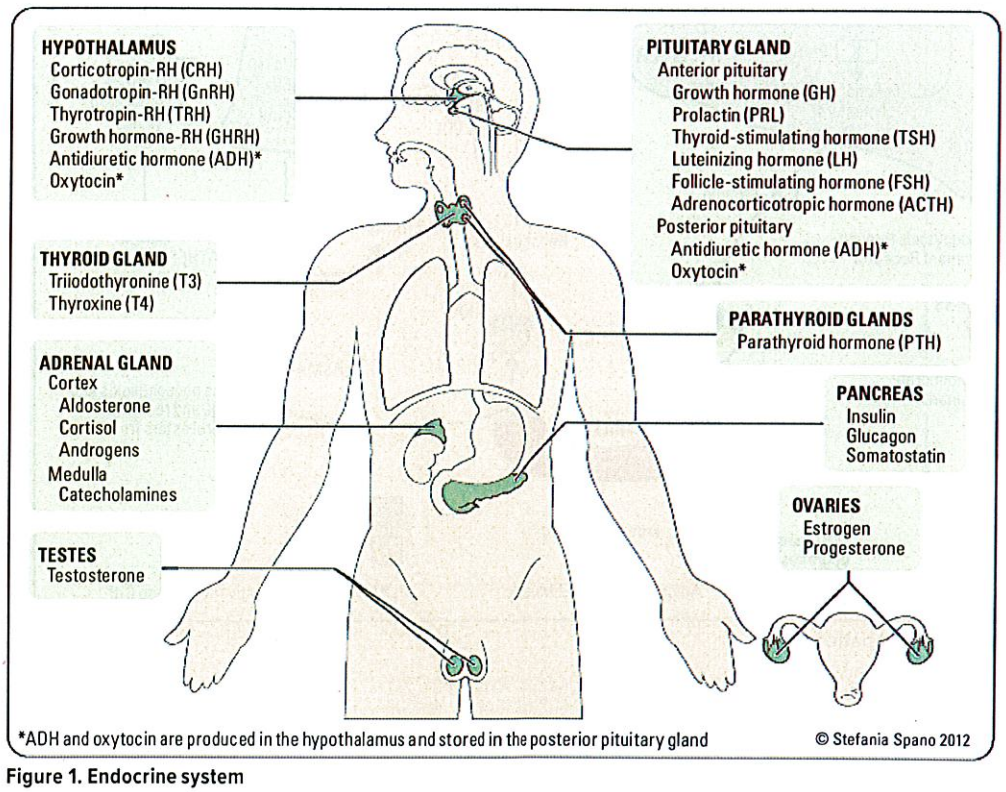


Figure 1. Endocrine system

Dyslipidemias

Definition

- metabolic disorders characterized by elevations of fasting plasma LDL-C, and/or TG, and/or low HDL-cholesterol

Overview of Lipid Transport

- lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apolipoproteins, and phospholipids
- lipoproteins transport lipids within the body
- apolipoproteins serve as enzyme cofactors, promote clearance of the particle by interacting with cellular receptors, and stabilize the lipoprotein micelle

Table 1. Lipoproteins

Lipoprotein	Function
Chylomicron	Transports dietary TG from gut to adipose tissue and muscle
VLDL	Transports hepatic synthesized TG from liver to adipose tissue and muscle
IDL	Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core Enriched in cholesterol esters
LDL	Cholesterol rich atherogenic particles Formed by further removal of residual TG from IDL core by hepatic lipase
HDL	Transports cholesterol from peripheral tissues to liver Acts as a reservoir for apolipoproteins

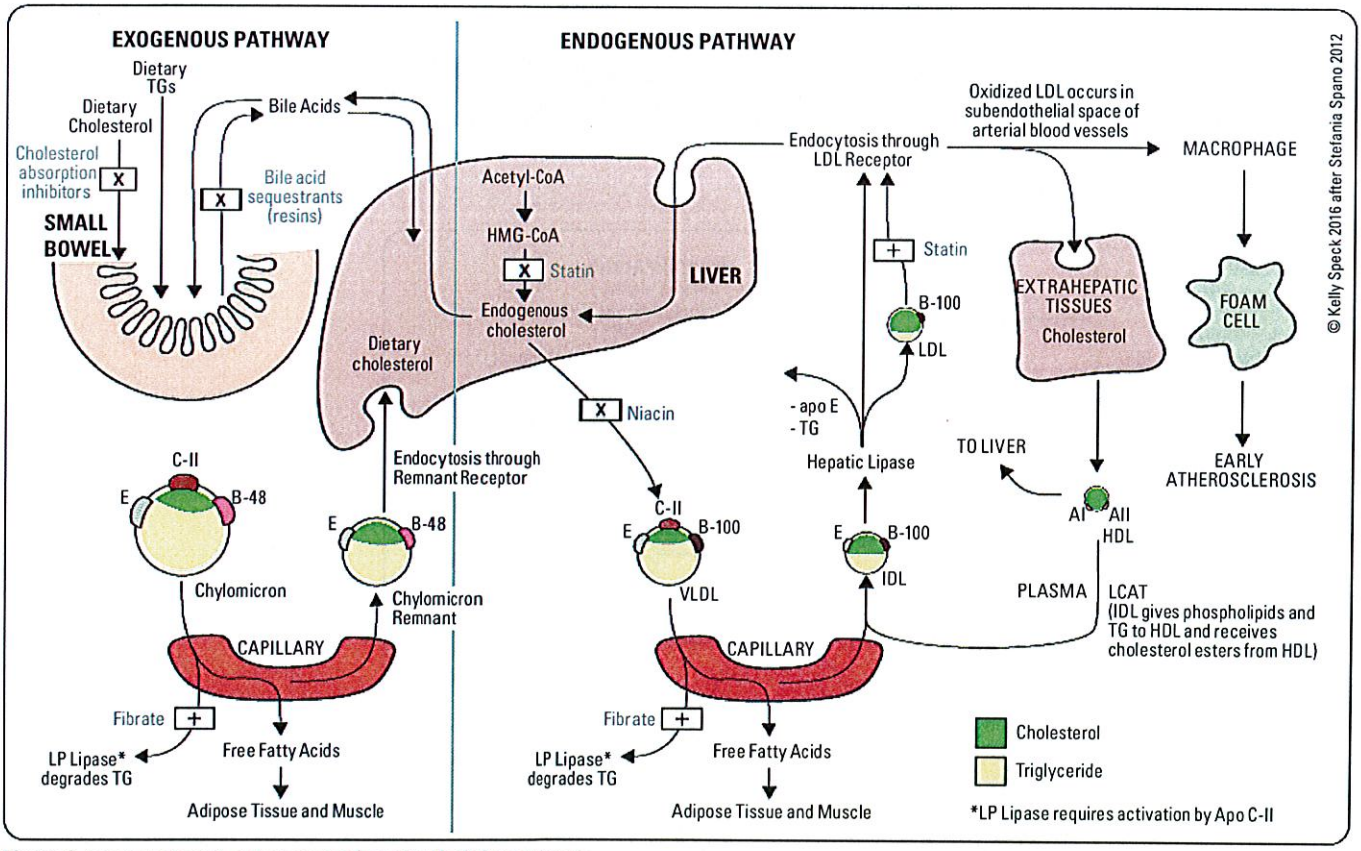


Figure 2. Exogenous and endogenous biosynthetic lipid pathways

Primary Dyslipidemias (rare)

Definition

- caused by a genetic defect(s) in lipid metabolism

Table 2. Primary Dyslipidemias

Condition	Main Lab Abnormality	Mechanism	Clinical Features	Treatment
Familial Hypercholesterolemia	↑ Total cholesterol ↑ LDL cholesterol	Genetic defect in LDLR (most common), PCSK9, or ApoB An autosomal dominant condition that can be homozygous or heterozygous Impacts liver's ability to clear LDL from the circulation	Tendinous xanthomatosis (achilles, patellar, and extensor tendons of hand) Arcus cornealis Xanthelasmata Heterozygotes: premature CAD, 50% risk of MI in men by age 30 Homozygotes: manifest CAD and other vascular disease early in childhood which can be fatal (in <20 y/o)	Maximally tolerated statin as initial drug therapy, addition of second drug (ezetimibe and/or PCSK9 inhibitor) as second line, third line for homozygotes is portacaval shunt or LDL apheresis; potential liver transplant Refer to lipid specialist in drug-resistant hypercholesterolemia
Familial Combined Hyperlipidemia	↑ ApoB ↑ TGs ↑ LDL	Increased production of ApoB-100-containing lipoproteins from the liver	Premature coronary heart disease, xanthelasma, and obesity	Statins as initial drug therapy Addition of ezetimibe and/or PCSK9 inhibitor if LDL lowering is not achieved. May consider fibrate if elevated TG
Polygenic Familial Hypercholesterolemia	↑ LDL	Mild defects in multiple genes responsible for LDL metabolism: LDL-R, ApoB, ApoE4	Higher risk of cardiovascular disease similar to familial hypercholesterolemia for patients older than 40	Statins as first line Use ezetimibe, bile acid sequestrants, PCSK9 inhibitor, or nicotinic acid as alternatives (if not tolerated) or in addition
Hereditary Chylomicronemia **Familial lipoprotein lipase deficiency** (e.g. Familial Hypertriglyceridemia/type IV familial dyslipidemia) **ApoC2 deficiency**	↑ TG from excess chylomicron particles	Lipoprotein lipase deficiency: prevents proper digestion and storage of fats leading to massive accumulation of triglyceride rich chylomicron particles $ApoC_2$ deficiency: prevents activation of lipoprotein lipase leading to massive accumulation of triglyceride rich chylomicron particles	Presents at infancy (LPL), adolescence to adulthood ($ApoC_2$) Abdominal complaints (pain, hepatosplenomegaly, pancreatitis) Lipemia retinalis Eruptive xanthomata	<10-15% of calories from fat Supplement with essential fatty acids, fat-soluble vitamins Plasmapheresis may help individuals with $ApoC_2$ mutation
Familial Hypoalphalipoproteinemia	↓ HDL cholesterol	Autosomal dominant inheritance of a mutation in the ABCA1 or the $ApoA_1$ gene	Premature atherosclerosis Cerebrovascular disease	Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present
Tangier Disease	↓ HDL cholesterol	Autosomal recessive inheritance of mutations in the ABCA1 gene Impaired HDL-mediated cholesterol efflux from macrophages and impaired intracellular lipid trafficking	Mild hypertriglyceridemia Neuropathy Enlarged, orange-coloured tonsils Premature atherosclerosis Splenomegaly Hepatomegaly Corneal clouding T2DM	Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present

Secondary Dyslipidemias

Definition

- caused by acquired medical conditions or lifestyle factors that affect lipid metabolism

Table 3. Etiology of Secondary Dyslipidemias

Hypercholesterolemia	Low HDL	Hypertriglyceridemia
Endocrine: hypothyroidism (small dense LDL with T2DM and obesity, with normal LDL level)	**Endocrine:** obesity/metabolic syndrome, DM	**Endocrine:** obesity/metabolic syndrome, DM
Renal: nephrotic syndrome, CKD	**Drugs:** β-blockers, anabolic steroids	**Renal:** nephrotic syndrome, CKD
Immunologic: monoclonal gammopathy	**Other:** acute infections, inflammatory conditions	**Drugs:** corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
Hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)		**Lifestyle:** alcohol, high carbohydrate/high fat diet
Nutritional: anorexia nervosa		**Other:** pregnancy
Drugs: cyclosporin, carbamazepine, steroids		
Lifestyle: smoking, obesity		

Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD
- increased HDL is associated with decreased CVD and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women

Screening

- screen men and women ≥40 yr or post-menopausal women
- if the following risk factors are present, screen at any age:
  - DM
  - current cigarette smoking or COPD
  - HTN (sBP >140, dBP >90), hypertensive diseases of pregnancy
  - obesity (BMI ≥30 kg/m^2)
  - family history of premature CVD or dyslipidemia



Familial Hypercholesterolemia and Cardiovascular Risk Calculators

Risk calculators such as Framingham and SCORE do not apply to patients with familial hypercholesterolemia

Consider all adults with familial hypercholesterolemia as "high-risk"



Treatment Effect

- Each 1.0 mmol/L decrease in LDL corresponds to approximately 20-25% relative risk reduction in cardiovascular disease
- Statins lower LDL by about 30-40%
- Ezetimibe lowers LDL by about 18%
- PCSK9 inhibitors lowers LDL by about 50%



6% Rule

If the dose of a statin is doubled, there is approximately a 6% increase in the LDL lowering efficacy

- clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
- clinical or radiological evidence of AAA
- clinical evidence of atherosclerosis
- inflammatory disease (rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease)
- HIV infection on highly active antiretroviral therapy (HAART)
- CKD (estimated GFR <60 mL/min/1.73 m²)
- erectile dysfunction
- high-risk ethnicity: South Asian, Indigenous peoples

• screen children with a family history of hypercholesterolemia or chylomicronemia
• components of screening:
  - history and physical examination, lipid panel (total cholesterol, LDL-C, HDL-cholesterol, TG), non-HDL cholesterol, BG, eGFR
  - optional: urine ACR, ApoB
• ApoB
  - each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of ApoB
  - serum (ApoB) reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high-risk patients and those with metabolic syndrome
• LP(a) levels may help stratify those at intermediate risk, but is not recommended for routine measurement (only measured once in a patient's lifetime)
• coronary artery calcium (CAC) may help stratify those at intermediate risk
• CRP levels
  - highly sensitive acute phase reactant (non-specific)
  - may be clinically useful to identify those at a higher risk of CVD than predicted by the global risk assessment

For Statin Follow-Up
- Liver enzymes and lipid profile: liver enzymes measured at the beginning of treatment, then once after therapy initiated. Lipids (once stabilized) measured annually. Order both if patient complains of jaundice, right upper quadrant pain, dark urine
- CK at baseline and if patient complains of myalgia
- Discontinue statin if CK >10x upper limit of normal or patient has persistent myalgia

See Landmark Endocrinology Trials for more information on the JUPITER trial. It details the effects of statin treatment on cardiovascular events in patients with elevated high-sensitivity CRP levels.

CVD Risk Assessment

• Framingham Risk Score (FRS): 10 yr risk of major CVD event. Calculated based on gender, age, total cholesterol, HDL-cholesterol, sBP, and smoking (≥20%: high-risk; 10-19.9%: moderate risk; <10%: low-risk)
• Reynolds Risk Score: 10 yr risk of major CVD event. Calculated based on age, sBP, total cholesterol, HDL-cholesterol, high sensitivity CRP, family history of MI

Treatment of Dyslipidemias

Approach to Treatment

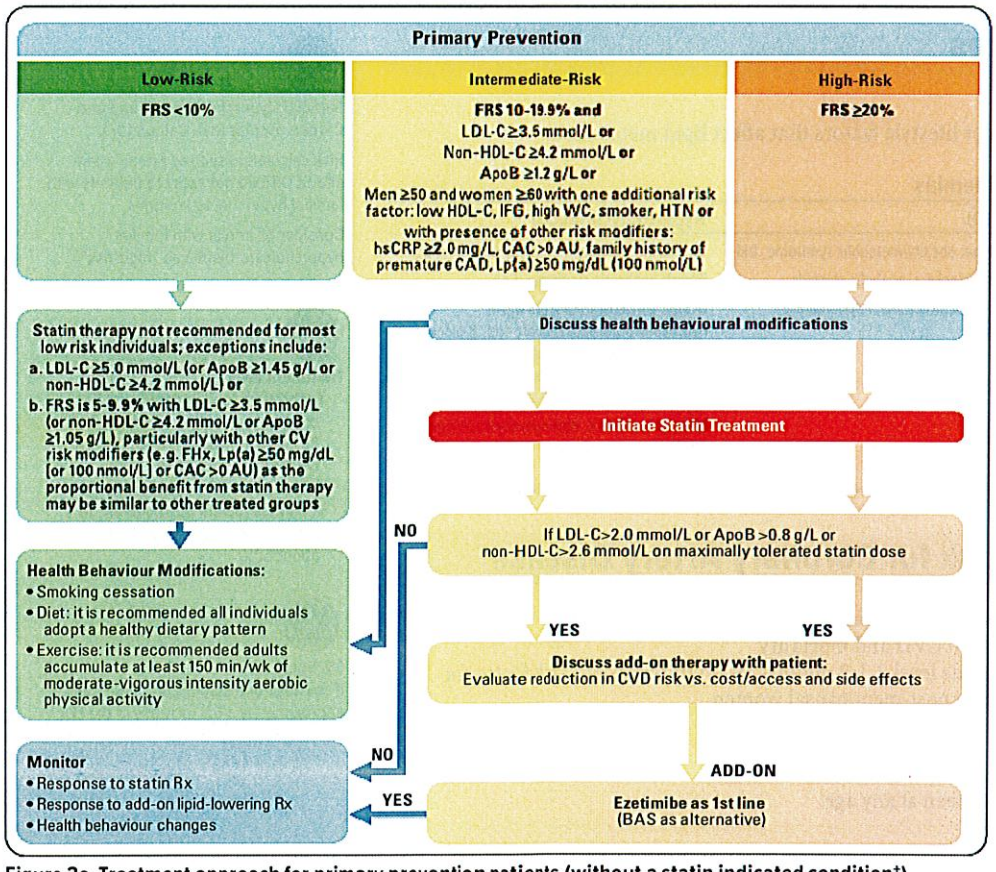


Figure 3a. Treatment approach for primary prevention patients (without a statin indicated condition‡)
Adapted from 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.

2021 Canadian Cardiovascular Society Guidelines on the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult
Can J Cardiol 2021; S0828-282X(21)00165-3
- Patients with clinical atherosclerosis, AAA, LDL-C ≥5.0 mmol/L, and most with diabetes or CKD should be started on statin therapy.
- Icosapent ethyl should be used to decrease the risk of CV events in people with ASCVD or with diabetes and >1 CVD risk factor who have TG 1.5-5.6 mmol/L even if on maximally tolerated statin.
- Lipid/lipoprotein screening is recommended in patients >40 yr or at any age for those at increased risk.
- Non-HDL cholesterol or ApoB are preferred to LDL-C as lipid parameters for screening in patients with TG >1.5 mmol/L.
- LP(a) should be measured once in a person's lifetime as part of initial lipid screening to assess cardiovascular risk.
- Lipid-lowering therapy should be intensified with ezetimibe and/or PCSK9 inhibitors in patients with LDL-C remaining ≥1.8 mmol/L (or non-HDL cholesterol ≥2.4 mmol/L or ApoB ≥0.7 g/L) on a maximally tolerated statin dose.

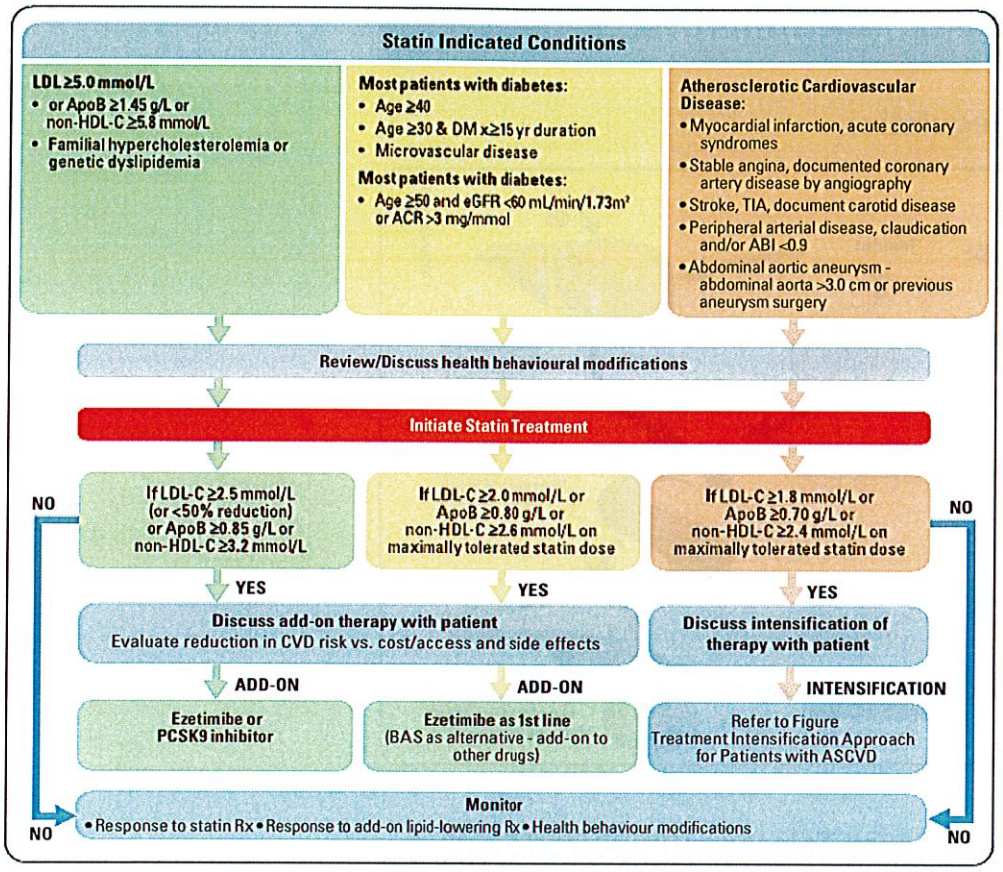


Figure 3b. Treatment approach for patients with a statin indicated condition
Adapted from 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.

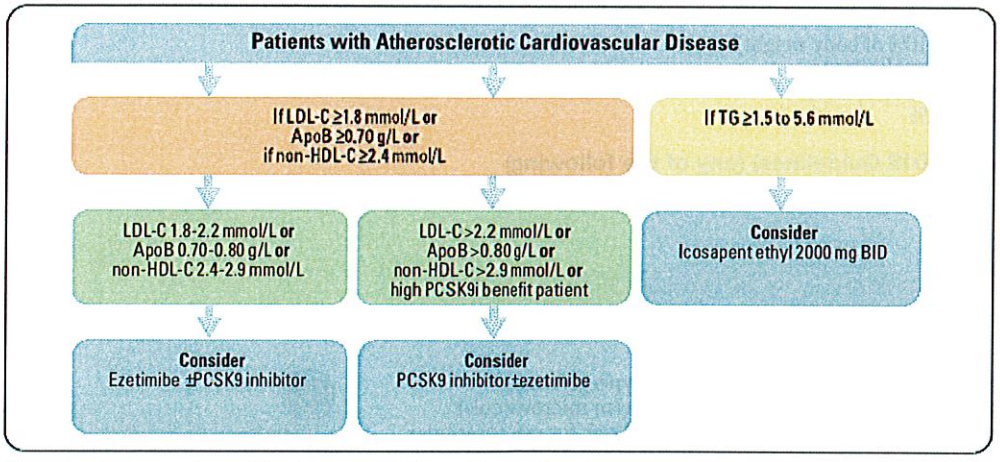


Figure 3c. Treatment intensification approach for patients with atherosclerotic cardiovascular disease (ASCVD)
Adapted from 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.



See Landmark Endocrinology Trials table for more information on the REDUCE-IT trial. This study investigates the use of icosapent ethyl to reduce cardiovascular events.



Effects of Icosapent Ethyl and a Mineral Oil Comparator on Biomarkers - A REDUCE-IT Substudy
Circulation 2022; 146(5):372-9
Purpose: To investigate if treatment assignment in the REDUCE-IT trial influenced various biomarkers related to the risk of atherosclerosis.
Methods: Serum levels of interleukin-1β, interleukin-6, hs-CRP, oxidized LDL, homocysteine, LP(a), and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels were measured at baseline, 12 mo, 24 mo, and end-of-study visit.
Results: Treatment with icosapent ethyl had minimal effect on LP(a), homocysteine, oxidized LDL, interleukin-6, Lp-PLA2 activity, interleukin-1β, hs-CRP, or LDL cholesterol levels at 12 mo. Conversely, patients treated with mineral oil comparator showed increases in these biomarkers.
Conclusions: In the REDUCE-IT study, treatment with icosapent ethyl had minimal impact on several biomarkers linked to atherosclerotic disease, while levels increased in participants treated with mineral oil. Implications of these findings on the interpretation of overall risk reductions in clinical events observed in REDUCE-IT are uncertain.

Disorders of Glucose Metabolism

Overview of Glucose Regulation

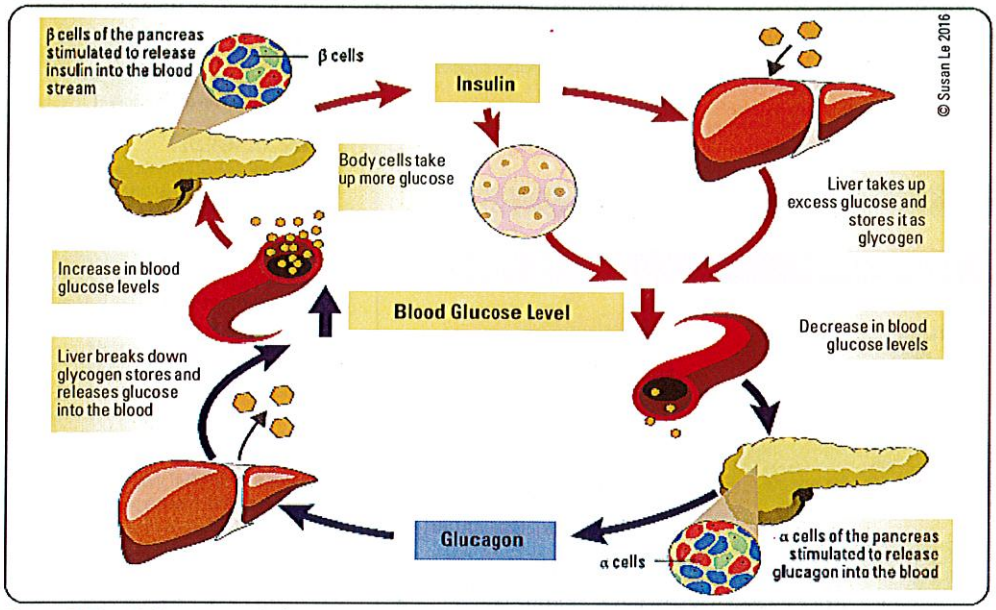


Figure 4. Blood glucose regulation

Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)

- 1-5% per yr go on to develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance (5-10% of body weight)
- increased risk of developing macrovascular complications
- lifestyle modifications decrease progression to DM by 58%
- metformin decreases progression to DM by 31%

Diagnostic Criteria (Diabetes Canada 2018 Guidelines) (any of the following)

- IFG: FPG 6.1-6.9 mmol/L
- IGT: 2 h 75 g OGTT 7.8-11.0 mmol/L
- A1c: 6.0-6.4%

Diabetes Mellitus

Definition

- DM is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia
- chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys, and nerves, as well as an increased risk for macrovascular complications such as CVD, stroke, and peripheral vascular disease. Diabetes also increases the risk of heart failure

Diagnostic Criteria (as per Diabetes Canada 2018 Clinical Practice Guidelines)

- any one of the following is diagnostic:

Table 4. Diagnosis of Diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 h
or
A1c ≥6.5% (in adults)
Not for diagnosis of suspected T1DM, children, adolescents, or pregnant women
or
2hPG in a 75 g OGTT ≥11.1 mmol/L
or
Random PG ≥11.1 mmol/L
Random = any time of the day, without regard to the interval since last meal

- in the presence of hyperglycemia symptoms (polyuria, polydipsia, polyphagia, weight loss, blurry vision), a confirmatory test is not required
- in the absence of hyperglycemia symptoms, a repeat confirmatory test (FPG, A1c, 2hPG in a 75 g OGTT) on another day is required for diagnosis of diabetes

See Landmark Endocrinology Trials table for more information on the 4T trial. It details the efficacy of complex insulin regimen for patients with T2DM.

See Landmark Endocrinology Trials table for more information on the UKPDS trial. It compares the safety and efficacy of intensive blood-glucose control with sulphonylurea or insulin vs. conventional treatment on the risk of complications in T2DM.

See Landmark Endocrinology Trials table for more information on the DCCT trial. It details the use of intensive insulin injection therapy for the treatment of T1DM in patients with no cardiovascular history or severe diabetic complications.

Etiology and Pathophysiology

Table 5. Etiologic Classification of Diabetes Mellitus

I. T1DM immune-mediated or idiopathic β cell destruction, usually leading to absolute insulin deficiency (includes latent autoimmune diabetes in adults (LADA))

II. T2DM occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced

III. Other Specific Causes of DM

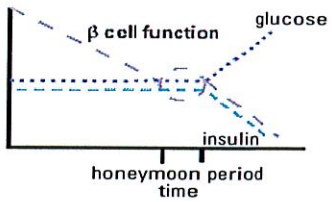
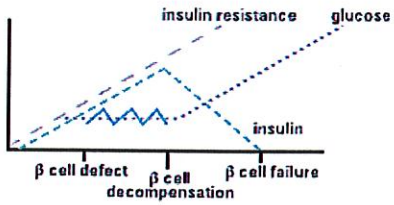
a. Genetic defects of β cell function (e.g. Maturity-Onset Diabetes of the Young (MODY; also known as monogenic diabetes)) or insulin action
b. Diseases of the exocrine pancreas:
Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis ("bronze diabetes")
c. Endocrinopathies:
Acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism
d. Drug-induced:
Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, antipsychotics
e. Infections:
Congenital rubella, CMV, coxsackie
f. Genetic syndromes associated with DM:
Down's syndrome, Klinefelter's syndrome, Turner's syndrome

IV. Gestational Diabetes Mellitus (see Obstetrics, OB28)

Diabetes Canada 2018 Clinical Practice Guidelines

	Target
A1c	<7.0% (most adults)
Fasting plasma glucose	4-7 mmol/L
2h post-prandial glucose	5-10 mmol/L 5-8 mmol/L if not meeting target A1c and can be safely achieved
Lipids	LDL <2.0 or 50%
Blood pressure	<130/80

Table 6. Comparison of Type 1 and Type 2 Diabetes Mellitus

	Type 1	Type 2
Onset	Usually <30 yr of age	Usually >40 yr of age Increasing incidence in pediatric population 2° to obesity
Epidemiology	Traditionally more common in European populations Less common in Asian, Hispanic, Indigenous, and Black populations Accounts for 5-10% of all DM	More common in Black, Hispanic, Indigenous, and Asian populations Accounts for >90% of all DM
Etiology	Autoimmune or idiopathic	Complex and multifactorial
Genetics	Monozygotic twin concordance is 30-40% Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of T1DM Certain DQ alleles also confer a risk	Greater heritability than T1DM Monozygotic twin concordance is 70-90% Polygenic Non-HLA associated
Pathophysiology	Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds) Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction 80% of β cell mass is destroyed before features of DM present	Impairment of insulin secretion, excess glucose production by the liver, insulin resistance in fat and muscle, impaired renal handling of glucose (SGLT2i), impaired incretin activity (decreased insulin production, excess glucagon production, enhanced carbohydrate absorption in the gut and increased appetite from the hypothalamus)
Natural History		
	After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin Once these cells are destroyed, there is complete insulin deficiency	Early on, glucose tolerance remains normal despite insulin resistance as β cells compensate with increased insulin production As insulin resistance and compensatory hyperinsulinemia continue, the β cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and DM
Circulating Autoantibodies	Islet cell Ab present in up to 60-85% Most common islet cell Ab is against glutamic acid decarboxylase (GAD) Up to 60% have Ab against insulin	<10%
Risk Factors	Personal history of other autoimmune diseases including Graves' disease, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia Family history of autoimmune diseases	Age >40 yr Schizophrenia Abdominal obesity/overweight Fatty liver First-degree relative with DM Hyperuricemia Race/ethnicity (Black, Indigenous, Hispanic, Asian-American, Pacific Islander) Hx of IGT or IFG HTN Dyslipidemia Medications e.g. 2nd generation antipsychotics PCOS Hx of gestational DM or macrosomic baby (>9 lb or >4 kg)
Body Habitus	Normal to thin	Typically overweight with increased central obesity
Treatment	Insulin	Lifestyle modification Non-insulin antihyperglycemic agents - unless contraindicated, metformin should be the initial antihyperglycemic agent of choice. Additional agents to be selected on the basis of clinically relevant issues, such as CV risk, eGFR, glucose-lowering effectiveness, risk of hypoglycemia, and effect on body weight Insulin therapy
Acute Complications	DKA	HHS DKA
Screening	Subclinical prodrome can be detected in first and second-degree relatives of those with T1DM by the presence of pancreatic islet autoantibodies	Screen individuals with risk factors

Treatment of Diabetes

Glycemic Targets

- A1c reflects glycemic control over 3 mo and is a measure of long-term glycemic control
- A1c is recommended to be measured once every 3-6 mo and personalized A1c targets should be set for patients based on their frailty or functional dependence and life expectancy
- therapy for most individuals living with T1DM or T2DM (especially younger patients) should be targeted to achieve an A1c ≤7.0% in order to reduce the risk of microvascular and, if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, A1c <6.5%, may be targeted to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia
- less stringent A1c targets (7.1-8.5%) may be more appropriate in patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to achieve an A1c <7.0% despite intensified basal and bolus insulin therapy
- there may be harm associated with strategy to target A1c <6.0% (see *ACCORD Trial, E62*)
- A1c can be slightly increased in iron deficiency, vitamin B12 deficiency, alcoholism, and CKD, independent of glycemic status
- A1c can be slightly decreased in chronic liver disease, reticulocytosis, ingestion of ASA, vitamin C or E, and splenomegaly, independent of glycemic status
- timing and frequency of self-monitored blood glucose is determined by the type of diabetes, treatment, and the individual's capacity to use the information
- most people with type 1 or type 2 diabetes should aim for time in range (glucose 3.9-10 mmol/l) >70%, time above range <25% and time below range <4%
- continuous glucose monitoring devices may be suggested for some people living with diabetes to optimize their diabetes self-management

Diet

- nutritional therapy can reduce A1c by 1-2%
- it is recommended to intake 45-60% carbohydrates, 15-20% protein, and <35% fats as a percentage of total daily energy
- it is recommended to intake <7% of saturated fats and <10% of polyunsaturated fats as a percentage of total daily calories
- it is recommended to replace high-glycemic-index carbohydrates with low-glycemic-index carbohydrates and increase fibre intake
- limit sodium, alcohol, and caffeine intake
- people with diabetes should adopt dietary patterns that result in the greatest adherence based on their values and preferences
- type 1: carbohydrate counting is used to titrate prandial insulin dose
- type 2: weight reduction to help control blood glucose levels

Lifestyle

- losing 5-10% of the initial body weight can improve insulin sensitivity, glycemic control, hypertension, and dyslipidemia in people with T2DM
- regular physical exercise can improve insulin sensitivity, lower lipid concentrations, and control blood pressure. At least 150 min per wk of moderate-vigorous aerobic exercise and at least 2 sessions per wk of resistance exercise are recommended
- smoking cessation, referral to diabetes education clinic, psychosocial support

Medical Treatment: Non-Insulin Antihyperglycemic Agents (T2DM)

- initiate non-insulin antihyperglycemic therapy (generally metformin first line) within 3 mo if lifestyle management does not result in adequate glycemic control
- if the initial A1c value is more than 1.5% higher than the patient's personalized A1c target, initiate pharmacologic therapy with metformin immediately, and consider insulin or a combination of therapies
- if presenting in metabolic decompensation, begin with insulin therapy immediately
- adjust dose or add additional pharmacologic therapy in a timely fashion to achieve target A1c within 3-6 mo of diagnosis
- see *Common Medications, E57* for details on antihyperglycemic agents

Medical Treatment: Insulin

- used for T1DM at onset, may be used in T2DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- basal insulin: to control blood sugar (produced by liver) during periods of fasting; slow onset of action, long-acting
- bolus insulin: required to dispose of glucose from a meal or BG correction; rapid onset of action, short-acting
- estimated total daily insulin requirement: often start with 0.3-0.5 units/kg/d (see *Table 7, E12*)



Who should receive statins (regardless of LDL-C level)

- Clinical CVD
- Age >40 yr
- Microvascular complications or
- Diabetes >15 yr duration and age >30 yr
- Warrants therapy based on the 2016 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia

Who should receive ACEI/ARB (regardless of baseline BP)

- Clinical CVD
- Age >55 years with an additional CV risk factor or end organ damage (albuminuria, retinopathy, left ventricular hypertrophy)
- Microvascular complications



ABCDES of Diabetes Care

A1c targets (<7.0%)
Blood pressure (<130/80)
Cholesterol (LDL-C <2.0 mmol/L)
Drugs for CVD risk reduction
Exercise goals and healthy eating
Smoking cessation
Screening for complications
Stress management



Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care
NEJM 2018;379:547-556
Purpose: To determine if a closed-loop delivery system (artificial pancreas) can improve glycemic control in patients with T2DM receiving noncritical care.
Methods: Patients (n=136) received either closed-loop insulin delivery or conventional subcutaneous insulin therapy. The percentage of time the sensor glucose measurement was within 5.6 to 10.0 mmol/L was measured.
Results: Closed-loop insulin delivery was more effective at maintaining glucose within the target range (95% CI: 18.6-30.0; P<0.001). Patients on closed-loop insulin therapy had lower mean glucose levels (P<0.001). There was no difference in duration of hypoglycemia or amount of insulin delivered between groups.
Conclusions: The use of an automated, closed-loop insulin-delivery system (artificial pancreas) resulted in significantly better glycemic control among inpatients with T2DM receiving non-critical care.



Closed-loop insulin delivery using an artificial pancreas has also shown promise in patients with T1DM (NEJM 2019;381:1707-17).



See Landmark Endocrinology Trials table for more information on the ACCORD trial. It details the effects of intensive glucose control in patients with T2DM and cardiovascular risk factors.



See Landmark Endocrinology Trials table for more information on the ACCORD Trial – Blood Pressure Control. It details the effects of intensive blood pressure control for patients with T2DM.

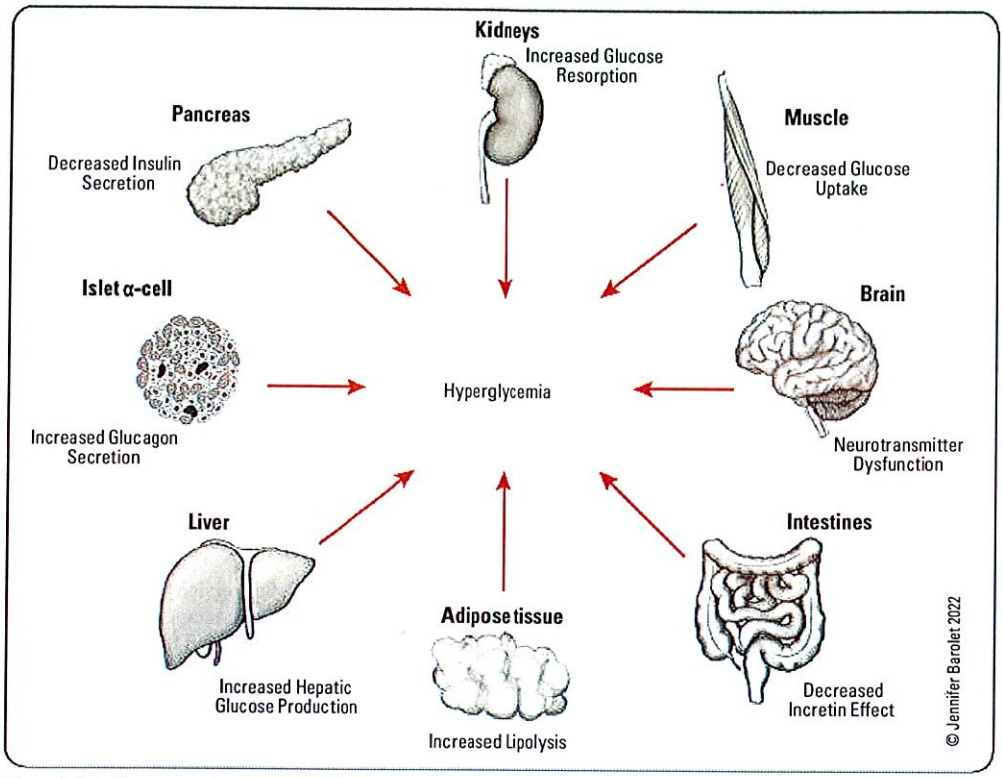
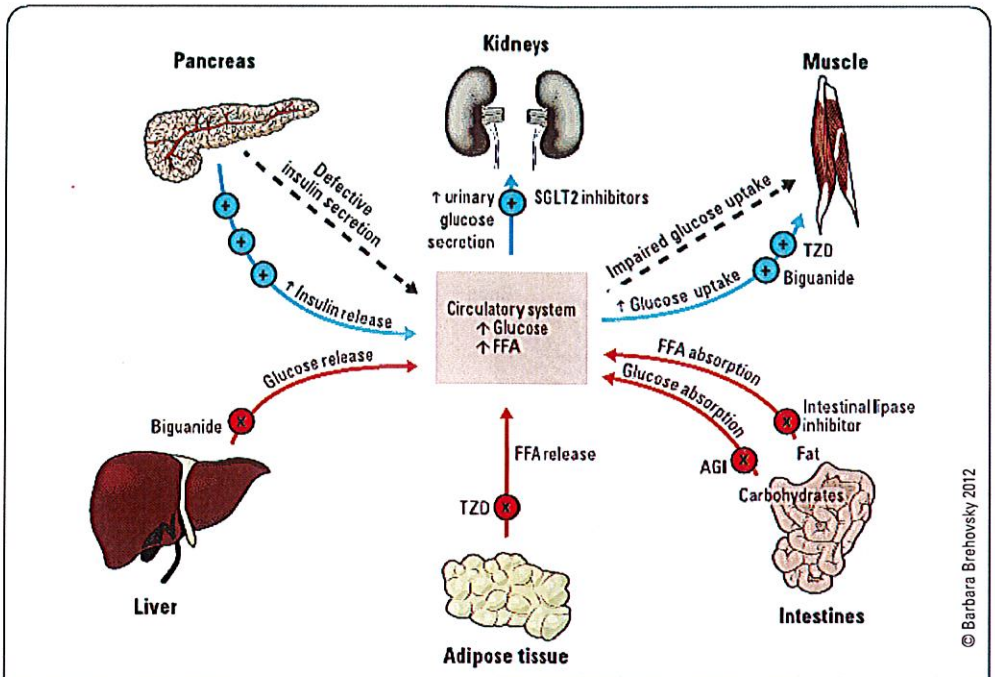


Figure 5. Ominous octet: factors leading to hyperglycemia

See Landmark Endocrinology Trials table for more information on the ACCORD Trial – Combination Lipid Therapy. It details the effects of combinational lipid therapy for patients with T2DM.

See Landmark Endocrinology Trials table for more information on the PREDIMED trial. It details the effects of a Mediterranean diet on reducing major cardiovascular events in patients with T2DM or other high cardiovascular risk factors.



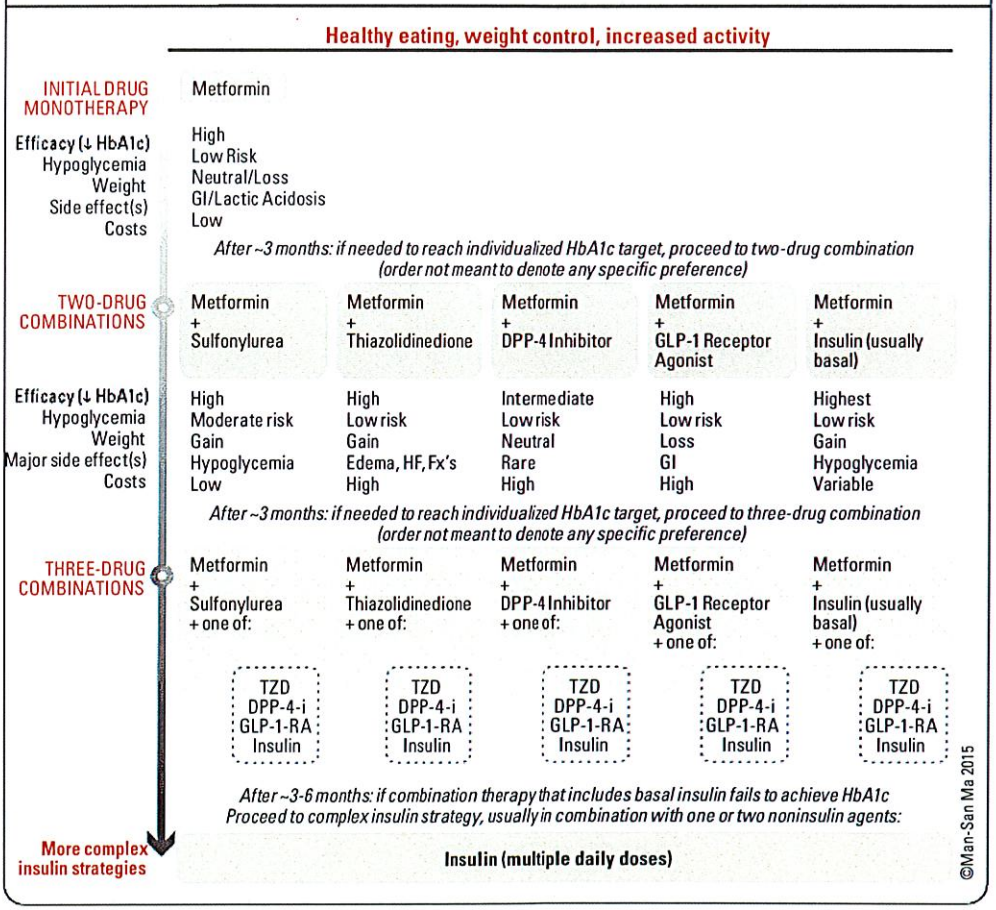


Figure 6. Management of hyperglycemia in T2DM

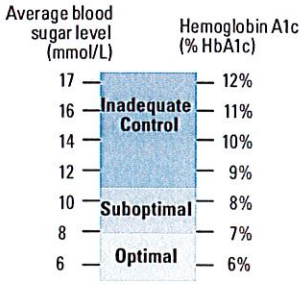
Adapted from Canadian Journal of Diabetes, Volume 42, Lipscombe L, Booth Gillian, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, Page S92, Copyright (2020), with permission from Elsevier

Sick Day Management

If patient is ill and is unable to maintain adequate fluid intake, or has an acute decline in renal function, they should hold the following medications:

SAD MANS
Sulfonylureas
ACEIs
Diuretics and direct renin inhibitors
Metformin
ARBs
NSAIDs
SGLT2i

Conversion Chart for Percentage HbA1c to Average Blood Sugar Control



Conversion chart adapted from Nathan DM, et al. The clinical information value of a glycosylated hemoglobin assay. NEJM 1984;310:341-346

The 8 I's Precipitating DKA
Infection
Ischemia or Infarction
Iatrogenic (glucocorticoids)
Intoxication
Insulin missed
Initial presentation
Intra-abdominal process (e.g. pancreatitis, cholecystitis)
Intraoperative/perioperative stress

Table 7. Available Insulin Formulations

Insulin Type (trade name)	Onset	Peak	Duration
PRANDIAL (BOLUS) INSULINS			
Rapid-acting insulin analogues			
Insulin aspart (NovoRapid®)	10-15 min	1-1.5 h	3-5 h
Insulin faster aspart (Fiasp®)	4 min	1 h	3-4 h
Insulin lispro (Humalog®, Humalog 200 units/mL)	10-15 min	1-2 h	3.5-4.75 h
Insulin glulisine (Apidra®)	10-15 min	1-1.5 h	3-5 h
Short-acting insulins	30 min	2-3 h	6.5 h
Humulin R®			
Novolin Toronto®			
BASAL INSULINS			
Intermediate-acting	1-3 h	5-8 h	Up to 18 h
Humulin N®			
Novolin NPH®			
Long-acting basal insulin analogues			
Insulin detemir (Levemir®)	90 min	Not applicable	Up to 24 h (detemir 16-24 h)
Insulin glargine 100 units/mL (Lantus®/Basaglar®)	90 min		Up to 24 h (glargine 24 h)
Insulin glargine 300 units/mL (Toujeo®)	Up to 6 h		Up to 30 h
Insulin glargine (Basaglar®)	90 min		Up to 24 h (glargine 24 h)
Insulin degludec (Tresiba®)	60 min		Ultralong acting (42 h)
PRE-MIXED INSULINS			
Premixed regular insulin – NPH	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Humulin 30/70®			
Novolin 30/70®			
Premixed insulin analogues			
Biphasic insulin aspart (NovoMix 30®)			
Insulin lispro/lispro protamine (Humulin 30/70, Novolin 30/70, Novomix 30 and Humalog Mix 25)			

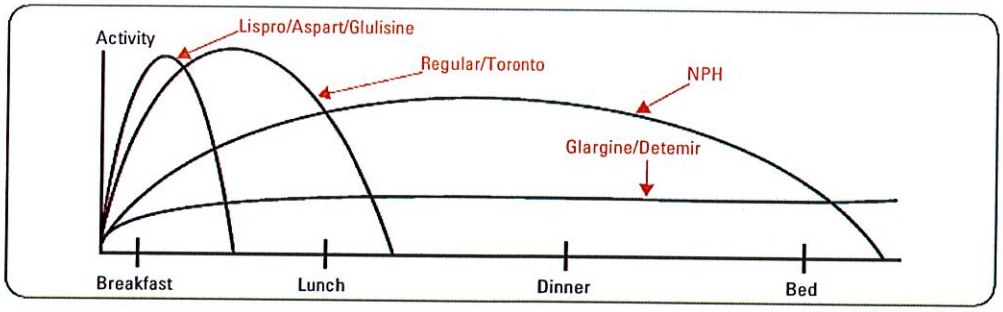


Figure 7. Duration of activity of different insulins

Table 8. Insulin Regimens for T2DM and T1DM

	Regimen	Administration
T1DM	Basal-bolus (multiple daily injections (MDI))	Estimated total insulin requirement is 0.5-0.7 U/kg 40% is given as basal insulin at bedtime 20% is given as bolus insulin before breakfast, lunch, and dinner
	Premixed	Estimated total insulin requirement is 0.5-0.7 U/kg 2/3 dose is given as pre-mixed insulin before breakfast 1/3 dose is given as pre-mixed insulin before dinner
T2DM	Non-insulin antihyperglycemic agent + basal insulin	Titrate up by 1 unit until FPG <7.0 mmol/L

*Bolus insulin: Aspart, Glulisine, Lispro; *Basal insulin: Glargine, Detemir, NPH; *Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, and Humalog Mix2

Table 9. Titrating Insulin Doses

Hyperglycemic Reading	Insulin Correction
High AM sugar	Increase bedtime basal insulin
High lunch sugar	Increase AM rapid/regular insulin
High supper sugar	Increase lunch rapid/regular insulin or increase AM basal insulin
High bedtime sugar	Increase supper rapid/regular insulin

Insulin Dose Schedules

Table 10. Insulin Titration and Titration Suggestions for T2DM (as per Diabetes Canada 2018 Clinical Practice Guidelines)

Basal Insulin Only – Add-on to Anti-hyperglycemic Agents	
See above summary for A1c, BG targets Most patients will need 40-50 units/d to achieve target but there is no maximum dose Start at a low dose of 10 U at bedtime (lower for lean patients <50 kg) Titrate dose accordingly until fasting BG target is achieved (see CDA guidelines for appropriate titration) If fasting hypoglycemia, dose of bedtime basal should be reduced If daytime hypoglycemia, reduce dose of oral antihyperglycemic agents (especially secretagogues)	Dosing and Titration Example Starting dose – 10 U at bedtime Increase dose by 1 U every 1 night until fasting BG has reached target of 4-7 mmol/L
Basal-Bolus Insulins	
When addition of basal insulin to anti-hyperglycemic agents is insufficient to reach target BG, bolus (prandial) insulin should be added before meals Option exists to only add bolus insulin to the meal with the highest postprandial BG as a starting point Insulin secretagogues typically stopped when bolus (prandial) insulin added; metformin is continued Maintain the basal dose and add bolus insulin with each meal at a dose equivalent to 10% of basal dose Total Daily Insulin (TDI) = 0.3-0.5 U/kg; 40% TDI = basal, 20% TDI = prandial (bolus) prior to each meal Adjust basal insulin to achieve target fasting BG, bolus insulin to achieve postprandial BG levels (5-10 mmol/L), or preprandial BG levels for subsequent meal (4-7 mmol/L)	Dosing and Titration Example TDI = 0.5 U/kg: 0.5 x 100 kg = 50 U Basal insulin = 40% of TDI 40% x 50 U = 20 U; basal bedtime = 20 U Bolus insulin = 60% of TDI 60% x 50 U = 30 U; 10 U dosed with each meal
Premixed Insulin Before Breakfast and Before Dinner	
Target fasting and pre-dinner BG levels of 4-7 mmol/L Most patients with T2DM need 40-50 U BID to achieve target, but no maximum dose Start at a low dose of 5-10 U BID (before breakfast and before dinner) Patients can self-titrate by increasing insulin dose by 1 U/d until pre-dinner (breakfast dose) or fasting BG (dinner dose) at target Continue metformin and consider stopping secretagogue	Dosing and Titration Example 10 U before breakfast, 10 U before dinner Increase breakfast dose by 1 U/d until pre-dinner BG has reached target Increase dinner dose by 1 U/d until fasting BG has reached target

- Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD) = change in blood glucose per unit of insulin
  - BG <4 mmol/L: call physician and give 15 g of rapid-acting carbohydrates and recheck in 15 min
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

Insulin Pump Therapy: Continuous Subcutaneous Insulin Infusion (CSII)

- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine, or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus based on carbohydrate:insulin ratios
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected or pump malfunctions
- coverage for insulin pumps for individuals with T1DM varies by province

Acute Complications

Table 11. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
Pathophysiology	Usually occurs in T1DM Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH) Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise) Unopposed hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na^+ (water shift to ECF causing pseudohyponatremia) Fat mobilization → ↑ FFA → ketoacids → metabolic acidosis Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria Total body K^+ depletion but serum K^+ may be normal or elevated, 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality	Occurs in T2DM Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglucagonemia and hepatic glucose production Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis Characterized by hyperglycemia, hyperosmolality, and dehydration without ketosis More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden patients Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma
Clinical Features	Hyperglycemia (polyuria, polydipsia, weakness) Acidosis (air hunger, nausea, vomiting, abdominal pain, Kussmaul respirations, acetone-odoured breath) Precipitating conditions (insulin omission, new diagnosis of diabetes, infection, MI, thyrotoxicosis, drugs)	Onset is insidious → preceded by weakness, polyuria, polydipsia History of decreased fluid intake History of ingesting large amounts of glucose containing fluids Dehydration (orthostatic changes) ↓ LOC → lethargy, confusion, comatose due to high serum osmolality Kussmaul respirations are absent unless the underlying precipitant has also caused a metabolic acidosis
Serum	↑ BG (typically 14-55 mmol/L, ↓ Na^+ (2° to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in Na^+ by 3 mmol/L) Normal or ↑ K^+, ↓ HCO_3^-, ↑ BUN, ↑ Cr, ketonemia, ↓ PO_4^{3-} ↑ osmolality corrected sodium = current sodium + [0.3 x (current glucose -5)] Be aware of possible euglycemic DKA (with near normal sugars) in pregnancy and with those who use SGLT2 inhibitors	↑ BG (typically 44.4-133.2 mmol/L) In mild dehydration, may have hyponatremia (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in Na^+ by 3 mmol/L) – if dehydration progresses, may get hypernatremia Ketosis usually absent or mild if starvation occurs ↑ osmolality

Table 11. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
ABG	Anion gap metabolic acidosis with possible 2° respiratory alkalosis If severe vomiting/dehydration there may also be a metabolic alkalosis	Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)
Urine	+ve for glucose and ketones	-ve for ketones unless there is starvation ketosis Glycosuria
Treatment	ABCs are first priority Monitor degree of ketoacidosis with AG, not BG or serum ketone level NOTE: AG is the most important endpoint used to monitor the resolution of the metabolic acidosis Rehydration – 500 mL/h x4 h, then 250 mL/h x4 h NS if mild-moderate deficit, 1-2 L/h NS if severe deficit (shock) – Switch to 0.45% NaCl once euvolemic (continue NS if corrected [Na^+] is low or rate of fall of plasma osmolality ≥3 mosm/kg/h) – Once BG reaches 14.0 mmol/L add D5W or D10W to maintain BG of 12-14 mmol/L Insulin therapy – Critical to resolve acidosis, not hyperglycemia – Do not use with hypokalemia (see below), until serum K^+ is corrected to >3.3 mmol/L – Maintain on 0.1 U/kg/h insulin R infusion – Check serum glucose hourly **K^+ replacement** – With insulin administration, hypokalemia may develop – If serum K^+ <3.3 mmol/L, give 40 mEq/L K^+ replacement and hold insulin until [K^+] ≥3.3mmol/L – When K^+ 3.3-5.0 mmol/L add KCl 10-40 mEq/L to keep K^+ in the range of 3.5-5 mEq/L HCO_3^- – If pH <7.0 or if hypotension, arrhythmia, or coma is present give HCO_3^- 1 ampoule (50 mmol) in 200 mL D5W (or sterile water if available) over 1 h, repeated q1-2 h until pH ≥7.0 – Do not give if pH >7.1 (risk of metabolic alkalosis) – Can give in case of life-threatening hyperkalemia	Same resuscitation and emergency measures as DKA Rehydration – IV fluids: 1 L/h NS initially – Evaluate corrected serum Na^+ – If corrected serum Na high or normal, switch to 0.45% NaCl (4-14 mL/kg/h) – If corrected serum Na low, maintain NS (4-14 mL/kg/h) – When serum BG reaches 13.9 mmol/L (250 mg/dL) switch to D5W **K^+ replacement** – Less severe K^+ depletion compared to DKA – If serum K^+ <3.3 mmol/L, give 40 mEq/L K^+ replacement and hold insulin until [K^+] ≥3.3mmol/L – When K^+ 3.3-5.0 mmol/L add KCL 10-40 mEq/L to keep K^+ in the range of 3.5-5 mEq/L – If serum K^+ ≥5.5 mmol/L, check K^+ every 2 h Search for precipitating event Insulin therapy – Achieved by monitoring plasma osmolality, adding glucose to infusions once BG reaches 14 mmol/L, using correct concentration of saline – Switch to 0.45% NaCl once euvolemic as urinary loss of electrolytes in osmotic diuresis are usually hypotonic – Increase saline concentration if falling too rapidly
Prognosis	<1-3.3% mortality in developed countries Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children)	Mortality rates between 12-17%, but studies looking at this included mixed DKA/HHS state

Macrovascular Complications

- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C30)
  - risk of MI is 3-5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in T2DM
  - most patients with DM are considered "high-risk" under the risk stratification for CAD (see *Dyslipidemias, E3*)
- ischemic stroke (see Neurology, N51)
  - risk of stroke in those with DM is approximately 2-3x higher for men and 2-5x higher for women
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - A1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS4)
  - manifests as intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- screening: A1c every 3 mo, BP monitoring, lipid profile every 1-3 yr, resting ECG every 3-5 yr for high-risk patients
- treatment
  - tight blood pressure control (<130/80 mmHg), especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight LDL control (LDL ≤2.0 mmol/L) or >50% LDL reduction from baseline
  - statin use in patients with clinical CVD, age ≥40, or either diabetes duration >15 yr and age >30, or microvascular complications
  - ACEI or ARB in high-risk patients
  - smoking cessation, healthy diet, physical activity, and maintenance of healthy weight goals
  - for adults with CVD who do not meet glycemic targets, recommended to add anti-hyperglycemic agent with demonstrated cardiovascular benefit (SGLT2i/GLP-1 RAs) to reduce the risk of major CV events



Laboratory Testing: Ketones

- The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect β-hydroxybutyrate (BHB), the ketone most frequently in excess in DKA. This has two clinical consequences:
- Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB
- As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving



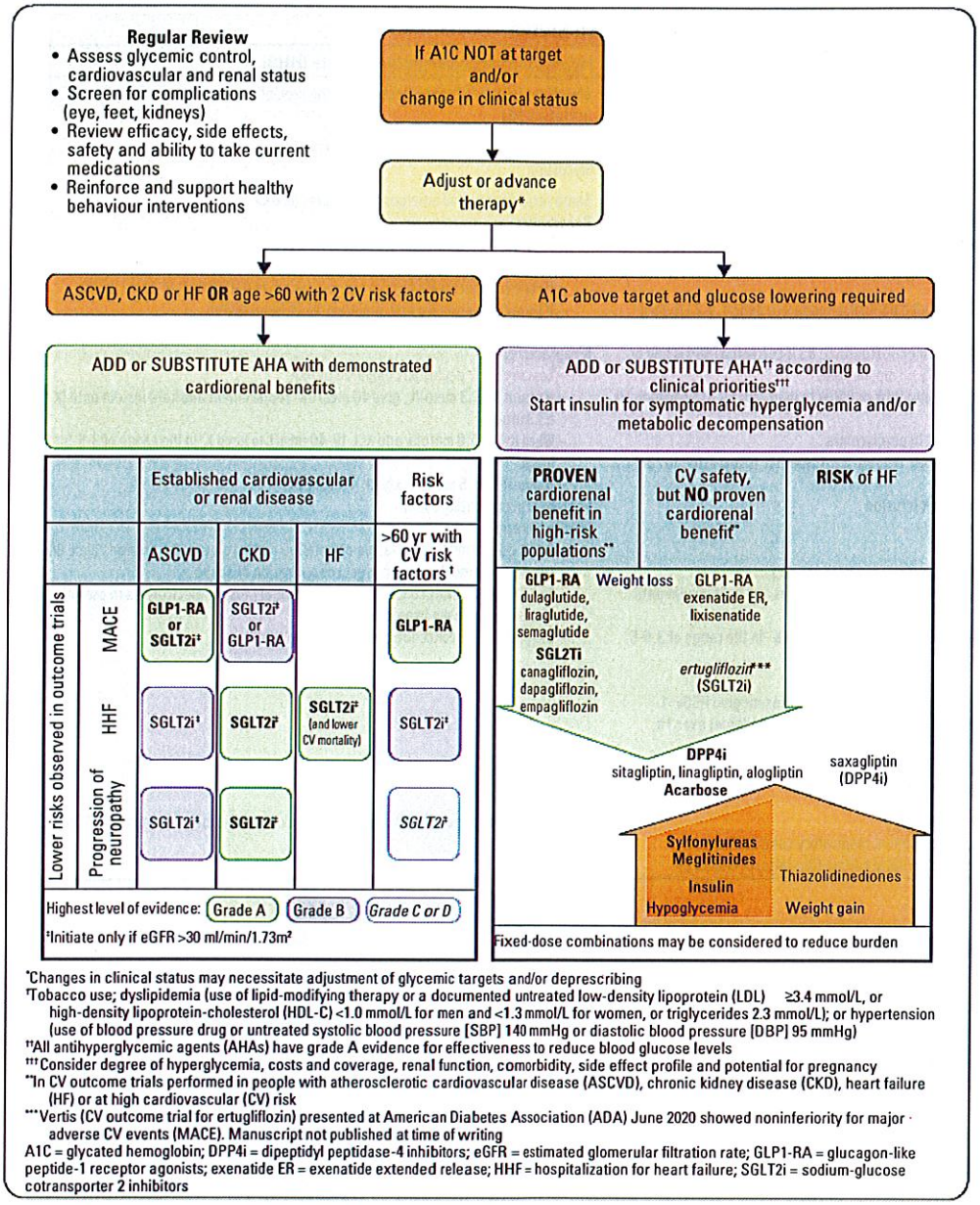
See Landmark Endocrinology Trials for more information on the Effects of ASA for Primary Prevention in Persons with Diabetes Mellitus trial. It details vascular and major bleeding events in patients with diabetes who received ASA compared to those who received a placebo.



See Landmark Endocrinology Trials table for more information on the EMPA-REG OUTCOME trial. It details the effects of empagliflozin (SGLT2 inhibitor) on cardiovascular risk in patients with T2DM.



See Landmark Endocrinology Trials table for more information on the LEADER trial. It details the effects of liraglutide (GLP-1 analogue) on cardiovascular risk in patients with T2DM.



*Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing
†Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides 2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] 140 mmHg or diastolic blood pressure [DBP] 95 mmHg)
††All antihyperglycemic agents (AHAs) have grade A evidence for effectiveness to reduce blood glucose levels
†††Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy
**In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk
***Vertis (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing
A1C = glycated hemoglobin; DPP4i = dipeptidyl peptidase-4 inhibitors; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide-1 receptor agonists; exenatide ER = exenatide extended release; HHF = hospitalization for heart failure; SGLT2i = sodium-glucose cotransporter 2 inhibitors

Figure 8. Treatment approach for patients living with diabetes

Microvascular Complications

Diabetic Retinopathy (see Ophthalmology, OP34 for a more detailed description)

Epidemiology

- diabetic retinopathy is the most common cause of incident blindness in people of working age
- among individuals with T1DM, limb amputation and vision loss due to diabetic retinopathy are independent predictors of early death

Clinical Features

- macular edema: diffuse or focal vascular leakage at the macula
- non-proliferative (microaneurysms, intraretinal hemorrhage, vascular tortuosity, vascular malformation) and proliferative (abnormal vessel growth)
- retinal capillary closure

Treatment and Prevention

- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- ophthalmological treatments available (see Ophthalmology, OP35 for more details)
- annual follow-up visits with an optometrist or ophthalmologist to examine whether symptomatic or not through dilated pupils (immediate referral after diagnosis of T2DM; 5 yr after diagnosis of T1DM for those ≥15 yr)
- interval for follow up should be tailored to severity of retinopathy

Diabetic Nephropathy (see Nephrology, NP34 for a more detailed description)

Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with T1DM (after 5-10 yr) and 4-20% with T2DM have progressive nephropathy

Screening
- serum creatinine for eGFR, random urine ACR
- ACR is used as albuminuria is considered the earliest clinical sign of diabetic nephropathy (microalbuminuria); diagnosis requires persistent elevated urinary albumin (2 out of 3 urinary samples required over 3 mo)
- 24 h urine collection for protein/albumin is the gold standard but is difficult to perform, inconvenient, and often incorrect; random urine albumin is insufficient as albumin levels vary with urine concentration
- begin screening annually at diagnosis for all T2DM, and >5 yr after diagnosis of T1DM for postpubertal patients

Treatment and Prevention
- appropriate glycemic control
- appropriate BP control (<130/80 mmHg)
- use either ACEI or ARB to delay progression of CKD (often used first line for CVD protection)
- use SGLT2i for nephroprotection
- limit use of nephrotoxic drugs and dyes

See Landmark Endocrinology Trials table for more information on the Steno-2 trial. It details the effects of intensive, multifactorial interventions on the rates of death in patients with T2DM and microalbuminuria

Diabetic Neuropathy

Epidemiology
- approximately 50% of patients within 10 yr of T1DM and T2DM onset

Pathophysiology
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve (CN) palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerves
- the more common motor and sensory neuropathies are thought to be related to metabolic, vascular, and possibly hormonal factors

Screening
- 128 Hz tuning fork or 10 g monofilament
- begin screening annually at diagnosis for all T2DM, and >5 yr after diagnosis of T1DM for post-pubertal patients

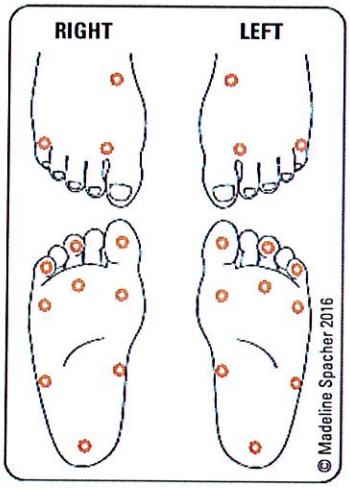


Figure 9. Monofilament testing for diabetic neuropathy

Clinical Features

Table 12. Clinical Features of Diabetic Neuropathies

Peripheral Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands Decreased ankle reflex Distal-predominant as the longest nerves are affected first Classic stocking-glove distribution May result in neuropathic ulceration of foot	Less common than sensory neuropathy and occurs later in the disease process Delayed motor nerve conduction and muscle weakness/atrophy May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex) Some of the motor neuropathies spontaneously resolve after 6-8 wk Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell's palsy) Diabetic amyotrophy i.e. Bruns-Garland Syndrome: refers to pain, weakness, and wasting of hip flexors or extensors	Postural hypotension, tachycardia, decreased cardiovascular response to valsalva maneuver Gastroparesis and alternating diarrhea and constipation Urinary retention and erectile dysfunction

Treatment and Management
- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anticonvulsants (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with dietary modification, domperidone and/or metoclopramide (dopamine antagonists), erythromycin (motilin receptor agonist)
- medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U33)

Pharmacologic Interventions for Painful Diabetic Neuropathy: An Umbrella Systematic Review and Comparative Effectiveness Network Meta-Analysis
Ann Intern Med 2014;161:639-49
Purpose: To compare the efficacies of various oral and topical analgesics for diabetic neuropathy.
Study Selection: RCTs that assessed pharmacologic treatments for painful diabetic peripheral neuropathy in adults.
Results: 65 RCTs involving 12632 patients were included. The following pharmacological agents demonstrated superiority over placebo for short-term pain control: serotonin and norepinephrine reuptake inhibitors (SNRIs) (standardized mean difference (SMD), -1.36; 95% credible interval (CrI), [-1.77 to -0.95]), topical capsaicin (SMD, -0.91; CrI [-1.18 to -0.08]), tricyclic antidepressants (TCAs) (SMD, -0.78; CrI [-1.24 to -0.33]), and anticonvulsants (SMD, -0.67; CrI [-0.97 to -0.37]). Specific agents included: carbamazepine (SMD, -1.57; CrI [-2.83 to -0.31]), venlafaxine (SMD, -1.53; CrI [-2.41 to -0.65]), duloxetine (SMD, -1.33; CrI [-1.82 to -0.86]), and amitriptyline (SMD, -0.72; CrI [-1.35 to -0.08]).
Conclusion: SNRIs, topical capsaicin, TCAs and anticonvulsants are effective in short-term management of painful diabetic neuropathy, but their relative efficacy compared to each other is unknown.

Other Complications

Dermatologic
- diabetic dermopathy: atrophic brown spots commonly in pretibial region ("tibia spots") secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necróbiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

Bone and Joint Disease
- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren's contracture
- increased fracture risk in both T1DM and T2DM due to decreased bone quality
- adhesive capsulitis ("frozen shoulder")

Cataracts
- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections
- see *Infectious Diseases, Diabetic Foot Infections, ID14*

Hypoglycemia

Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish hypoglycemia that occurs in critically ill or medicated patients from hypoglycemia that presents in individuals who are seemingly well
  - each invokes a separate DDx
  - the timing of hypoglycemia may also provide a clue to the diagnosis (e.g. individuals with an insulinoma typically have fasting hypoglycemia whereas those with non-insulinoma pancreatogenous hypoglycemia experience predominantly postprandial hypoglycemia)
  - must be distinguished from pseudohypoglycemia, defined as situations in which either BG >3.9 mmol/L with clinical signs of hypoglycemia (e.g. fatigue, headache, visual disturbances, or lightheadedness) or BG <3.9 mmol/L but patient is asymptomatic

Table 13. Causes of Hypoglycemia

Insulin-Dependent Causes	Insulin-Independent Causes
Exogenous insulin	Hepatic failure
Sulfonylurea or meglitinide	Renal failure
Pentamidine (possibly due to β-cell destruction resulting in insulin release)	Inanition
Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor)	Hormone deficiency (cortisol, glucagon, and epinephrine in insulin-deficient DM)
Insulinoma	Non-islet cell tumours (typically the result of mesenchymal tumour overproduction of IGF-2)
Non-insulinoma pancreatogenous hypoglycemia	Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme
Post-gastric bypass hypoglycemia	Alcohol
	Drugs (e.g. quinine, indomethacin, gatifloxacin, lithium, ACEI, β-adrenergic receptor blockers)

Clinical Features
- Whipple's triad – suggests a patient's symptoms are from hypoglycemia
  1. serum glucose <4.0 mmol/L
  2. neuroglycopenic symptoms (below)
  3. rapid relief provided by administration of glucose
- autonomic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia, hunger
- neuroglycopenic symptoms (caused by brain glucose deprivation)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations
- depend on a thorough history, physical exam, and available biochemical investigations as these may provide clues to the etiology of hypoglycemia
  - for example, if suspecting insulin and insulin secretagogues in patients with diabetes, assess for cortisol deficiency. In a patient with weight loss, hyperpigmentation, and hyperkalemia, consider the possibility of IGF-2 mediated hypoglycemia. In an individual with a gastrointestinal stromal tumour (GIST), think about renal/hepatic failure in the setting of critical illness



Other Players in Glucose Homeostasis
These hormones act to increase:
Blood glucose levels
Glucagon
Epinephrine
Cortisol
Growth hormone



C-Peptide
A short peptide released into the circulation when proinsulin is cleaved to insulin



Use of C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia
Increased = endogenous
Decreased or normal = exogenous



Treatment of an Acute Hypoglycemic Episode (Blood Glucose <4.0 mmol/L) in the Awake Patient (e.g. able to self-treat)

1) Eat 15 g of rapid-acting carbohydrates (e.g. 3 packets of sugar dissolved in water; 3/4 cup of juice)
↓
2) Wait 15 min
↓
3) Retest BG
↓
4) Repeat steps 1-3 until BG >5 mmol/L
↓
5) Eat next scheduled meal. If next meal is >1 h away, eat snack including 15 g of carbohydrate and protein



Hypoglycemia Unawareness (T1DM >>> T2DM)
- Patient remains asymptomatic until severe hypoglycemic levels are reached
- Often occurs after repeated episodes of hypoglycemia as the patient develops blunted/minimal autonomic response
- **Causes:**
  - Decreased glucagon/epinephrine response
  - History of repeated hypoglycemia or low A1c
  - Autonomic neuropathy
- May not be safe for patient to drive
- Suggest that patient obtain a Medic-Alert™ bracelet if at risk for hypoglycemia, especially with hypoglycemia unawareness and consider use of advanced monitoring systems (continuous glucose monitor, flash glucose monitor)



Refer to Diabetes Canada 2018 guidelines for advice around diabetes and driving

- when the cause of hypoglycemia is not evident, screen for oral hypoglycemic agents (ideally all available sulfonylureas and glinides) and measure plasma glucose, insulin, proinsulin, C-peptide, b-hydroxybutyrate, and insulin Ab during a spontaneous hypoglycemic episode or a supervised fast of up to 72 h. If hypoglycemia occurs only in the postprandial state, evaluate the patient first with a mixed meal test
- correct hypoglycemia with injection of 1.0 mg glucagon IV with measurement of plasma glucose response. This will distinguish endogenous and exogenous hyperinsulinism from other causes of hypoglycemia

Treatment

- for tumoural hypoglycemia, definitive treatment requires resection of the tumour. If that is not possible, certain medications can be helpful such as diazoxide for patients with insulinoma
  - for non-insulinoma pancreatogenous hypoglycemia and post-bariatric bypass hypoglycemia, dietary changes including reducing the amount of carbohydrate intake and small frequent meals may be helpful. For patients who do not respond to nutritional modification or have severe symptoms, acarbose can be utilized
- see Emergency Medicine, ER35
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV in 1-3 min or 1 mg glucagon SC or IM (if no IV access is available)
  - may need ongoing glucose infusion once BG >5 mmol/L

Metabolic Syndrome

- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Features of Metabolic Syndrome (≥3 measures to make a Dx)

Measure	Men	Women
Abdominal Obesity (Elevated Waist Circumference)		
Canada, USA	≥102 cm (40 inches)	≥88 cm (35 inches)
Europid, Middle Eastern, Sub-Saharan Africa, Mediterranean	≥94 cm (37 inches)	≥80 cm (31.5 inches)
Asian, Japanese, South & Central America	≥90 cm (35 inches)	≥80 cm (31.5 inches)
TG Level	≥1.7 mmol/L (150 mg/dL)	
HDL-C Level	<1.0 mmol/L (<40 mg/dL)	<1.3 mmol/L (<50 mg/dL)
Blood Pressure	≥130/85 mmHg	
Fasting Glucose Level	≥5.6 mmol/L (>100 mg/dL)	

Drug treatment for any elevated marker is an alternate indicator

Obesity

- see Family Medicine, FM9

Pituitary Gland

Pituitary Hormones

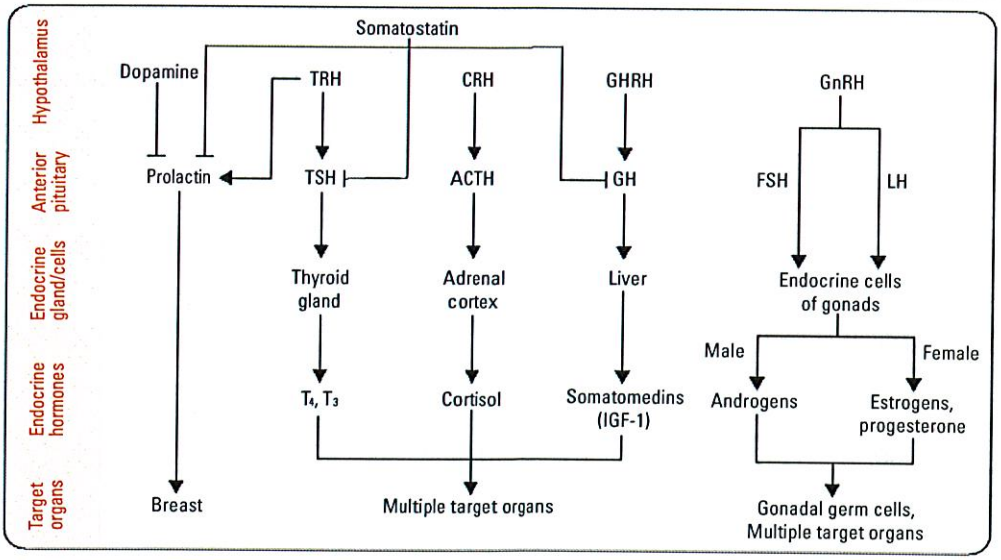


Figure 10. Hypothalamic-pituitary hormonal axes

Hypothalamic Control of Pituitary

- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except PRL, which is primarily under inhibitory control by dopamine. GH and TSH are stimulated by GHRH and TRH respectively while inhibition by somatostatin is less important for control
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of PRL and hyposecretion of all remaining hormones

Anterior Pituitary Hormones

- FSH, LH, ACTH, TSH, GH, PRL
  - sequential loss of anterior pituitary hormones due to mass effect: GH, LH, FSH, TSH, ACTH, PRL ("Go Look For the Adenoma Please")
- these hormones are produced, stored, and released from the anterior pituitary but regulated by hormones produced by the hypothalamus

Posterior Pituitary (Hypothalamic) Hormones

- ADH and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus, these hormones are stored in and released from the posterior pituitary

Table 14. The Physiology and Action of Pituitary Hormones

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
LH/FSH	Stimulate gonads via cAMP Ovary: LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles FSH: growth of granulosa cells in ovarian follicle; controls estrogen production Testes: LH: production of testosterone (Leydig cells) FSH: production of spermatozoa (Sertoli cells)	Polypeptide Glycoproteins (same α subunit as TSH and hCG) Secreted in pulsatile fashion	Estrogen Progesterone Testosterone Inhibin Continuous (i.e. non-pulsatile) GnRH infusion	Pulsatile GnRH (low frequency pulsation = FSH release, high frequency pulsation = LH release)
ACTH	Stimulates growth of adrenal cortex and secretion of its hormones via cAMP	Polypeptide Circadian rhythm (highest in the morning, lowest at midnight)	Dexamethasone, cortisol, and other glucocorticoids	Corticotropin-Releasing Hormone Metyrapone hypoglycemia Vasopressin Fever, pain, stress
TSH	Stimulates growth of thyroid and secretion of T4 and T3 via cAMP	Glycoprotein Note: hCG can activate the TSH receptor and therefore have thyroid-stimulating activity	Thyroid hormones (T4 and T3) and analogues, dopamine, somatostatin, cytokines, high dose glucocorticoids	TRH AVP α adrenergic agonist
PRL	Promotes milk production and breast tissue development Inhibits gonadotropin secretion	Polypeptide Episodic secretion	Dopamine (only pituitary hormone under tonic inhibition of secretion)	Sleep Stress, hypoglycemia Pregnancy, breastfeeding Mid-menstrual cycle Sexual activity TRH (primary hypothyroidism) Drugs: antipsychotics, tricyclic antidepressants, metoclopramide, domperidone, verapamil, methyldopa, opioids, high dose estrogen
GH	Has direct effects on peripheral target cells Needed for linear growth and also has metabolic effects to increase serum glucose Stimulates secretion of IGF-1 by the liver, a potent growth and differentiation factor	Polypeptide Acts indirectly through IGF-1 (somatomedin-C) synthesized in the liver and has direct effects Serum GH undetectable for most of the day and suppressed after meals high in glucose Sustained rise during sleep	Glucose challenge Glucocorticoids Somatostatin Dopamine D2 receptor agonists in some GH-secreting tumours IGF-1 (long-loop)	GHRH Insulin-induced hypoglycemia Ghrelin Exercise REM sleep Arginine, clonidine, propranolol, L-dopa Sex hormones Dopamine agonists in normal individuals
ADH	Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine	Octapeptide Secreted by posterior pituitary Osmoreceptors in hypothalamus detect serum osmolality Contracted plasma volume detected by baroreceptors is a more potent stimulus than ↑ osmolality	↓ serum osmolality	Hypovolemia or ↓ effective circulatory volume ↑ serum osmolality Stress, pain, fever, system CNS disorders
Oxytocin	Causes uterine contraction Breast milk secretion	Nonapeptide Secreted by posterior pituitary	EtOH	Suckling Distention of female genital tract during labour via stretch receptors

Growth Hormone

GH Deficiency

- cause of short stature in children (see Pediatrics, P34)
- adults exhibit increased fat and decreased lean body mass, decreased bone mineral density, and fatigue
- diagnosis made with low serum IGF-1 levels in individuals with deficiencies in three or more pituitary axes, or by failure to increase GH with a provocative test (see above under GH secretory stimulus); insulin tolerance test to induce hypoglycemia is the gold standard dynamic test
- Tx: GH replacement is not always indicated after max linear height and peak bone mass is reached; consider in an adult patient with childhood onset irreversible GH deficiency (some children who are diagnosed with idiopathic GH deficiency will have normal GH responses when tested as adults and do not require GH treatment). GH replacement can also be provided to patients with adult onset GH deficiency who do not have an active malignancy and prefer treatment after a discussion about its potential benefits, adverse effects, and cost

GH Excess

Etiology

- GH secreting pituitary adenoma, neuroendocrine tumours secreting ectopic GH or GHRH (very rare)

Pathophysiology

- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in GH excess states, secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

Clinical Features

- leads to gigantism in children (before epiphyseal fusion)
- leads to acromegaly in adults (after epiphyseal fusion)
- dermatologic (thickening of skin, increased sebum production, sweating, acne, sebaceous cysts), musculoskeletal (enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, carpal tunnel syndrome, osteoarthritis), cardiometabolic (HTN, DM, acanthosis nigricans, cardiomyopathy), sleep apnea, sexual (low libido)

Investigations

- first line test: serum IGF-1 (expected to be elevated)
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- CT, MRI, or skull x-rays may show cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica
- MRI of the sella turcica is needed to look for a tumour

Treatment

- surgery is the recommended initial therapy for the majority of patients with acromegaly; second line options include somatostatin analogue (octreotide), dopamine agonist (cabergoline), GH receptor antagonist (pegvisomant), radiation
  - radiation may be considered in patients whose disease is not controlled by surgery or medical treatment



Risks Associated with GH Excess

- Cardiac disease (e.g. cardiomyopathy, valvulopathy, arrhythmias, CAD) in 1/3 of patients
- Two-fold increase in mortality in acromegaly due to acromegaly-associated complications such as HTN, diabetes, CVD, and cerebrovascular disease
- Increased risk of OSA
- HTN in 1/3 of patients
- Increased risk of cancer (particularly colon cancer)

Prolactin

Hyperprolactinemia

Etiology

- prolactinoma: most common pituitary adenoma
- pituitary stalk compression: from sellar masses or damage causing reduced dopamine inhibition of PRL release
- primary hypothyroidism (increased TRH), PCOS, acromegaly
- decreased clearance due to CKD or severe liver disease (PRL is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high PRL levels: antipsychotics (common), antidepressants, antihypertensives (verapamil/methyldopa), bowel motility agents (metoclopramide/domperidone), H2-blockers, opiates (morphine), estrogens (e.g. oral contraceptives)
- macroprolactinemia (high molecular weight PRL also known as big-big PRL) that has no action but results in falsely elevated serum prolactin
- physiologic causes: pregnancy, stress, sleep, nipple stimulation, factors affecting the chest wall

Clinical Features

- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, oligomenorrhea, erectile dysfunction



Approach to Nipple Discharge

- Differentiate between galactorrhea (fat droplets present) vs. breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation) vs. pathologic
- If abnormal breast discharge, must rule out a breast malignancy

Investigations
- serum PRL, TSH, liver enzyme tests, creatinine, hCG in all women of reproductive age
- macroprolactin level in patients with hyperprolactinemia but no symptoms of PRL excess
- MRI of the sella turcica when a secondary cause is not identified or when PRL levels suggest that there may be underlying tumoural hyperprolactinemia

Treatment
- first line: dopamine agonists (bromocriptine, cabergoline, quinagolide)
- surgery ± radiation (rare)
- PRL-secreting tumours are often slow-growing; treatment may not be necessary in the setting of small tumours associated with hyperprolactinemia which does not result in hypogonadism or bothersome galactorrhea
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP



Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline
J Clin Endocr Metab 2011;96:273-88
- Indications to treat:
  - Symptomatic patients, in particular those with galactorrhea, hypogonadism-amenorrhea, low libido, or infertility
  - Adenomas ≥1 cm or any size causing structural compression
- For patients with symptomatic prolactinomas, dopamine agonist therapy should be used to lower prolactin levels, decrease tumour size, and restore gonadal function
- Cabergoline should be preferentially used due to higher efficacy in normalizing PRL levels and shrinking pituitary tumours
- For symptomatic patients with treatment-resistant prolactinomas, increase the dose to maximal tolerable dose before referring for surgery
- Most women with prolactinomas should discontinue dopamine agonist therapy immediately if they become pregnant (except for patients with large invasive tumours)

Thyroid Stimulating Hormone

- see *Thyroid, E24*

Adrenocorticotropic Hormone

- see *Adrenal Cortex, E33*

Luteinizing Hormone and Follicle Stimulating Hormone

Hypogonadotropic Hypogonadism
- hypogonadism due to impaired release of FSH and LH, causing low FSH, low LH, low estrogen and testosterone

Etiology
- congenital: Kallmann syndrome, CHARGE syndrome, GnRH insensitivity
- secondary: CNS or pituitary tumours, pituitary apoplexy, hypothalamic-pituitary radiation, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy, drugs causing hyperprolactinemia, opioids), functional deficiency due to another cause (hyperprolactinemia, chronic systemic illnesses, eating disorders, hypothyroidism, DM, Cushing's disease), systemic diseases involving the hypothalamus/pituitary (hemochromatosis, sarcoidosis, histiocytosis)

Clinical Features
- amenorrhea, low libido, decrease in energy, erectile dysfunction (see Urology, U33), loss of body hair, thin skin, testicular atrophy, decrease in muscle mass, failure of pubertal development (if developed before puberty)

Treatment
- treat underlying cause if present
- combined FSH/LH hormone therapy, hCG, recombinant FSH, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

Hypergonadotropic Hypogonadism
- hypogonadism due to impaired response of the gonads to FSH and LH; pts have high FSH/high LH and low estrogen or testosterone

Etiology
- congenital:
  - chromosomal abnormalities (Turner's syndrome, Klinefelter syndrome, XX gonadal dysgenesis)
  - enzyme defects (17α-hydroxylase deficiency, 17,20-lyase deficiency)
  - gonadotropin resistance (Leydig cell hypoplasia, FSH insensitivity, pseudohypoparathyroidism type 1A)
- acquired:
  - gonadal toxins (chemotherapy, radiation)
  - drugs (antiandrogens, alcohol)
  - infections (STIs, mumps)
  - gonadal failure in adults (androgen decline and testicular failure in men, premature ovarian insufficiency and menopause in women)

Clinical Features
- amenorrhea, erectile dysfunction (see Urology, U33, loss of body hair, fine skin, testicular atrophy, failure of pubertal development, low libido, decrease in energy, and infertility

Treatment
- hormone replacement therapy consisting of androgen (for males) and estrogen and progesterone (for females) administration

Antidiuretic Hormone

Diabetes Insipidus (see Nephrology, NP12)

Definition
- disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

Etiology and Pathophysiology
- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, infiltration or lesion of the stalk, hydrocephalus, Langerhans cell histiocytosis, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, CKD, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out

Clinical Features
- passage of large volumes of dilute urine (>3L/day), polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism (hypernatremia not necessary for diagnosis)
- central DI: visual field defect, headache, other neurological features, or evidence of other pituitary hormone deficiencies may be present

Diagnosing Subtypes of Diabetes Insipidus with Desmopressin Response

Concentrated urine = **C**entral
No effect = **N**ephrogenic

Diagnostic Criteria
- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic polydipsia
- response to exogenous ADH (DDAVP) will distinguish central DI from nephrogenic DI

Treatment
- central DI: first line = desmopressin; second line = chlorpropamide, thiazides, NSAIDs, and carbamazepine
- nephrogenic DI: solute restriction, thiazide diuretics

Syndrome of Inappropriate ADH Secretion

Syndrome of inappropriate ADH secretion (SIADH) vs. Cerebral Salt Wasting (CSW)
CSW can occur in cases of subarachnoid hemorrhage. Na^+ is excreted by malfunctioning renal tubules, mimicking findings of SIADH; hallmark is hypovolemia

Diagnostic Criteria
- 1) hyponatremia (serum Na^+<135 mEq/L) with 2) plasma hypo-osmolality (<275 mOsm/kg), 3) urine Na^+concentration >40 mEq/L, 4) urine osmolality >100 mOsm/kg), 5) euvolemia (no edema), and 6) absence of adrenal, renal, or thyroid insufficiency

Etiology and Pathophysiology
- stress (post-surgical)
- malignancy (ectopic ADH production by tumours including small cell carcinoma of the lung, extrapulmonary small cell carcinomas, squamous cell carcinoma of the head and neck)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (tuberculosis, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

Clinical Features
- symptoms of hyponatremia: headaches, nausea, vomiting, muscle cramps, tremors, cerebral edema if severe (confusion, mood swings, hallucinations, seizures, coma)

Treatment
- goal is to increase serum sodium
- treat underlying cause, fluid restriction (800-1000 mL/d), vasopressin receptor antagonists (tolvaptan, conivaptan), and furosemide

Pituitary Pathology

Pituitary Adenoma (see Neurosurgery, NS18)

Clinical Features

- local mass effects
- visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies; rare), loss of colour vision, headaches; increased ICP is rare
- hypofunction
- hypopituitarism
- hyperfunction
- PRL (galactorrhea, hypogonadism), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
- tumours secreting TSH are rare

Important Deficiencies to Recognize are:

Adrenal insufficiency

Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis

Investigations

- radiological evaluation (MRI sella is imaging of choice)
- formal visual field testing for tumours compressing the optic chiasm
- laboratory tests of hypothalamic-pituitary hormonal function

Hypopituitarism

Etiology (The Eight I's)

- **I**nvasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- **I**nfarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive postpartum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache, and altered LOC; can be fatal if not recognized and treated early)
- **I**nfiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- **I**nfectious
  - syphilis, tuberculosis, fungal (histoplasmosis), parasitic (toxoplasmosis)
- **I**njury
  - severe head trauma
- **I**mmunologic
  - autoimmune destruction (hypophysitis)
- **I**atrogenic
  - following surgery, radiation, or medications (immunotherapy)
- **I**diopathic
  - familial forms, congenital midline defects

The Pituitary Hormones

Compression of the pituitary by a mass leads to loss of pituitary hormones in the following usual order:

"Go Look For The Adenoma Please"

GH, LH, FSH, TSH, ACTH, PRL + posterior pituitary hormones: ADH and oxytocin

Clinical Features

- symptoms depend on which hormone is deficient:
  - ACTH (central adrenal insufficiency): fatigue, weight loss, hypoglycemia, anemia, hyponatremia, failure to thrive, and delayed puberty in children
  - GH: short stature in children; adults exhibit increased fat and decreased lean body mass, decreased BMD, fatigue
  - TSH (central hypothyroidism): tiredness, cold intolerance, constipation, weight gain
  - LH and FSH (hypogonadotropic hypogonadism): oligo- or amenorrhea, infertility, decreased facial/body hair and muscle mass in men, erectile dysfunction, delayed puberty
  - Prolactin: usually asymptomatic, inability to breastfeed
  - ADH: symptoms of DI (extreme thirst, polydipsia, hypernatremia)
  - Oxytocin: usually asymptomatic – only needed during labour and breastfeeding

Investigations

- 8 am cortisol, PRL, TSH, Free T4, LH, FSH, Estradiol or Testosterone, GH, IGF-1, Na**I**, Osmolality
- initial test if 8 am is low/borderline: cosyntropin stimulation test (if results equivocal, proceed to insulin tolerance test)
- insulin tolerance test: insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and cortisol (normal response)
- triple bolus test (rarely done)

Thyroid

Thyroid Hormones

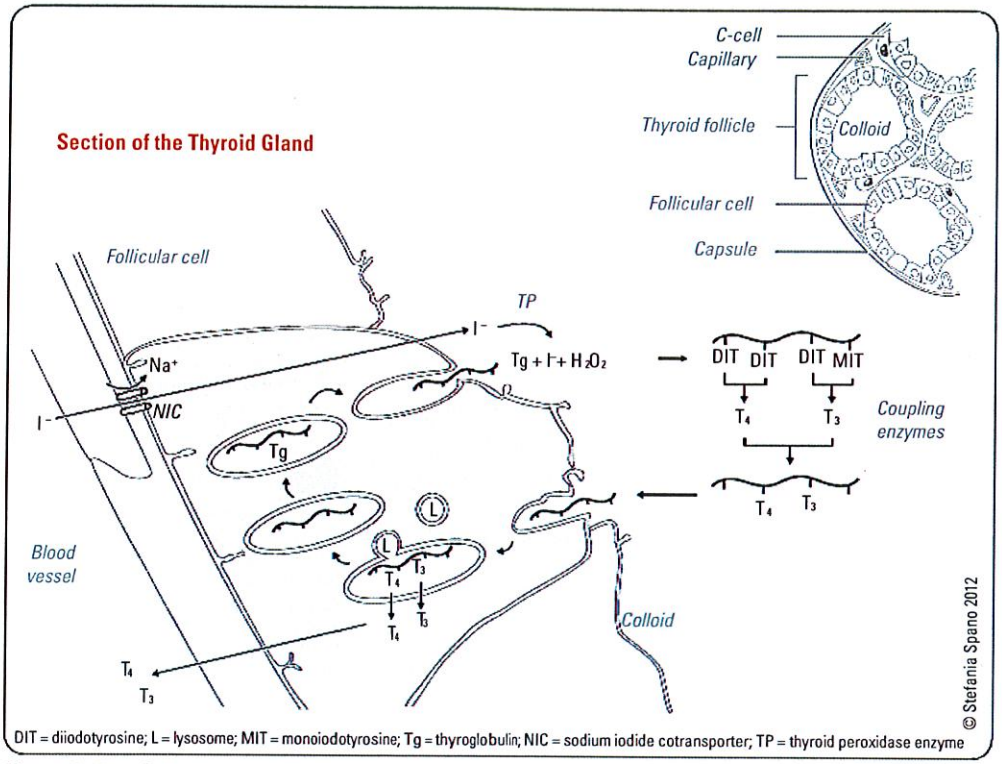


Figure 11. Thyroid hormone synthesis

Synthetic Function of the Thyroid Gland

- the synthesis of thyroid hormones T4 and T3 by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, proteolysis of thyroglobulin, and release of T4 and T3
  - more than 90% of thyroid hormone secreted by the thyroid is T4
- free T4 (0.02%) and free T3 (0.3%) represent the hormonally active fraction of thyroid hormones
  - the remaining fraction is bound to TBG, albumin, and transthyretin, and is biologically inactive
- T3 is more biologically active (approximately 4x as potent as T4), but T3 is present in the blood in smaller quantities and has a shorter half-life compared to T4
- 85% of T4 is converted to T3 or reverse T3 in the periphery by deiodinase enzymes
- reverse T3 is metabolically inactive but produced in times of stress to decrease metabolic activity
- most of the plasma T3 pool is derived from the peripheral conversion of T4
- calcitonin, a peptide hormone, is also produced in the thyroid by the parafollicular cells (C cells)
  - calcitonin functions by inhibiting osteoclast activity and increasing renal calcium excretion

Role of Thyroid Hormones

- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- diffuse actions, affecting nearly every organ system
- tissue-specific effects determined by the expression of the types of thyroid receptor isoform and the local production of T3
- increase basal metabolic rate through increased Na^+/K^+ ATPase activity, increased O_2 consumption, increased respiration, heat generation, and increased cardiovascular activity
- when present at higher than normal levels, potentiate the actions of GH, catecholamines (epinephrine, norepinephrine), glucagon, and cortisol, resulting in increased gluconeogenesis, ketogenesis, and proteolysis, mimicking what happens in starvation
- increase sensitivity to catecholamines by up-regulating their receptors, but do not alter their blood concentrations
- required for normal growth in the fetus and child, including the CNS, via stimulation of GH release, in synergism with cortisol

Regulation of Thyroid Function

- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators); the negative feedback mechanism of T3 acts on the anterior pituitary to inhibit TSH and on the hypothalamus to inhibit TRH

Extra-Thyroidal Factors Impacting Thyroid Hormone Homeostasis: A Review
JRM 2015;4(1):40-49

- Most peripheral thyroid metabolism occurs in the liver and kidneys, thus severe liver disease and CKD can significantly alter the T3:T4 ratio.
- Alcohol dependence results in hypothalamic-pituitary-thyroid axis dysfunction demonstrated by decreased TSH, T4, and T3 levels.
- Smoking is associated with lower TSH levels in a dose-dependent manner, with heavy smokers (8-12 cigarettes/d) being associated with more TSH suppression than light smokers (<4 cigarettes/d).
- Heavy metal exposure including lead, mercury, and cadmium has been shown to alter thyroid hormone function and peripheral metabolism.

Patterns of Hormone Levels

	TSH	T_3, T_4
1° Hyper	↓	↑
2° Hyper	↑	↑
1° Hypo	↑	↓
2° Hypo	↓	↓

- T3 intrathyroid (autoregulation)
  - synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  - varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T3 to T4 in iodide deficiency
  - increased activity of peripheral 5'-deiodinase in hypothyroidism increases T3 production despite low T4 levels

Tests of Thyroid Function and Structure

TSH

- third generation TSH is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating T4 and T3
  - secondary: increased TSH results in increased T4 and T3
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T4 and T3
  - secondary: TSH is low or inappropriately normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T4 and Free T3

- standard assessment of thyroid function measures TSH and, if necessary, free T4. Free T3 should only be measured in the small subset of patients with hyperthyroidism and suspected T3 toxicosis. In this case, TSH would be suppressed, free T4 normal, and free T3 elevated

Thyroid Autoantibodies

- TgAb, TPOAb, and TRAb of the blocking variety are increased in Hashimoto's disease; normal variant in 10-20% of individuals
- TRAb of the stimulating variety are also referred to as TSI and can cause Graves' disease. TRAb receptor blocking and stimulating antibodies are seen in patients with Graves' disease

Plasma Thyroglobulin

- used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumour marker for thyroid cancer recurrence
- detectable or elevated levels may suggest persistent, recurrent, or metastatic disease
- assay can be impacted by the presence of TgAb. Therefore, both must be tested to ensure accurate thyroglobulin results

Serum Calcitonin

- not routinely done to investigate thyroid nodules
- ordered if suspicion of MTC (e.g. in patients with a thyroid nodule and suspected or confirmed MEN 2A or 2B syndromes or those who have a pathogenic mutation in *RET* gene)
- used to monitor for residual or recurrent MTC

Thyroid Imaging/Scans

- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, characterize thyroid nodules, facilitate FNA biopsy (FNAB)
  - U/S is the first line tool for identification of thyroid nodules that require FNAB; exception is hyperthyroid patients with thyroid nodules where use of a radioisotope thyroid scan and RAIU (see below) permits identification of hyperfunctioning nodules, which generally do not need to be biopsied
- radioisotope thyroid scan (Technetium-99) only if 1) one or more thyroid nodule(s) and 2) patient is hyperthyroid to determine whether nodules are hot (functioning → excess thyroid hormone production) or cold (non-functioning)
- hot nodule → very low chance of malignancy; treat hyperthyroidism
- cold nodule → further workup required (U/S, then FNAB if concerning sonographic features)
- RAIU
  - test of function: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland in vivo
  - if ↑ uptake (e.g. incorporated), gland is overproducing thyroid hormone (hyperthyroid)
  - if ↓ uptake (e.g. not incorporated), gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)
- see *Figure 12, E33* for further information regarding the utility of these scans

Thyroid Biopsy

- FNA for cytology
  - differentiates between benign and malignant disease
  - best done under U/S guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule is located posteriorly in the gland



Thyroid Assessment

- TSH
- Serum free thyroid hormones (T_4, T_3)
- Antibodies (TRAb, TgAb, and TPOAb)
- Thyroglobulin (to monitor thyroid cancer)
- Thyroid U/S when there is a palpable thyroid abnormality or suspected thyroid mass
- Nuclear uptake and scan (for hyperthyroidism)
- Biopsy (FNA) of thyroid nodules warranting a cytological evaluation



Does this Patient have a Goitre?
From The Rational Clinical Examination
JAMA 2009; https://jamaevidence.mhmedical.com/content.aspx?bookid=845&sectionid=61357508
Study: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of a goitre.
Results: Clinical diagnosis was based on degree of lateral prominence, visibility, and palpability of the thyroid gland. No evidence exists to support the superiority of any one method.
The combined results of 4 studies detail the predictive utility of assessing grades of thyroid gland weight:

Weight	Reference	LR+	95% CI
0-20 g	Normal	0.15	(0.10-0.21)
20-40 g	1-2x	1.9	(1.1-3.0)
>40 g	>2x	25.0	(2.6-175)

Alternatively, defining a goitre as a mass larger than the distal phalanx of the thumb has been shown to have an LR+ of 3.0 (95% CI 2.5-3.5) and LR- of 0.30 (95% CI: 0.24-0.37) in children, and an LR+ of 4.7 (95% CI 3.6-6.0) and LR- of 0.08 (95% CI 0.02-0.27) for the presence of a goitre.
Conclusions: Use of weight of thyroid tissue is an appropriate method of diagnosing a goitre, while comparing the size of the thyroid mass to the distal phalanx of the thumb may be a useful alternative.

Table 15. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

	Hyperthyroidism	Hypothyroidism
TSH	Decreased in 1° hyperthyroidism Increased in 2° hyperthyroidism	Increased in 1° hypothyroidism Decreased in 2° hypothyroidism
Free T_4	Increased in 1° hyperthyroidism Increased in 2° hyperthyroidism	Decreased in 1° hypothyroidism Decreased in 2° hypothyroidism
Antibodies	Graves': TRAb	Hashimoto's: TPOAb, TgAb
RAIU	Increased uptake Graves' Toxic multinodular goitre Toxic adenoma	Decreased uptake Subacute thyroiditis Recent iodine load Exogenous thyroid hormone
Radioisotope Thyroid Scan	Graves': homogenous diffuse uptake Multinodular goitre: heterogeneous uptake Toxic adenoma: single intense area of uptake with suppression elsewhere	

Drugs Affecting Thyroid Function

Montanelli, L., Benvenga, S., Hegedüs, L., Vitti, P., Latrofa, F., Duntas, L.H. Endocrinology. Springer, Cham. c2018. Drugs and Other Substances Interfering with Thyroid Function; p733-761

(a) Lithium
(b) Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)
(c) Antiepileptics
(d) Rifampin
(e) Metformin
(f) Amiodarone

Thyrotoxicosis

Definition

- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

Epidemiology

- 1% of general population have hyperthyroidism
- F:M=5:1

Etiology and Pathophysiology

Table 16. Differential Diagnosis of Thyrotoxicosis

Disorder	TSH	Free T_4/T_3	Thyroid Antibodies	RAIU	Other
HYPERTHYROIDISM					
Graves' Disease	Decreased	Increased	TRAb	Increased	Homogeneous diffuse uptake on scan
Toxic Nodular Goitre	Decreased	Increased	None	Increased	Heterogeneous uptake on scan
Toxic Nodule	Decreased	Increased	None	Increased	Intense uptake in hot nodule on scan with suppressed uptake in the rest of the gland
THYROIDITIS					
Subacute, Silent, Postpartum	Decreased	Increased	Up to 50% of cases (TPOAb, TgAb)	Decreased (increases once entering hypothyroid phase, when TSH rises)	In classical subacute painful thyroiditis, ESR increased
EXTRATHYROIDAL SOURCES OF THYROID HORMONE					
Endogenous (struma ovarii, ovarian teratoma, metastatic follicular carcinoma)	Decreased	Increased	None	Decreased	Low thyroglobulin since endogenous thyroid hormone production suppressed
Exogenous (drugs)	Decreased	Increased (T_4 would be decreased if taking T_3)	None	Decreased	
EXCESSIVE THYROID STIMULATION					
Pituitary Thyrotropinoma	Increased or inappropriately normal	Increased	None	Increased	Pituitary mass; possible PRL or GH excess
Pituitary Thyroid Hormone Receptor Resistance	Increased or normal	Increased	None	Increased	Abnormal THRB gene analysis
Increased hCG (e.g. pregnancy)	Decreased	Increased	None	Test is contraindicated in pregnancy	

Signs and Symptoms of HYPERthyroidism

THYROIDISM
Tremor
Heart rate up
Yawning (fatigue due to insomnia)
Restlessness
Oligomenorrhea/amenorrhea
Intolerance to heat
Diarrhea
Irritability
Sweating
Muscle wasting/weight loss

Common Etiologies

Thyrotoxicosis	Hypothyroidism
Graves' Disease	Hashimoto's
Toxic Nodular Goitre	Congenital
Toxic Nodule	Iatrogenic (thionamides, radioactive iodine, or surgery)
Hyperthyroid phase of thyroiditis	Hypothyroid phase of thyroiditis

Clinical Features

Table 17. Clinical Features of Thyrotoxicosis

General	Fatigue, heat intolerance, irritability, fine tremor
CVS	Tachycardia, atrial fibrillation, palpitations Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation
GI	Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
Neurology	Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asian individuals)
GU	Oligomenorrhea, amenorrhea, decreased fertility
Dermatology	Fine hair, moist and warm skin, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritus Graves' disease: clubbing (acropachy), pretibial myxedema (rare)
MSK	Decreased bone mass, proximal muscle weakness
Hematology	Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)
Eye	Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjunctival injection NOTE: Lid lag is a reflection of a hyperadrenergic state and can be present in any form of thyrotoxicosis

Treatment

- β-blockers for control of adrenergic symptoms
- antithyroidals (thionamides): methimazole (MMI) recommended, or propylthiouracil (PTU)
  - to prepare patients with endogenous hyperthyroidism for surgery, for patients with Graves' disease, and for patients with toxic nodules who do not wish to have definitive treatment with radioactive iodine or surgery
- radioactive iodine thyroid ablation for Graves' disease and toxic nodules/adenoma
- surgery in the form of hemi, subtotal, or complete thyroidectomy for toxic nodules
- surgery in the form of total thyroidectomy for Graves' disease

Graves' Disease

Definition

- an autoimmune disorder characterized by autoantibodies that stimulate the TSH receptor leading to hyperthyroidism

Epidemiology

- most common cause of hyperthyroidism
- occurs at any age with peak in 3rd and 4th decade
- F:M=7:1, 1.5-2% of women in the United States
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA-B8 and DR3
- may be associated with other autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology

- autoimmune disorder due to breakdown in thyroid tolerance likely due to a combination of factors including autoreactive B lymphocytes and an imbalance favouring a TH2 vs. TH1 immune response
- B lymphocytes produce TSI that binds and stimulates the TSH receptor, and thus, the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, viral or bacterial infections, and glucocorticoid withdrawal
- ophthalmopathy (thyroid associated orbitopathy) is a result of increased connective and extraocular muscle tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit; this leads to fluid accumulation and forward displacement of the eyeball
- dermopathy (pretibial or localized myxedema) may be related to cutaneous glycosaminoglycan deposition

Clinical Features

- signs and symptoms of thyrotoxicosis
- diffuse goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity (plus signs of hyperthyroidism: lid retraction, characteristic stare)
- dermopathy (rare): pretibial myxedema (thickening of dermis that manifests as non-pitting edema)
- acropachy: clubbing and thickening of distal phalanges

Investigations

- low TSH
- increased free T4 (and/or increased T3)
- positive for TRAb (the currently available third-generation TRAb tests have sensitivity and specificity over 98%, allowing their use for determining the etiology of hyperthyroidism)
- increased RAIU
- homogeneous diffuse uptake on thyroid scan



Graves' Ophthalmopathy

NO SPECS (in the usual order of changes)
No signs
Only signs: lid lag, lid retraction
Soft tissue: periorbital puffiness, conjunctival injection, chemosis
Proptosis/exophthalmos
Extraocular (diplopia)
Corneal abrasions (unable to close eyes)
Sight loss



Other Medications Used in the Treatment of Graves'

Glucocorticoids have been useful in the treatment of severe Graves' hyperthyroidism and thyroid storm, by inhibiting the conversion of peripheral T_4 to T_3

Lithium can also be used to treat Graves' hyperthyroidism. It acts by blocking thyroid hormone release, but its toxicity has limited its use in practice



Caution with Thionamides

These drugs are highly effective inhibitors of thyroid hormone synthesis, inducing permanent remission in 20-30% of patients with Graves' disease. They are most often employed to achieve a euthyroid state before definitive treatment. Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity, and ANCA-positive vasculitis

Treatment

- thionamides (antithyroid medications): MMI or PTU
  - PTU and MMI inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines
  - PTU also inhibits peripheral deiodination of T4 to T3
  - treat for approximately 12-18 mo aiming for a normal TSH and TRAb prior to consideration of treatment discontinuation
  - small goitre, mild hyperthyroidism, and low TRAb titres are good predictors for long-term remission with medical therapy
  - remission (normal thyroid indices one yr after discontinuation of PTU or MMI) rates range between 20-50% following 12-18 mo of antithyroid medication
  - major side effects: hepatotoxicity (cholestasis, hepatitis), agranulocytosis, vasculitis
  - minor side effects: mild rash, pruritus
  - MMI is preferred to PTU due to longer duration of action (once daily dosing for most), more rapid resolution of hyperthyroidism, and lower incidence of side effects
  - in pregnancy: use PTU during the first 16 wk of pregnancy and MMI after. MMI is contraindicated in the first trimester due to risk of aplasia cutis; MMI is preferred in the second and third trimester due to the potential risk of hepatotoxicity with PTU in the second and third trimesters
- symptomatic treatment with β-blockers
- thyroid ablation with radioactive I-131 if PTU or MMI trial does not produce disease remission or patient prefers definitive treatment with RAI
  - high incidence of hypothyroidism after I-131 requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
  - may worsen ophthalmopathy; concurrent treatment with prednisone if high risk for or if ophthalmopathy present
- total or near total thyroidectomy
  - indicated for large goitres, suspicious nodule for cancer, if patient is intolerant to thionamides and declines/is not a candidate for RAI ablation, women who wish to conceive in the near future warranting rapid control of hyperthyroidism, uncontrolled hyperthyroidism not responding to anti-thyroid drugs in pregnancy (surgery safest in second trimester), patient preference
  - risks: permanent hypothyroidism, hypoparathyroidism, and vocal cord palsy due to potential laryngeal nerve damage
- ophthalmopathy/orbitopathy
  - smoking cessation is important
  - prevent drying of eyes and ulceration of cornea by using artificial tears during the day and lubricants at night
  - high dose prednisone or IV methylprednisolone in severe cases
  - high dose glucocorticoids (preferably IV) as well as potential orbital decompression surgery for sight-threatening orbitopathy
  - orbital radiation, surgical decompression

Prognosis

- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- total and subtotal thyroidectomy are rapid cures with low-risk of recurrence (2% and 10%, respectively)
- radioactive iodine is less invasive than surgery, but also results in permanent hypothyroidism and requires precautions in contacts several days after treatment
- medical therapy with thionamides is not invasive, but has high recurrence rate at ~50%
- lifetime follow-up needed

Subacute Thyroiditis (Thyrotoxic Phase)

- there are two main types: painful (de Quervain's) and painless (silent)

Table 18. Painful vs. Painless Subacute Thyroiditis

	Painful Thyroiditis (de Quervain's, granulomatous)	Painless Thyroiditis (silent, autoimmune)
Pathophysiology	Presumed to be caused by viral infection or postviral inflammatory process Strongly associated with HLA-D35 Thyroid inflammation damages thyroid follicles, resulting in release of large amounts of T4 and T3 until stores are exhausted State of hypothyroidism often persists until thyroid can generate sufficient thyroid hormones	Considered variant of Hashimoto's thyroiditis Associated with HLA-DR3 Postpartum subtype occurs following pregnancy Also caused by inflammatory damage leading to unregulated release of T_4 and T_3 into circulation
Clinical Features	Painful swelling of the thyroid (may radiate to jaw and ears), transient vocal cord paresis, malaise, fatigue, myalgia, fever Often preceded by URTI Painful condition lasts for a week to few months Signs of hyperthyroidism during hyperthyroid phase (palpitations, tachycardia, stare)	Thyroid enlargement without discomfort in association with the typical thyroid function test abnormalities consisting of hyperthyroidism, hypothyroidism, and recovery Signs of hyperthyroidism during hyperthyroid phase (palpitations, tachycardia, stare) Affects women more than men
Laboratory Investigations	Initial elevated T_4 and T_3 Near absent RAIU ESR and CRP often elevated	Initial elevated T_4 and T_3 Near absent RAIU
Treatment	NSAID/prednisone for pain β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms If symptomatically hypothyroid, may treat short-term with thyroxine	β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms If symptomatically hypothyroid, may treat short-term with thyroxine
Prognosis	Complete spontaneous recovery to normal thyroid function in 90% of patients 10% of patients may become hypothyroid and require permanent replacement	10% of patients may become permanently hypothyroid At risk of recurrent episodes of thyroiditis

Toxic Adenoma/Toxic Multinodular Goitre

Etiology and Pathophysiology

- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T4 and T3
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre (Plummer's disease))
- more common in elderly people as opposed to Graves' disease, which is more common in younger individuals

Clinical Features

- may have multinodular goitre
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- local neck compression symptoms such as dysphagia, dysphonia, or dyspnea may be present with large goitres

Investigations

- low TSH, high free T4 and free T3
- thyroid scan with increased RAIU in nodule(s) and suppression of the remainder of the gland

Treatment

- use high dose radioactive iodine (I-131) to ablate hyperfunctioning nodules
- β-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as first-line treatment
- initiate therapy with MMI or PTU to attain euthyroid state in individuals who do not wish to have definitive treatment of their disease, in preparation for thyroidectomy, or prior to RAI in patients at risk for complications due to exacerbation of hyperthyroidism following RAI such as the elderly with cardiovascular disease

Thyrotoxic Crisis/Thyroid Storm

Definition

- medical emergency – acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism
- rare, but serious with mortality rate between 10-30%

Etiology and Pathophysiology

- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Clinical Features
- hyperthyroidism
- extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, hepatic failure with jaundice, atrial fibrillation, CHF
- CNS manifestations including agitation, delirium, psychosis, lethargy, seizures, coma

Laboratory Investigations
- increased free T4 and T3, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or other β-blockers can additionally be used
  - use with caution in patients with decompensated heart failure as they may worsen condition
  - propranolol is frequently used because it decreases peripheral conversion of T4 to T3

Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses (200 mg q4 h)
- give iodide, which acutely inhibits the release of thyroid hormone, 1 h after the first dose of PTU is given
  - sodium iodide 1 g IV drip over 12 h q12 h
    OR
  - Lugol's solution 10 drops q8 h
    OR
  - potassium iodide (SSKI) 5 drops q6 h
- hydrocortisone 100 mg IV q8 h or dexamethasone 2-4 mg IV q6 h for the first 24-48 h; inhibits peripheral conversion of T4 to T3

Hypothyroidism

Definition
- clinical syndrome caused by insufficient thyroid hormone production

Epidemiology
- 2-3% of general population
- F:M=10:1
- 10-20% of women >50 have subclinical hypothyroidism (normal T4, TSH mildly elevated)
- iodine deficiency is the most common cause worldwide, but not in North America

Etiology and Pathophysiology
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production due to an intrinsic thyroid defect
  - iatrogenic: post-ablative (I-131 or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4000 births)
  - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
- insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
- decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

Table 19. Interpretation of Serum TSH and Free T_4 in Hypothyroidism

	Serum TSH	Free T_4
Overt Primary Hypothyroidism	Increased	Decreased
Subclinical Primary Hypothyroidism	Increased	Normal
Secondary Hypothyroidism	Decreased or not appropriately elevated	Decreased

Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review
Clin Ther 2017;39(2):378-403
- GI disorders such as celiac disease, atrophic gastritis, lactose intolerance, H. pylori infection may impede levothyroxine absorption.
- Drugs decreasing stomach acidity have been shown to significantly reduce exogenous thyroid hormone absorption from the GI tract. These include proton-pump inhibitors, H2 receptor antagonists, calcium carbonate, sucralfate, and aluminum hydroxide.
- Iron citrate is shown to reduce intestinal absorption of levothyroxine.
- Food, especially soybeans and coffee, have been shown to reduce absorption of levothyroxine significantly.
- Roughly 80% of levothyroxine is absorbed within 3 h after administration of the drug. Thus, patients should be educated to take levothyroxine on empty stomach at least 1 h prior to eating breakfast.

Clinical Features

Table 20. Clinical Features of Hypothyroidism

General	Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia
CVS	Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart
Respiratory	Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia
GI	Weight gain despite poor appetite, constipation
Neurology	Paresthesia, slow speech, muscle cramps, delayed deep tendon reflex relaxation ("hung reflexes"), carpal tunnel syndrome, asymptomatic elevated CK, seizures
GU	Menorrhagia, amenorrhea, impotence, pre-menopausal abnormal vaginal bleeding
Dermatology	Facial puffiness, periorbital edema, cool and pale, dry and rough skin, dry and coarse hair, eyebrows thinned (lateral 1/3), discolouration (carotenemia)
Hematology	Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis

Treatment
- L-thyroxine (dose range: 0.05-0.2 mg PO once daily, up to 1.6 μg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; adjust dose until TSH returns to normal reference range
- once maintenance dose achieved, follow up TSH with patient annually
- secondary/tertiary hypothyroidism: monitor via measurement of free T4 (TSH is unreliable in this setting)

CONGENITAL HYPOTHYROIDISM
- see Pediatrics, P35

Hashimoto's Thyroiditis

Definition
- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a small, rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from onset
- risk factor for rare primary thyroid lymphoma

Etiology and Pathophysiology
- defect in a T-suppressor clone leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na+/I– symporter

Risk Factors
- F:M=7:1
- genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake

Investigations
- high TSH, low T4 (not necessary to measure T3 as it will be low as well)
- presence of TPOAb and TgAb in serum

Treatment
- if hypothyroid, replace with L-thyroxine (analog of T4)

Myxedema Coma

Definition
- medical emergency – severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events
- rare; high level of mortality (up to 40%, despite therapy)



Subclinical Hypothyroidism: A Review
JAMA 2019;322:153-160
Background: Up to 10% of the adult population experiences subclinical hypothyroidism, defined as elevated TSH (>4.4 mU/L) with normal levels of free T4. The degree of abnormality that warrants management is controversial.
Observations: Subclinical hypothyroidism is most often caused by autoimmune thyroiditis. It may be associated with increased risk of CHF and CAD events. Further, a substantial portion of patients with subclinical hypothyroidism progress to overt hypothyroidism. Evidence from large RCTs to support levothyroxine therapy in these patients is lacking. The rationale for treatment is therefore based on levothyroxine's potential to prevent cardiovascular events and progression to overt hypothyroidism.
Recommendations: Most individuals with subclinical hypothyroidism can be observed without treatment. Candidates for levothyroxine therapy include those with serum TSH levels >10 mU/L and young and middle-aged patients with symptoms of mild hypothyroidism.



Signs and Symptoms of HYPOthyroidism

HIS FIRM CAP
Hypoventilation
Intolerance to cold
Slow HR
Fatigue
Impotence
Renal impairment
Menorrhagia/amenorrhea
Constipation
Anemia
Paresthesia

Clinical Features
- decreased mental status and hypothermia are hallmark symptoms
- hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized non-pitting edema often present

Investigations
- decreased T4, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- aggressive and immediate treatment required
- ABC's: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8 h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV once daily until oral therapy tolerated; also consider T3 therapy
- supportive measures: mechanical ventilation, vasopressors, passive rewarming, IV dextrose, fluids if necessary (risk of overload)
- monitor for arrhythmia

Non-Thyroidal Illness (Sick Euthyroid Syndrome)

Definition
- changes in the regulation of the hypothalamic-pituitary-thyroid axis, and thyroid hormone metabolism and transport among patients with severe illness, trauma, surgery, or starvation
- not due to intrinsic thyroid, pituitary, or hypothalamic disease
- initially low free T3 may be followed by low TSH and, if severe illness, low free T4
- with recovery of illness, TSH may become transiently high

Pathophysiology
- abnormalities include alterations in:
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
- may be protective during illness by reducing tissue catabolism

Labs
- initially decreased free T3 followed by decreased TSH and finally decreased free T4
- with recovery of illness, TSH may become elevated

Treatment
- treat the underlying disease; thyroid hormone replacement has not shown to be beneficial
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

Non-Toxic Goitre
Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology
- the appearance of a goitre is more likely to present during adolescence, pregnancy, and lactation due to increased thyroid hormone requirements
- early stages: goitre is usually diffuse
- later stages: multinodular non-toxic goitre with nodule, cyst formation, and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

Treatment
- remove goitrogens
- radioiodine therapy (very high doses required given low iodine uptake, used as last resort in very highly selected cases where the goiter is causing symptoms and surgery is not feasible)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary if severe compressive symptoms develop (rare); patients are often asymptomatic

Complications
- compression of neck structures causing stridor, dysphagia, pain, and hoarseness of voice
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid Nodules

Definition
- discrete lesion that can be distinguished sonographically from the rest of the thyroid parenchyma
- 19-67% prevalence based on incidentally found nodules on U/S

Etiology
- benign tumours (e.g. follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations
- approach to thyroid biopsy depending on U/S characteristics of the nodule
- benign or very small nodules suspicious for thyroid cancer do not require ongoing surveillance
- small nodules suspicious for thyroid cancer require up to five years of surveillance
- larger nodules suspicious for thyroid cancer require biopsy

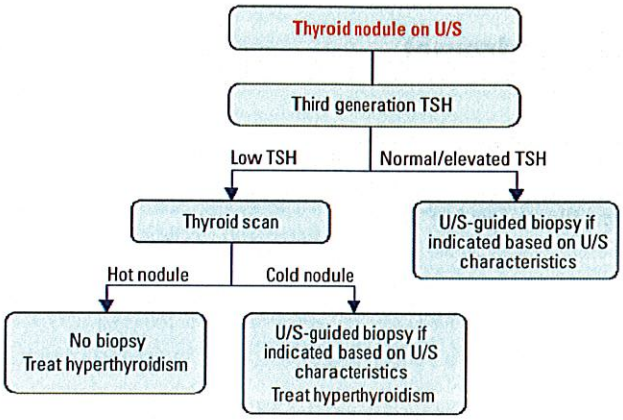


Figure 12. Approach to the evaluation of a thyroid nodule
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

Thyroid Malignancies

- see Otolaryngology, OT38

Adrenal Cortex

Adrenocorticotropic Hormone
- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400 h; trough: 1800-2400 h)
- secretion regulated by CRH and AVP
- stimulates growth of adrenal cortex and release of glucocorticoids, adrenal androgens and, to a very limited extent, mineralocorticoids
- ACTH can directly bind to MSH receptors on melanocytes, enhancing melanogenesis

Adrenocortical Hormones

Aldosterone
- a mineralocorticoid which regulates ECFV through Na^+ (and Cl^-) retention and K^+ (and H^+) excretion (stimulates distal tubule Na^+/K^+ATPase)
- regulated by the RAAS and hyperkalemia
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone ↑ volume expansion) and short loop (angiotensin II ↑ peripheral vasoconstriction)

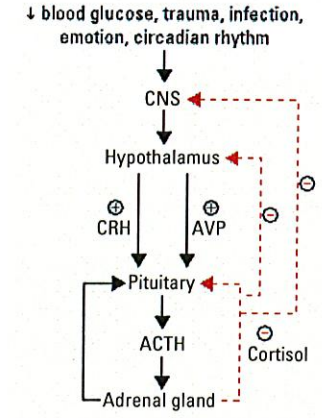
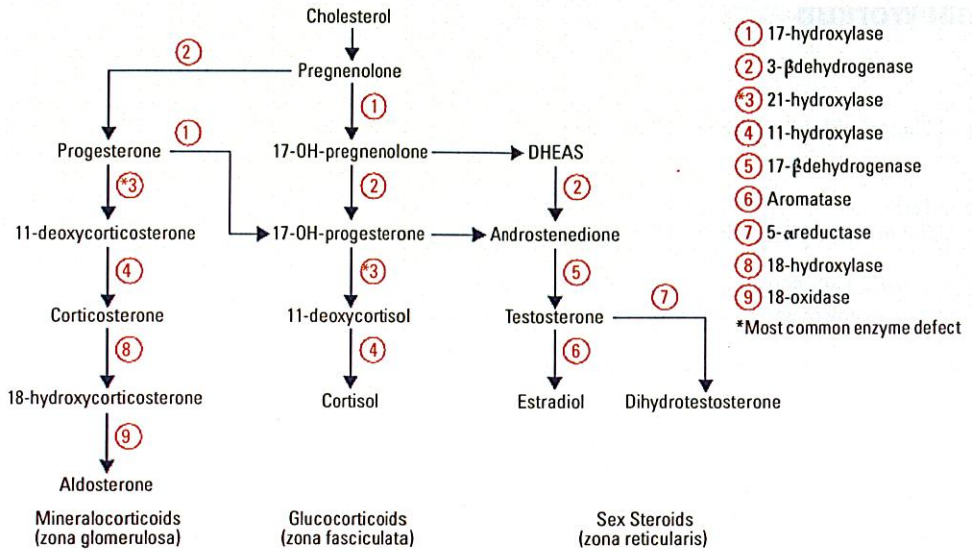


Figure 13. Regulation of CRH-ACTH-adrenal gland axis



Layers of the Adrenal Cortex

OUTSIDE

Zona Glomerulosa produces mineralocorticoids (aldosterone)

Zona Fasciculata produces glucocorticoids (cortisol)

Zona Reticularis produces androgens (DHEA, androstenedione)

INSIDE

Figure 14. Pathways of major steroid synthesis in the adrenal gland and their enzymes

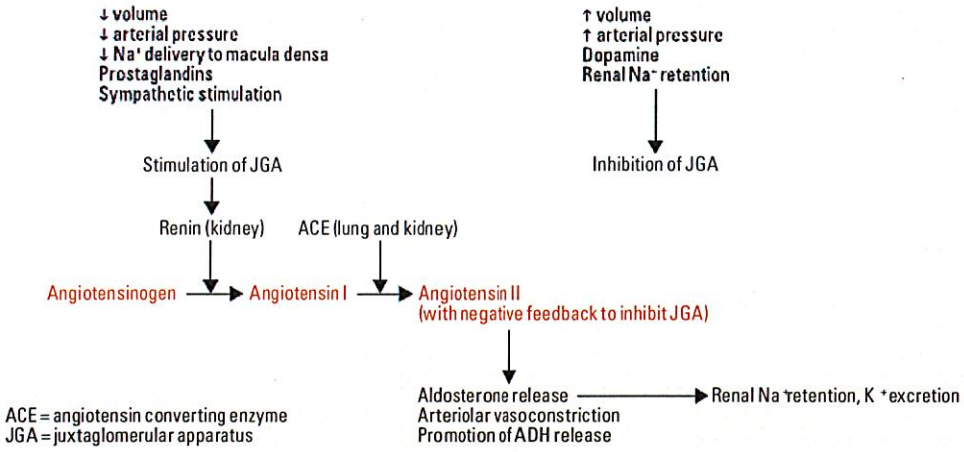


Figure 15. Renin-angiotensin-aldosterone axis (see Nephrology, NP5)

Cortisol

- a glucocorticoid regulated by the HPA axis
- involved in metabolism regulation
- supports blood pressure and vasomotor tone
- also involved in behavioural regulation and immunosuppression

Table 21. Physiological Effects of Glucocorticoids

Stimulatory Effects	Inhibitory Effects
Stimulate hepatic glucose production (gluconeogenesis)	Inhibit bone formation; stimulate bone resorption
Increase insulin resistance in peripheral tissues	Inhibit fibroblasts, causing collagen and connective tissue loss
Increase protein catabolism	Suppress inflammation; impair cell-mediated immunity
Stimulate leukocytosis and lymphopenia	Inhibit growth hormone axis*
Increase cardiac output, vascular tone, Na^+ retention	Inhibit reproductive axis*
Increase PTH release, urine calcium excretion	Inhibit vitamin D_3 and inhibit calcium uptake

*Typically only occurs with cortisol excess

Androgens

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are: DHEA, androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases with age

Adrenocortical Functional Workup

Stimulation Test
- purpose: diagnose hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

Tests of Glucocorticoid Reserve
- Cosyntropin (ACTH analogue) Stimulation Test
  - administer 250 µg cosyntropin IV/IM, and measure plasma cortisol levels before and 30 and 60 min after administration
  - physiologic response: stimulated plasma cortisol of >500 nmol/L (>18 µg/dL) at 30 or 60 min
    - physiologic response rate threshold may be lower with newer assays and should be confirmed with local lab
  - inappropriate response: inability to stimulate increased plasma cortisol; peak cortisol levels below 500 nmol/L (18 µg/dL) at 30 or 60 min

Suppression Tests
- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

1. Tests of Pituitary-Adrenal Suppressibility
- DXM suppression test
- principle: DXM suppresses pituitary ACTH, plasma cortisol should be lowered if HPA axis is normal
- screening test: low-dose overnight DXM suppression test
    - oral administration of 1 mg DXM between 11 pm and midnight, then measure plasma cortisol levels the following day between 8 am and 9 am
    - physiologic response: plasma cortisol <50 nmol (<1.8 µg/dL)
    - inappropriate response: failure to suppress plasma cortisol
    - false positive results due to obesity, depression, alcoholism, pregnancy, medications or oral contraceptive pills inducing the metabolism of DXM
  - testing of excess cortisol production
    - elevated 24 h urine free cortisol (shows overproduction of cortisol)
    - midnight salivary cortisol (if available) shows lack of diurnal variation
      - inappropriately remains high, >145 ng/dL (4 nmol/L) (normally will be low at midnight)

2. Tests of Mineralocorticoid Suppressibility
- multiple medications can interfere with the interpretation of screening and confirmatory tests for PA and these may need to be held prior to testing
- positive screen for PA is elevated aldosterone:renin ratio in the presence of high aldosterone
  - there is variability in the interpretation of aldosterone:renin ratio depending on the assays used
- confirmation of PA requires lack of aldosterone suppression: with expansion of ECFV, plasma aldosterone should be lowered
- ECFV Expansion with NS
  - IV infusion of 500 mL/h of NS for 4 h, then measure plasma aldosterone levels
  - plasma aldosterone >277 pmol/L is consistent with PA, <140 pmol/L is normal
  - inappropriate response: failure to suppress plasma aldosterone

Mineralocorticoid Excess Syndromes

Definition
- PA: excess aldosterone production (intra-adrenal cause) (previously called hyperaldosteronism)
- SA: aldosterone production in response to excess RAAS (extra-adrenal cause)

Etiology
- aldosterone-producing adrenal adenoma (Conn's syndrome)
- bilateral or idiopathic adrenal hyperplasia
- glucocorticoid-remediable aldosteronism
- aldosterone-producing adrenocortical carcinoma
- unilateral adrenal hyperplasia
- ectopic aldosterone-producing tumours
- familial hyperaldosteronism (FH) types I-IV

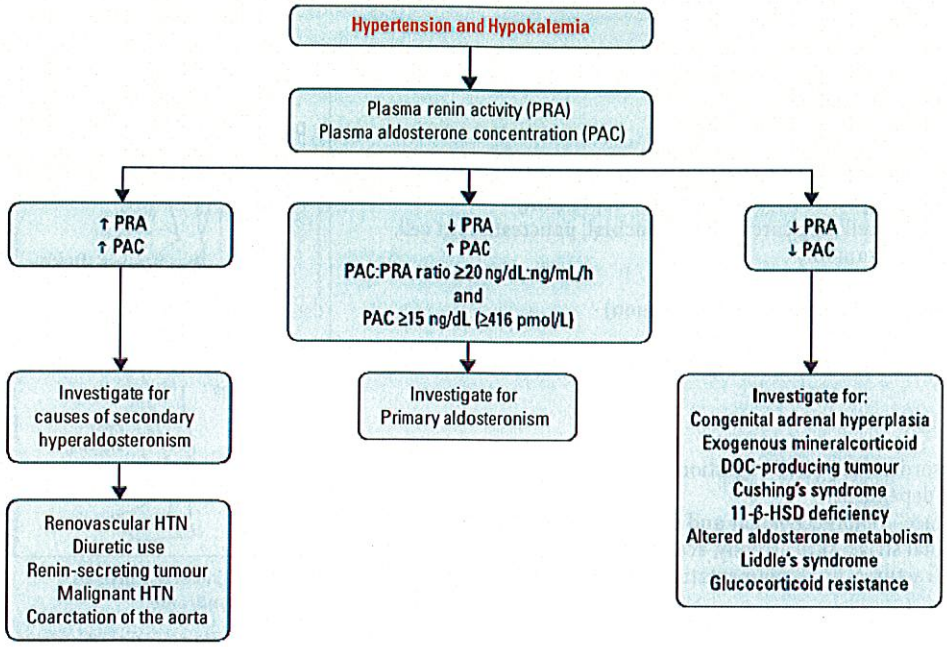


Figure 16. Approach to mineralocorticoid excess syndromes

Clinical Features

- HTN
- hypokalemia (± mild hypernatremia), metabolic alkalosis
- normal K^+, hyponatremia in secondary hyperaldosteronism (low effective circulating volume leads to ADH release)
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, and MI
- elevated risk of metabolic syndrome and T2DM
- fatigue, weakness, paresthesia, headache; severe cases present with tetany, intermittent paralysis (only if K^+<2.5 mEq/L)

Diagnosis

- investigate plasma aldosterone:renin ratio in patients with HTN and hypokalemia, drug resistant HTN, HTN and a first degree relative with PA, HTN and a family history of stoke in a first degree relative ≤40 yr, HTN and adrenal incidentaloma
- confirmatory testing for PA: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECF volume expansion), adrenal vein sampling may be required to determine whether there is lateralization of aldosterone excess
- imaging: CT adrenal glands

Table 22. Diagnostic Tests in Hyperaldosteronism

Test	Primary Hyperaldosteronism	Secondary Hyperaldosteronism
Plasma Aldosterone to Renin Ratio (PAC/PRA)	Elevated (↑ aldosterone, ↓ renin)	Normal (↑ aldosterone, ↑ renin)
Salt Loading Test (confirmatory test)		
A) Oral Salt Test	↑ 24 hour urine aldosterone	Not performed
B) IV Saline Test	Plasma aldosterone concentration >277 pmol/L (140-277 indeterminant range)	Not performed

Treatment

- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause

Cushing's Syndrome

Definition
- metabolic disorder caused by chronic glucocorticoid excess

Etiology
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and cortisol hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumour)
- ACTH-independent (15%)
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia
- iatrogenic Cushing's syndrome is likely more common than endogenous cortisol excess; it is ACTH-independent

Clinical Features
- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
- signs: central obesity, round face ("moon face"), supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism (if ACTH-dependent)

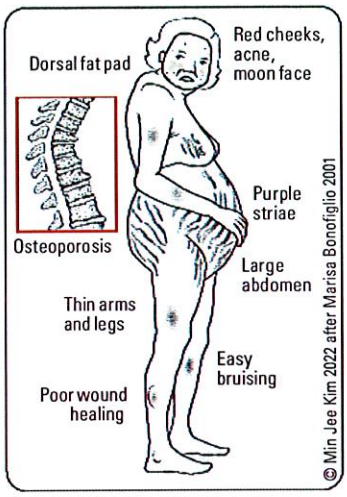


Figure 17. Clinical features of Cushing's syndrome

Diagnosis
- rule out excessive glucocorticoid exposure leading to iatrogenic Cushing's syndrome by conducting a thorough drug history before conducting biochemical testing
- perform at least one of: 1) 24 h urine free cortisol (≥2 tests), 2) low dose DXM suppression test, or 3) late night salivary cortisol (≥2 tests)
- consider reasons for a false positive (e.g. pregnancy, depression, alcoholism, morbid obesity, poorly controlled DM, glucocorticoid resistance, physical stress, malnutrition, anorexia nervosa, intense chronic exercise, hypothalamic amenorrhea, on oral contraceptive pills)
- confirm with one of the remaining tests

Treatment
- adrenal
  - adenoma: unilateral adrenalectomy (curative) with glucocorticoid supplementation postoperatively, tapering slowly until HPA axis has recovered
  - carcinoma: adrenalectomy in patients with disease localized to the adrenal, adjunctive mitotane for individuals with high-risk for current disease. Mitotane ± chemotherapy for patients with metastatic disease
  - medical treatment: ketoconazole to reduce cortisol, mitotane can be used – typically reserved for patients with malignant disease
- pituitary
  - transsphenoidal resection, with glucocorticoid supplementation postoperatively
  - if surgery delayed, contraindicated, or unsuccessful, consider medical management e.g. ketoconazole, mitotane, pasireotide, or cabergoline
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis) - surgical resection, if possible; chemotherapy/radiation for primary tumour
  - medical treatment with mitotane or ketoconazole to reduce cortisol synthesis. Often required when surgery is delayed, contraindicated, or unsuccessful
- treat comorbidities associated with hypercortisolism

Congenital Adrenal Hyperplasia

- see Pediatrics, P37

Hyperandrogenism

Definition

- state of having excessive secretion of androgens (DHEA, DHEA-sulfate, testosterone)

Etiology and Pathophysiology

Table 23. Etiology of Hyperandrogenism

Medications Androgen-Mediated	Anabolic steroids, ACTH, androgens, progestational agents
Ovarian	PCOS Ovarian hyperthecosis Theca cell tumours Pregnancy: placental sulfatase/aromatase deficiency
Adrenal	Congenital adrenal hyperplasia (CAH, late-onset CAH) Tumours (adenoma, carcinoma)
Pituitary	Cushing's disease – high ACTH Hyperprolactinemia

Clinical Features

Females

- hirsutism
  - male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism (score of >8 is abnormal for white/black women, ≥9 abnormal for Mediterranean/Hispanic/Middle-Eastern women, ≥2 for Asian women)
    - scores should be interpreted in the context of the specific patient and acknowledge limitations such as the use of cosmetic hair removal
  - scores between 8-15 are mild, 16-25 moderate, and >25 severe hirsutism
- alopecia (male pattern hair loss)
- acne
- virilization
  - frontal balding, clitoromegaly, increased muscle mass, deepening of the voice
- amenorrhea, ↓ breast size, infertility, anabolic appearance

Conditions that do Not Represent True Hirsutism

Androgen-independent hair (e.g. lanugo hair)

Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)

Topical steroid use

Males

- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in testicular size, testicular testosterone production, and spermatogenesis

Investigations

- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency; check on day 3 of menstrual cycle with a progesterone level
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose and lipids

Treatment

- discontinue causative medications (e.g. oral DHEA, valproate, danazol)
- antiandrogens, e.g. spironolactone
- oral contraceptives (increase sex hormone binding globulin, which binds androgens>estrogens; reduces ovarian production of androgens)
- surgical resection of tumour
- glucocorticoid ± mineralocorticoid if CAH confirmed
- treat specific causative disorders, e.g. tumours, Cushing's, etc.
- cosmetic therapy (laser, electrolysis)

Adrenocortical Insufficiency

Definition

- state of inadequate cortisol and/or aldosterone production by the adrenal glands

Etiology

PRIMARY ADRENOCORTICAL INSUFFICIENCY

Table 24. Etiology of Primary Adrenocortical Insufficiency

Autoimmune (70-90%)	Isolated adrenal insufficiency (Addison's Disease) Polyglandular autoimmune syndromes types I and II Antibodies often directed against adrenal enzymes and 3 cortical zones
Infections	Tuberculosis (7-20%) (most common in developing world) Fungal: histoplasmosis, paracoccidioidomycosis HIV, CMV Syphilis African trypanosomiasis
Infiltrative	Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma Sarcoidosis, amyloidosis, hemochromatosis
Vascular	Bilateral adrenal hemorrhage (risk increased by heparin and warfarin) Sepsis (meningococcal, Pseudomonas) Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children Thrombosis, embolism, adrenal infarction
Drugs	Inhibit cortisol: ketoconazole, etomidate, megestrol acetate Increase cortisol metabolism: rifampin, phenytoin, barbiturates
Others	Adrenoleukodystrophy and adrenomyeloneuropathy Congenital adrenal hypoplasia (impaired steroidogenesis) Familial glucocorticoid deficiency or resistance Defective cholesterol metabolism

SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see *Hypopituitarism, E23*), including withdrawal of exogenous steroid

Clinical Features

Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

	Primary AI (Addison's or Acute AI)	Secondary AI
Skin and Mucosa	Dark (palmar crease, extensor surface)	Pale
Potassium	High	Normal
Sodium	Normal or low	Normal or Low
Metabolic Acidosis	Present	Absent
Associated Diseases	Primary hypothyroidism, T1DM, vitiligo	Central hypogonadism or hypothyroidism, growth hormone deficiency, DI
Associated Symptoms	Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia GI: N/V, abdominal pain, diarrhea	Weakness, fatigue, weight loss, hypotension, postural dizziness, myalgia, arthralgia, headaches, visual abnormalities
Diagnostic Test	Cosyntropin Stimulation Test High morning plasma ACTH High renin	Insulin tolerance test Cosyntropin Stimulation Test Low or inappropriately normal morning plasma ACTH

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

Treatment

- acute adrenal crisis – can be life-threatening
  - IV NS 1 L within the first hour followed by continuous IV NS guided by patient requirements; add D5W if hypoglycemic
  - hydrocortisone 100 mg IV stat followed by 50 mg IV q6 h
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-25 mg PO or cortisone acetate 20-35 mg PO total daily dose in 2-3 divided doses, highest dose in the morning
  - prednisolone 3-5 mg once daily or 3-5 mg BID can be used as an alternative to hydrocortisone, especially in patients with reduced compliance
  - Florinef™ (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO once daily in primary adrenal insufficiency
  - stress dosing
    - increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
    - major stress (e.g. surgery, trauma) requires 150-300 mg hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

Adrenal Medulla

Catecholamine Metabolism

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine



ABC of Adrenaline

Adrenaline activates β-receptors, increasing Cyclic AMP

Pheochromocytoma/Paraganglioma

Definition

- paragangliomas are rare neuroendocrine tumours that arise from the extra-adrenal autonomic paraganglia (small organs comprised of neuroendocrine cells that secrete catecholamines)
- pheochromocytomas are catecholamine-secreting tumours derived from chromaffin cells of the adrenal gland

Epidemiology

- most commonly a single tumour of adrenal medulla
- rare cause of HTN (<0.2% of all hypertensives)

Etiology and Pathophysiology

- pheochromocytomas and paragangliomas have the greatest genetic inheritance among neuroendocrine tumours
- 30-40% cases are linked to germline mutations, including mutations in the RET, VHL, SDHx, NF1, and SDHAF2 genes
- pheochromocytomas and paragangliomas are divided into clusters: cluster 1 - Pseudohypoxia subtype (FH, VHL/EPAS1-related), cluster 2 - Kinase signaling group (HRAS), cluster 3 - WNT signaling group (CSDE1, UBTF-MAML3 fusion)
- most cases are sporadic; 40% of affected patients have an associated familial disorder. In these patients, the tumours are more likely bilateral adrenal pheochromocytomas/paraganglioma
- hereditary forms present earlier than sporadic cases
- several familial disorders are associated with adrenal pheochromocytoma, all have autosomal dominant inheritance, e.g. multiple endocrine neoplasia type 2 (MEN2) - 50% frequency, von Hippel-Lindau (VHL) syndrome - 10-20% frequency, and less commonly, neurofibromatosis type 1 (NF1) - 0.1-5.7% frequency
- some tumours, via an unknown mechanism, are able to synthesize and release excessive catecholamines

Clinical Features

- 50% suffer from paroxysmal HTN; others have sustained HTN
- classic triad (not found in most patients): episodic "pounding" headache, palpitations/tachycardia, diaphoresis
- other symptoms: tremor, anxiety, chest or abdominal pain, N/V, visual blurring, weight loss, polyuria, polydipsia
- other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
- symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods – such as aged/strong cheese and cured meats)

Investigations

- urine metanephrines
  - increased catecholamine metabolites (metanephrines) and catecholamines
  - plasma metanephrines, if available (most sensitive)
    - cut-off values will depend on assay used
- CT abdomen
  - if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

Treatment

- surgical excision of tumour (curative) with careful pre- and postoperative ICU monitoring
- adequate preoperative preparation
  - α-blockade for BP control: doxazosin or phenoxybenzamine (these are the most frequently used alpha blockers) (10-21 d preoperative), IV phentolamine (perioperative if required)
  - β-blockade if needed for HR control once α blocked for a few days
  - metyrosine (catecholamine synthesis inhibitor) + alpha blocker
  - volume restoration with vigorous salt-loading and fluids
- monitor for hypoglycemia postoperatively
- rescreen urine 1-3 mo postoperatively
- all patients are currently offered genetic testing - probability of germline disease increases with young age, multifocal disease, in the setting of paraganglioma

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasia



MEN 1 Affects the 3 Ps
Pituitary
Parathyroid
Pancreas

Definition

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin
- autosomal dominant inheritance with variable penetrance

Table 26. MEN Classification

Type	Tissues Involved	Clinical Manifestations
MEN 1 (chromosome 11)		
3 Ps (Pituitary, parathyroid and pancreas)	Pituitary (30-40%) Anterior pituitary adenoma	Headache, visual field defects, most commonly secrete PRL (prolactinomas are the most common pituitary functional tumour in MEN 1 leading to galactorrhea, erectile dysfunction, decreased libido, amenorrhea), GH (acromegaly). GH+PRL, ACTH (Cushing's), non-functional less common
	Parathyroid (≥95%) Primary hyperparathyroidism from hyperplasia or adenomas	Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia
	Entero-pancreatic endocrine (30-80%) Pancreatic islet cell tumours Gastrinoma Insulinomas Vasoactive intestinal peptide (VIP)-omas Glucagonoma Carcinoid syndrome Non-functional pancreatic neuroendocrine tumours	Epigastric pain (peptic ulcers and esophagitis) Hypoglycemia Secretory diarrhea Rash (necrolytic migratory erythema), anorexia, anemia, diarrhea, glossitis Flushing, diarrhea, bronchospasm
	Adrenal tumours (~40%)	
MEN 2 (chromosome 10)		
1. MEN 2A (Sipple's Syndrome)	Thyroid (>90%) Medullary thyroid cancer (MTC)	Physical signs are variable and often subtle
	Adrenal medulla (40-50%) Pheochromocytoma (40-50%)	Neck mass or thyroid nodule; non-tender, anterior lymph nodes HTN, palpitations, headache, sweating
	Parathyroid (20-30%) 1° parathyroid hyperplasia	Symptoms of hypercalcemia
	Skin Cutaneous lichen amyloidosis	Scaly skin rash
2. Familial MTC (a variant of MEN 2A)	Thyroid MTC (100%)	MTC without other clinical manifestations of MEN 2A or MEN 2B
3. MEN 2B (also known as MEN3)	Thyroid MTC (>90%)	MTC: most common component, more aggressive and earlier onset than MEN 2A
	Adrenal medulla Pheochromocytoma (≥50%)	HTN, palpitations, headache, sweating
	Neurons Mucosal neuroma, intestinal ganglioneuromas (100%)	Chronic constipation; megacolon
	MSK Marfanoid	Marfanoid habitus (no aortic abnormalities)

Investigations

- MEN 1
  - laboratory
    - offer genetic testing to all patients with a clinical diagnosis of MEN1 and their first-degree relatives
    - gastrinoma: significantly elevated serum gastrin level with a low gastric pH; when gastrin is <10x ULN a secretin stimulation test may be required
    - insulinoma: hypoglycemia with insulin and C-peptide levels that are inappropriately high for the level of glucose
    - glucagonoma: elevated glucagon levels
    - pituitary tumours: assess GH, IGF-1, 24 h urine cortisol, and PRL levels (for over-production), TSH, free T4, 8 am cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
    - hyperparathyroidism: serum Ca^{2+} and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - MRI for pituitary tumours, CT or MRI for gastrinoma, CT, MRI, or endoscopic ultrasound for insulinoma, parathyroid scan for parathyroid adenomas

- MEN 2
  - laboratory
    - genetic screening for RET mutations on chromosome 10 is the clinical standard of care in all individuals with a family history of MEN2 and has long-term benefits (early cure and prevention of MTC)
    - calcitonin levels (MTC); 24 h urine and serum metanephrines (pheochromocytoma); serum $Ca^{2+}$and PTH levels (hyperparathyroidism)
    - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - FNA for thyroid nodules cytology
  - imaging
    - neck U/S or CT to identify thyroid nodules and lymphadenopathy
    - CT or MRI of adrenal glands to localize pheochromocytoma
    - metastatic disease generally picked up with cross-sectional imaging

Treatment

- MEN 1
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress PRL secretion and shrink prolactinomas
    - somatostatin analogue for control of symptoms of some of the GI neuroendocrine tumours such as glucagonoma
  - surgery for hyperparathyroidism when surgical indications met, functional pancreatic tumours (e.g. insulinoma, glucagonoma, gastrinoma), functioning pituitary tumours (except for prolactinomas where dopamine agonists are used), and nonfunctioning pituitary tumours if associated with mass effect
    - trans-sphenoidal approach is generally preferred for pituitary tumours, pituitary irradiation if surgery is not possible or has failed
- MEN 2
  - prophylactic thyroidectomy recommended in individuals with documented pathogenic RET mutation and an increased risk of aggressive MTC; if incident case, thyroidectomy after diagnosis of MTC
    - rule out presence of pheochromocytoma and hyperparathyroidism prior to thyroidectomy
    - thyroid hormone supplementation following total thyroidectomy
  - prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
  - pheochromocytoma managed with resection
    - α-blocker for at least 10-21 d for pheochromocytoma preoperatively
  - hyperparathyroidism managed with resection of parathyroid adenoma
    - hydration, IV bisphosphonates, or denosumab for severe hypercalcemia

Primary Hyperparathyroidism
Increased PTH secretion commonly due to parathyroid adenoma, lithium therapy; less often due to parathyroid carcinoma or parathyroid hyperplasia

Secondary Hyperparathyroidism
Elevated PTH in response to low calcium, often in patients with renal failure and osteomalacia (due to low or low-normal serum calcium levels)

Tertiary Hyperparathyroidism
Irreversible monoclonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis

PH is the most common cause of hypercalcemia in healthy outpatients. PH is most commonly related to a solitary adenoma or, less commonly, multiple gland hyperplasia. Surgical excision is the definitive treatment and is recommended for patients who have symptomatic hypercalcemia, loss in bone density, kidney stones, or renal failure. For asymptomatic disease, medical surveillance may be appropriate with annual serum calcium, creatinine, and bone mineral density (BMD)

For asymptomatic patients, surgery is recommended for those who meet ≥1 of the following criteria:

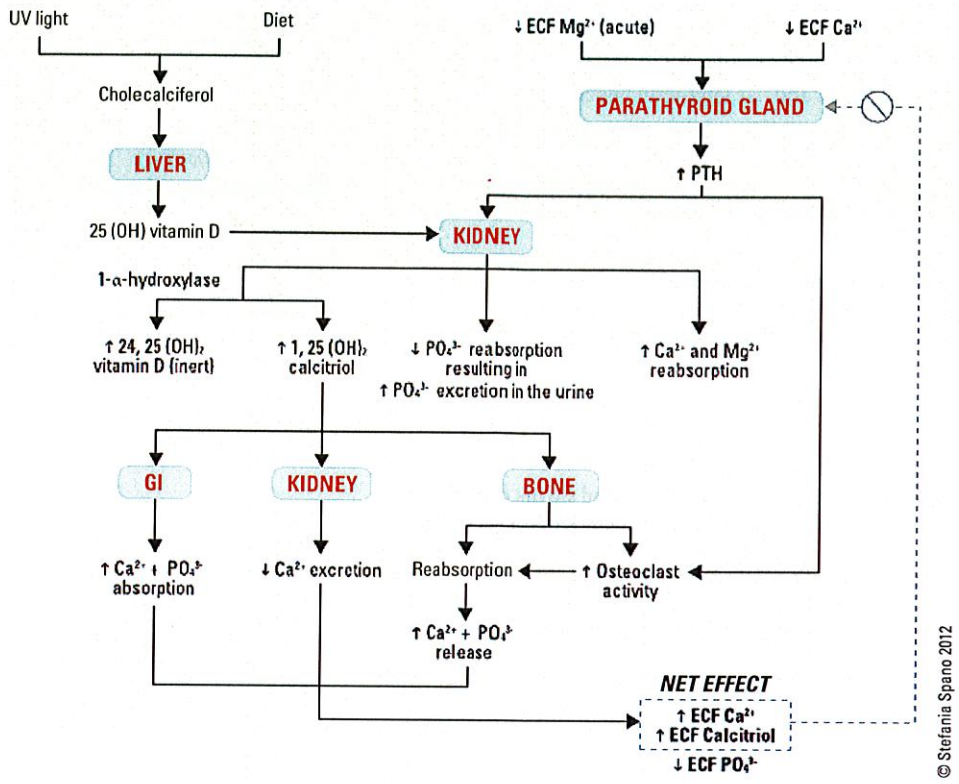
- Serum [Ca^{2+}] >0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
- Skeletal involvement: 1) a fracture by Vertebral Fracture Assessment or vertebral x-ray, or 2) BMD T-score ≤−2.5 at any site
- Renal involvement: 1) eGFR or creatinine clearance <60 mL/min, or 2) nephrocalcinosis or nephrolithiasis by x-ray, ultrasound, or other imaging modality, or 3) hypercalciuria (>250 mg/day in women; >300 mg/day in men)
- Age <50 yr (no other indications are necessary; age <50 yr is a sufficient indication)

Calcium Homeostasis

- normal total serum Ca^{2+}: 2.2-2.6 mmol/L
- ionic/free Ca^{2+}levels: 1.15-1.31 mmol/L
- serum $Ca^{2+}$is 40% protein bound (mostly albumin), 45% ionized, and 15% complexed with PO_4^{3-} and citrate
- regulated mainly by: PTH and vitamin D, whose actions are on three main organs: GI tract, bone, and kidney

Table 27. Major Regulators in Calcium Homeostasis

Major Regulators	Source	Regulation	Net Effect
PTH	Parathyroid glands	Stimulated by low serum $Ca^{2+}$and high serum PO_4^{3-} Inhibited by high serum Ca^{2+}, high calcitriol, FGF23, and chronic low serum Mg^{2+}	↑ Ca^{2+} ↑ Calcitriol ↓ PO_4^{3-}
Calcitriol ($1,25\text{-}(OH)_2D_3$)	Dietary intake of cholecalciferol (D3) or ergocalciferol (D2) OR Synthesized from cholesterol: UV light on skin makes cholecalciferol (D3). Liver then converts it to calcidiol (25-(OH)D3) and kidneys convert it to calcitriol	Stimulated by: Low serum PO_4^{3-} High PTH Inhibited by: High serum PO_4^{3-} Low PTH Calcitriol (negative feedback) FGF23	↑ Ca^{2+} ↑ PO_4^{3-}
Calcitonin	Thyroid C cells	Stimulated by: Pentagastrin (GI hormone) and high serum Ca^{2+}; inhibited by low serum Ca^{2+}	↓ Ca^{2+}(in pharmacologic doses) ↓ PO_4^{3-}
$MgCa^{2+}$	Major intracellular divalent cation	See Nephrology, NP16	Cofactor for PTH secretion
PO_4^{3-}	Intracellular anion found in all tissues	See Nephrology, NP15	↓ Ca^{2+}



Total Ca^{2+} does not reflect ionized Ca^{2+} in the following circumstances:

- Abnormal albumin levels
- Critical illness
- Chronic hepatic failure/renal failure

When albumin is low, ionized calcium assessment should be performed

If ionized calcium is not available, total calcium can be corrected for albumin using this approximation:
Corrected Ca^{2+}(mmol/L) = measured Ca^{2+} + 0.02 (40 – albumin)

- for every decrease in albumin by 10, increase in Ca^{2+} by 0.2

Treatment of Hypercalcemia in Clinical Practice

In clinical practice, treatment is required if the patient has a) symptomatic hypercalcemia or b) extremely high levels of corrected Ca^{2+}. Laboratory cutoffs may not always be used

The symptoms and signs of hypercalcemia include:
"Bones, stones, groans, and psychiatric overtones"

Figure 18. Parathyroid hormone (PTH) regulation

Hypercalcemia

Definition

- total corrected serum Ca^{2+} >2.6 mmol/L OR ionized Ca^{2+} >1.35 mmol/L

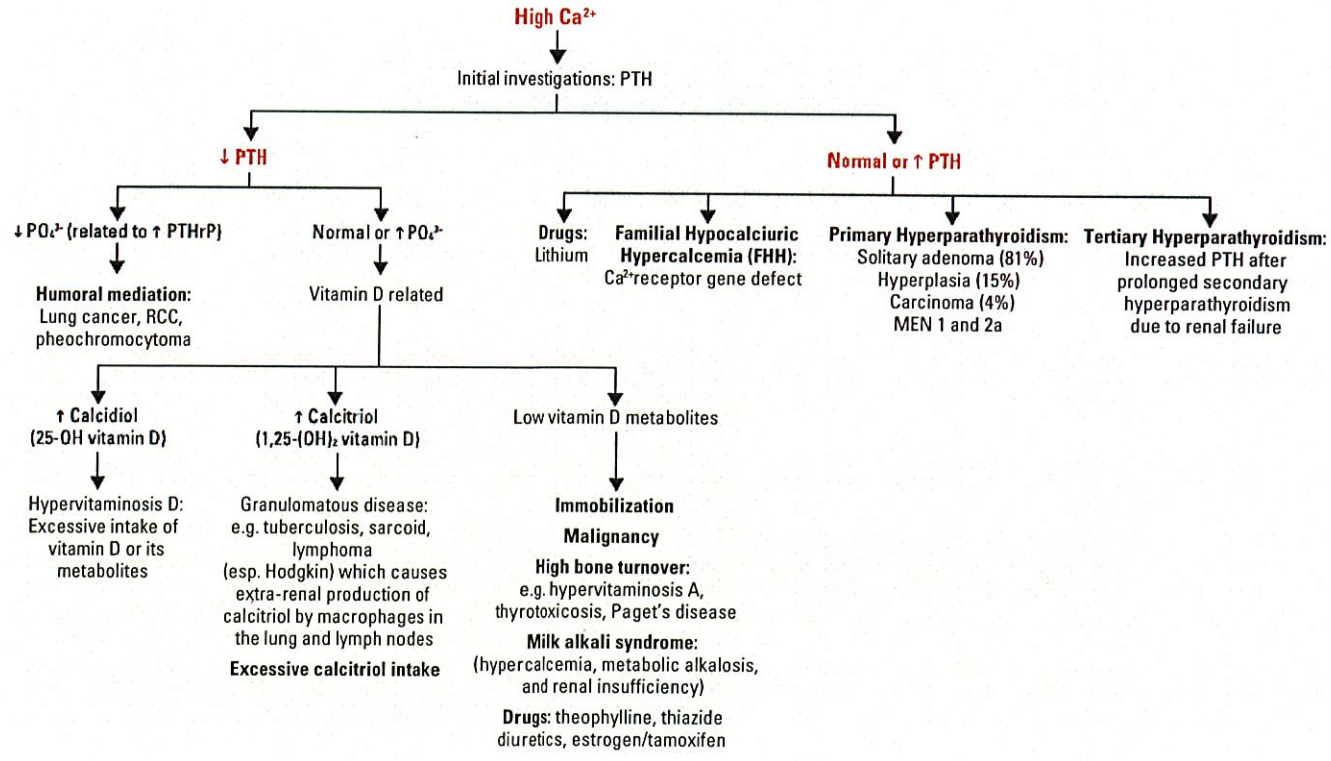


Figure 19. Differential diagnosis of hypercalcemia

Approach to Hypercalcemia

1. is the patient hypercalcemic?
2. is the PTH high/normal or low?
3. if PTH is low, is phosphate high/normal or low?
4. if phosphate is high/normal, is the level of vitamin D metabolites high or low?

Clinical Features

- symptoms depend on the absolute Ca^{2+} value and the rate of its rise (may be asymptomatic)

Table 28. Symptoms of Hypercalcemia

Cardiovascular	GI	Renal	Rheumatological	MSK	Psychiatric	Neurologic
HTN Arrhythmia Short QT Deposition of Ca^{2+} on valves, coronary arteries, myocardial fibres	Constipation Anorexia Nausea Vomiting **(groans)** PUD Pancreatitis	Polyuria (Nephrogenic DI) Polydipsia **Nephrolithiasis (stones)** Renal failure (irreversible) Dehydration	Gout Pseudogout Chondrocalcinosis	Weakness Bone pain **(bones)**	>3 mmol/L (12 mg/dL) Increased alertness Anxiety Depression Cognitive dysfunction Organic brain syndromes >4 mmol/L (16 mg/dL) **Psychosis (moans)**	Hypotonia Hyporeflexia Myopathy Paresis

** **Hypercalcemic crisis (usually >4 mmol/L or 16 mg/dL)**: primary symptoms include oliguria/anuria and mental status changes including somnolence and eventually coma → this is a medical emergency and should be treated immediately!

Treatment

- <3.0 mmol/L: mild, often asymptomatic and does not usually require urgent correction
- 3.0-3.5 mmol/L: may be well tolerated chronically and may not require immediate treatment but may be symptomatic and prompt treatment is usually indicated
- >3.5 mmol/L: severe hypercalcemia requiring urgent correction due to risk of dysrhythmia and coma
- aggressive treatment of acute symptomatic hypercalcemia
- next treat the underlying cause
- mild asymptomatic hypercalcemia: monitor and avoid thiazide, volume depletion, high Ca^{2+} diet, lithium, and bed rest

Table 29. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis

Increase Urinary Ca^{2+} Excretion	**FLUIDS, FLUIDS, FLUIDS!** Isotonic saline (4-6 L) over 24 h ± loop diuretic (e.g. furosemide) but only if hypervolemic (urine output >200 mL/h) Calcitonin: 4 IU/kg IM/SC q12 h 8 IU/kg IM/SC q6 h Only works for 48 h, can develop tachyphylaxis Rapid onset within 4-6 h Before prescribing calcitonin, remember to ask about fish allergies
Diminish Bone Resorption	Bisphosphonates (treatment of choice) Suggest zoledronic acid 4 mg IV over 15 min or pamidronate 60-90 mg IV over 2 h Inhibits osteoclastic bone resorption, preventing calcium release from bone Effects on calcium levels are typically seen at 24-48 h after administration Calcitonin often given in conjunction with bisphosphonate, given rapid onset of effect Indicated in malignancy-related hypercalcemia (IV pamidronate or zoledronic acid used) If bisphosphonates are contraindicated (i.e. severe renal impairment), denosumab can be administered concurrently with calcitonin
Decrease GI Ca^{2+} Absorption	Corticosteroids can be used in hypercalcemia mediated by 1,25 vitamin D. Corticosteroids are potent inhibitors of 1a-hydroxylase and therefore, decrease calcitriol production by activated mononuclear cells (e.g. in lymphoma, granuloma) Effects will be seen in 2-5 d
Dialysis	Treatment of last resort Indication: severe malignancy-associated hypercalcemia and renal insufficiency or heart failure

The most common cause of hypercalcemia in hospital is malignancy-associated hypercalcemia

- Usually occurs in the later stages of disease
- Most commonly seen in lung, renal, breast, ovarian, and squamous tumours, as well as lymphoma and multiple myeloma

Mechanisms:

- Secretion of PTHrP which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
- Cytokines in multiple myeloma
- Calcitriol production by lymphoma
- Osteolytic bone metastases direct effect
- Excess PTH in parathyroid cancer

Before prescribing calcitonin, remember to ask about fish allergies

Differential Diagnosis of Hypercalcemia

- Primary hyperparathyroidism
- Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)
- Renal disease: tertiary hyperparathyroidism
- Drugs: calcium carbonate, milk alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
- Familial hypocalciuric hypercalcemia
- Granulomatous disease: sarcoidosis, tuberculosis, Hodgkin's lymphoma
- Thyroid disease: thyrotoxicosis
- Adrenal disease: adrenal insufficiency, pheochromocytoma
- Immobilization

Acute Management of Hypercalcemia/ Hypercalcemic Crisis

- Volume expansion (e.g. NS IV 300-500 cc/h): initial therapy
- Calcitonin (SC): transient, partial response
- Bisphosphonate (IV): treatment of choice, adjust dose if CrCl <30 ml/min
- Corticosteroid: most useful in vitamin D toxicity, granulomatous disease, some malignancies
- Saline diuresis + loop diuretic (for volume overload): temporary measure

Hypocalcemia

Definition

- total corrected serum Ca^{2+} <2.2 mmol/L
- mild, asymptomatic: serum Ca^{2+} <1.9 mmol/L, ionized Ca^{2+} >0.8 mmol/L
- severe: serum Ca^{2+} <1.9 mmol/L and/or symptomatic

Table 30. Clinical Features of Hypocalcemia

Acute Hypocalcemia	Chronic Hypocalcemia
Paresthesia Laryngospasm (with stridor) Hyperreflexia Tetany Chvostek's sign (tap CN VII) Trousseau's sign (carpal spasm) ECG changes Delirium Psychiatric Sx: emotional instability, anxiety, and depression Seizure Note: tetany is a hallmark of hypocalcemia – can be mild or severe Mild: perioral numbness, paresthesia of hands and feet, muscle spasm Severe: carpopedal spasm, laryngospasm, focal/generalized seizures	CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson's, dystonia, hemiballismus, papilledema, pseudotumour cerebri CVS: prolonged QT interval → Torsades de pointes (ventricular tachycardia) GI: steatorrhea ENDO: impaired insulin release SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition OCULAR: cataracts MSK: generalized muscle weakness and wasting

Approach to Hypocalcemia

1. is the patient hypocalcemic?
2. is the PTH high or low?
3. if PTH is high, is phosphate low or normal?
4. is the Mg^{2+} level low?

Approach to Treatment

1. rapidity of treatment depends on severity of symptoms and serum calcium level
   a) mild, asymptomatic
      - calcium supplementation (i.e. elemental calcium 1 g then 500 mg PO TID)
   b) severe and/or symptomatic
      - severe hypocalcemia is a medical emergency
      - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion
      - if positive Chvostek's and Trousseau or seizures, first give IV calcium bolus, i.e. 1 amp IV push, then run Ca^{2+} IV drip at 1-2 mg/kg/h
2. vitamin D replacement
   - needed for GI absorption of calcium; must use 1,25 vitamin D if PTH level low (hypoparathyroidism)
3. must treat concurrent hypomagnesemia or calcium will not normalize
4. if underlying cause is hypoparathyroidism, the goal is to raise Ca^{2+} to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion

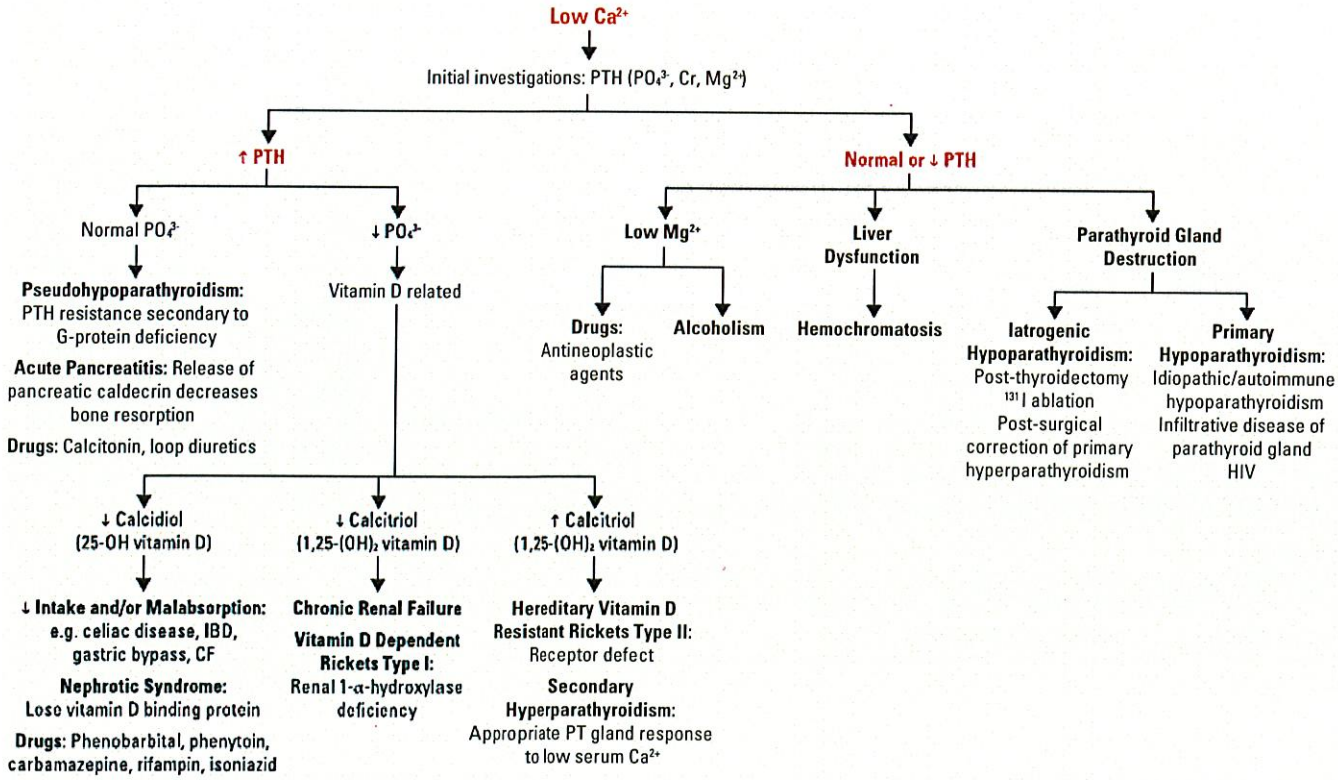


Figure 20. Etiology and clinical approach to hypocalcemia

Signs and Symptoms of Acute Hypocalcemia

- Paresthesias: perioral, hands, and feet
- Chvostek's sign: percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
- Trousseau's sign: inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia

Hypomagnesemia can impair PTH secretion and action

Watch Out for:

- Volume depletion via diuresis
- Arrhythmias

Differential Diagnosis of Tetany

- Hypocalcemia
- Metabolic alkalosis (with hyperventilation)
- Hypokalemia
- Hypomagnesemia

Transient hypoparathyroidism (resulting in hypocalcemia) is common after total thyroidectomy (permanent in <3% of surgeries)

Metabolic Bone Disease

- see 2023 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis for details

Osteoporosis

Definition

- a condition characterized by decreased bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture
- BMD is measured at hip and lumbar spine, BMD T-score ≤-2.5 is diagnostic of osteoporosis
- osteopenia (low bone mass): BMD with T-score between –1.0 and –2.5

ETIOLOGY AND PATHOPHYSIOLOGY

Table 31. Secondary Osteoporosis

Gastrointestinal diseases	Rheumatologic disorders
Gastrectomy	Rheumatoid arthritis
Malabsorption (e.G. Celiac disease, IBD, bariatric surgery)	SLE
Chronic liver disease	Ankylosing spondylitis
Eating disorder	Drugs and chemotherapy
Poor nutrition	Corticosteroid therapy
Bone marrow disorders	Anti-epileptic drugs
Multiple myeloma	Chronic heparin therapy
Lymphoma	Androgen deprivation therapy
Leukemia	Aromatase inhibitors
Endocrinopathies	Renal disease
Cushing's syndrome	Immobilization
Hyperparathyroidism	COPD (due to disease, tobacco, and glucocorticoid use)
Hyperthyroidism	
Premature menopause	
Dm	
Hypogonadism	
Malignancy	
Secondary to chemotherapy	
Myelomasevere: carpopedal spasm, laryngospasm, focal/ generalized seizures	

Clinical Features

- always asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist (see *Figure 21, E48*)
  - fragility fractures: fracture with fall from standing height or less (does not include fractures of hand, face, cervical spine, fingers, and toes)
  - Kyphosis: collapse fracture of vertebral bodies in thoracic region
  - x-ray: vertebral compression fractures (described as wedge fractures, require a minimum of 20% height loss), "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
  - pain, especially backache, associated with fractures

Approach to Osteoporosis

1. assess risk factors for osteoporosis on Hx and physical
2. decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr (or younger if presence of risk factors, see *Table 33, E47*)
3. initial investigations
   - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis if vertebral fractures, celiac workup, PTH, and 24 h urinary Ca^{2+}excretion to rule out additional secondary causes
   - 25-OH-vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture (or in individuals at moderate risk of fracture to help decide if they require medical therapy)
4. assess 10 yr fracture risk by combining BMD result and risk factors
   1) WHO Fracture Risk Assessment Tool (FRAX)
   2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
   - approach to management guided by 10 yr risk stratification into low, medium, and high-risk
5. for all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see *Table 34, E37*).

Corticosteroid Therapy is a Common Cause of Secondary Osteoporosis
Individuals receiving ≥7.5 mg of prednisone daily for over 3 mo should be assessed for bone-sparing therapy
Mechanism: increased resorption + decreased formation + increased urinary calcium loss + decreased intestinal calcium absorption + decreased sex steroid production

Calcium plus Vitamin D Supplementation and Risk of Fractures
Osteoporosis Int 2015;27:367-376
Purpose: To review trials of vitamin D and calcium therapy for reducing fracture risk in osteoporosis.
Study: Systematic review searching 2011-2015, inclusive, identified 8 RCTs totaling 30970 participants. RCTs reviewed included healthy adults and ambulatory older adults with medical conditions (excluding cancer). Vitamin D and calcium combination therapy was compared to placebo.
Results: Analysis of RCT data revealed that calcium plus vitamin D supplementation produced a statistically significant reduction in risk of total fractures (0.85; CI:0.73-0.98) and in hip fractures (0.70; CI:0.56-0.87). Subgroup analysis was significant for community dwelling or institutionalized patients.
Conclusions: Systematic analysis suggests that vitamin D and calcium therapy significantly decreases fracture risk. This study did not specifically look at individuals with osteoporosis. However, it still supports that vitamin D and calcium should continue to be used as preventive treatment for individuals at increased risk of fractures.

Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis
JAMA Netw Open 2019;2:e1917789
Purpose: To investigate if fracture risk is associated with supplementation with vitamin D alone or vitamin D in combination with calcium.
Study Selection: Observational studies with ≥200 fracture cases and RCTs with ≥500 participants that reported ≥10 incident fractures.
Results: Vitamin D supplementation alone was not associated with a reduced risk of any fracture or hip fracture (RR, 1.14; 95% CI, 0.98-1.32). However, combined supplementation with vitamin D (400-800 IU daily) and calcium (1000-1200 mg daily) was associated with a 6% reduction in fracture risk (RR, 0.94; 95% CI, 0.89-0.99) and a 16% reduction of hip fracture risk (RR, 0.84; 95% CI, 0.72-0.97).
Conclusion: Vitamin D alone was not associated with reduced fracture risk but daily supplementation with a combination of vitamin D and calcium was.

Clinical Signs of Fractures or Osteoporosis
- Height loss >3 cm (Sn 92%)
- Weight <51 kg (Sp 97%)
- Kyphosis (Sp 92%)
- Tooth count <20 (Sp 92%)
- Grip strength
- Armspan-height difference >5 cm (Sp 76%)
- Wall-occiput distance >4 cm (Sp 92%)
- Rib-pelvis distance ≤2 finger breadth (Sn 88%)

Table 32. Indications for BMD Testing

Older Adults (age ≥50 yr)	Younger Adults (age <50 yr)
All women and men age ≥65 yr Menopausal women, and men 50-64 yr with clinical risk factors for fracture: Fragility fracture after age 40 Prolonged glucocorticoid use Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy) Parental hip fracture Vertebral fracture or osteopenia identified on x-ray Current smoking High alcohol intake Low body weight (<60 kg) or major weight loss (>10% of weight at age 25 yr) Rheumatoid arthritis Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. inflammatory bowel disease)	Fragility fracture: Prolonged use of glucocorticoids Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy, anticonvulsants) Hypogonadism or premature menopause Malabsorption syndrome Primary hyperparathyroidism Other disorders strongly associated with rapid bone loss and/or fracture

Table 33. Osteoporosis Risk Stratification

Low-Risk 10 yr fracture risk <10%	Unlikely to benefit from pharmacotherapy; encourage lifestyle changes Reassess risk in 5 yr
Medium-Risk 10 yr fracture risk 10-20%	Discuss patient preference for management and consider additional risk factors Factors that warrant consideration for pharmacotherapy: Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray Previous wrist fracture in individuals ≥65 yr or with T-score ≤−2.5 Lumbar spine T-score much lower than femoral neck T-score Rapid bone loss Men receiving androgen-deprivation therapy for prostate cancer Women receiving aromatase-inhibitor therapy for breast cancer Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use Recurrent falls (defined as falling 2 or more times in the past 12 mo) Other disorders strongly associated with osteoporosis Repeat BMD and reassess risk every 1-3 yr initially
High-Risk 10 yr fracture risk >20%; OR Prior fragility fracture of hip or spine; OR More than one fragility fracture	Start pharmacotherapy (need to consider patient preference)

Treatment of Osteoporosis

Table 34. Treatment of Osteoporosis in Women and Men

Treatment for Both Men and Women	
Lifestyle	Diet: elemental calcium 1000-1200 mg/d; vitamin D 1000 IU/d Exercise: 3x30 min weight-bearing exercises, balance exercise, and aerobic exercise/wk Cessation of smoking, reduce caffeine intake Stop/avoid osteoporosis-inducing medications
Drug Therapy	
Bisphosphonate: inhibitors of osteoclasts	1st line in prevention of hip, nonvertebral, and vertebral fractures (Grade A): alendronate (PO), risedronate (PO), zoledronic acid (IV)
RANKL Inhibitors	Denosumab: 1st line in prevention of hip, nonvertebral, vertebral fractures (Grade A) *Denosumab should not be abruptly stopped/administration delayed. Increased risk of multiple vertebral fractures due to increased bone turnover on discontinuation. Used as an alternative initial treatment in postmenopausal women with osteoporosis who are at high risk for osteoporitic fractures.
Parathyroid Hormone Analogue	Teriparatide: 18-24 mo duration, followed by long-term anti-resorptive therapy with bisphosphonate or RANKL inhibitor
Sclerostin Inhibitors	Romosozumab: 12 mo duration
Treatment Specific to Post-Menopausal Women	
SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast	Raloxifene: evidence for prevention of vertebral fractures (Grade A) Advantages: prevents osteoporotic fractures (Grade A to B evidence), improves lipid profile, decreased breast cancer risk Disadvantages: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps
HRT: combined estrogen + progesterone (see Gynecology, GY36)	Indicated for vasomotor symptoms of menopause For most women, risks > benefits Combined estrogen/progestin prevents hip, vertebral, total fractures Increased risks of breast cancer, cardiovascular events, and DVT/PE

Online Clinical Tools
FRAX
www.shef.ac.uk/FRAX/tool.aspx
CAROC
www.osteoporosis.ca/multimedia/pdf/CAROC.pdf

Prevention - Hip

Alendronate	0.61 RR (0.42-0.90)
Risedronate	0.73 RR (0.58-0.92)
Denosumab	0.56 RR (0.35-0.90)
Teriparatide	0.64 RR (0.25-1.68)
Romosozumab	0.44 RR (0.24-0.79)

Prevention - Nonvertebral

Alendronate	0.84 RR (0.74-0.94)
Risedronate	0.78 RR (0.68-0.89)
Denosumab	0.80 RR (0.67-0.96)
Teriparatide	0.62 RR (0.47-0.80)
Romosozumab	0.67 RR (0.53-0.86)

Prevention - Vertebral

Alendronate	0.57 RR (0.45-0.71)
Risedronate	0.61 RR (0.48-0.78)
Denosumab	0.32 RR (0.22-0.45)
Teriparatide	0.27 RR (0.19-0.38)
Romosozumab	0.33 RR (0.22-0.49)

Factors Necessary for Mineralization
- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial
JAMA 2019;322:736-45
Purpose: To investigate the effects of vitamin D supplementation on volumetric BMD and strength.
Methods: 311 healthy adults (ages 55-70) without osteoporosis, with baseline concentrations of 25-hydroxyvitamin D of 30-125 nmol/L, were randomized to receive daily doses of 400 IU, 4000 IU, or 10000 IU vitamin D3 for 3 years. For participants with calcium dietary intake <1200 mg/d, supplementation was provided. Primary Outcome: Total volumetric BMD at radius and tibia.
Results: Compared with the 400 IU group, radial volumetric BMD was significantly lower for the 4000 IU group (-3.9 mg HA/cm3; 95% confidence interval (CI), -6.5 to -1.3) and 10000 IU group (-7.5 mg HA/cm3; 95% CI, -10.1 to -5.0) with mean % change of -1.2% (400 IU), -2.4% (4000 IU), and -3.5% (10000 IU). Compared with the 400 IU group, tibial volumetric BMD differences were -1.8 mg HA/cm3 (95% CI, -3.7 to 0.1) (4000 IU) and -4.1 mg HA/cm3 (95% CI, -6.0 to -2.2) (10000 IU), with mean % change values of -0.4% (400 IU), -1.0% (4000 IU), and -1.7% (10000 IU).
Conclusion: In healthy adults, supplementation with daily 4000 IU or 10000 IU vitamin D for 3 years was associated with lower radial BMD compared with 400 IU. 10000 IU was associated with lower tibial BMD. There were no apparent benefits of high-dose vitamin D supplementation for bone health.

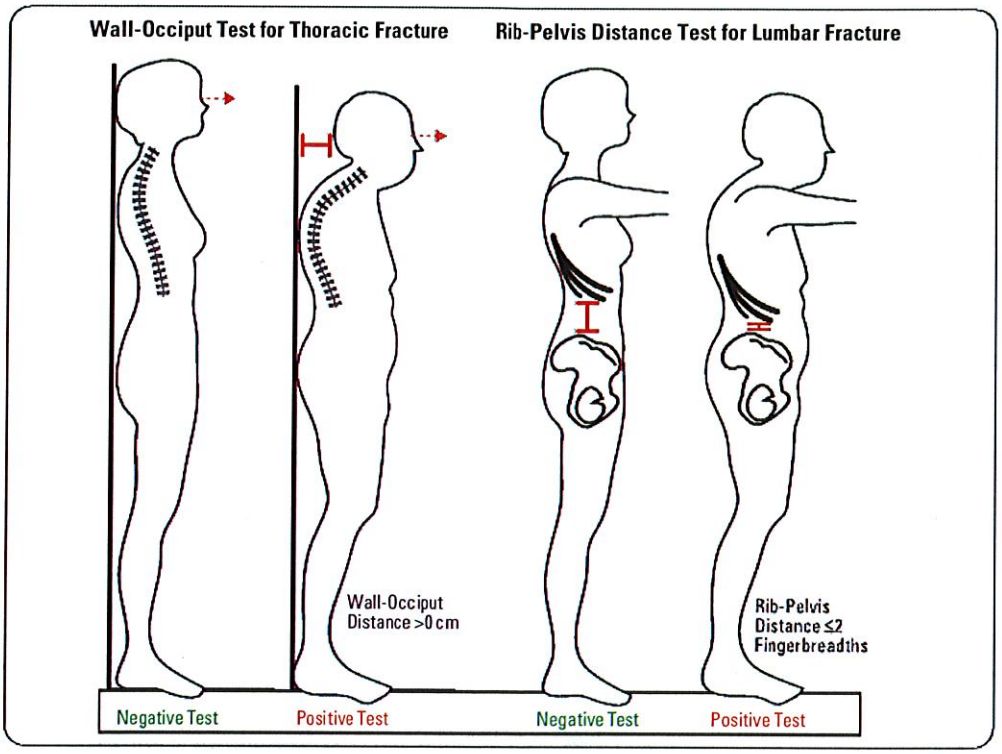


Figure 21. Physical examination test for vertebral fractures

Osteomalacia and Rickets

Definition

- osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure: rickets (in childhood), osteomalacia (in adulthood)

Etiology and Pathophysiology

Vitamin D Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
- loss of vitamin D binding protein
  - nephrotic syndrome
- decreased 1-α-25 hydroxylation
  - hypoparathyroidism
- renal failure

Mineralization Defect

- abnormal matrix
  - osteogenesis imperfecta
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - aluminum, high dose fluoride, anticonvulsants

Calcium Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption
- hypercalciuria (in combination with renal phosphate wasting)

Hypophosphatemia

- gastrointestinal: poor nutritional intake, chronic diarrhea, excessive phosphate binders
- renal phosphate wasting
  - tumour-induced osteomalacia
  - Fanconi syndrome
  - X-linked/autosomal dominant/recessive hypophosphatemic rickets

Matrix Abnormalities
- type IV osteogenesis imperfecta
- fibrogenesis imperfecta ossium
- axial osteomalacia

Table 35. Clinical Features of Rickets and Osteomalacia

Rickets	Osteomalacia
Skeletal pain and deformities, bow-legged	Not as severe
Fracture susceptibility	Diffuse skeletal pain
Weakness and hypotonia	Bone tenderness
Disturbed growth	Fractures
Rachitic rosary (prominent costochondral junctions)	Gait disturbances (waddling)
Harrison's groove (indentation of lower ribs)	Proximal muscle weakness
Hypocalcemia	Hypotonia

Investigations

Table 36. Laboratory Findings in Osteomalacia and Rickets

Disorder	Serum Phosphate	Serum Calcium	Serum ALP	Other Features
Vitamin D Deficiency	Decreased	Decreased to normal	Increased	May have decreased calcitriol
Hypophosphatemia	Decreased	Normal	Increased	
Proximal Renal Tubular Acidosis	Decreased	Normal	Normal	Associated with hyperchloremic metabolic acidosis
Conditions Associated with Abnormal Matrix Formation	Normal	Normal	Normal	

- radiologic findings
  - pseudofractures (i.e. Looser zones), fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

Treatment
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO_4^{3-} supplements if low serum PO_4^{3-}, Ca^{2+} supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

KDIGO 2017 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease
- Kidney Inter Suppl 2017;7(1):1-60
- Recommendations for Metabolic Bone Disease (MBD) in Chronic Kidney Disease (CKD)

Screening
- In CKD patients with evidence of CKD-MBD and/or risk factors for osteoporosis, perform BMD testing to assess fracture risk if results will impact treatment decisions
- In patients with CKD-BMD, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions

Management
- Treatment of CKD-MBD should be based on serial assessments of PO_4^{3-}, Ca^{2+}, and PTH levels, considered together
- Suggest lowering elevated PO_4^{3-} levels towards the normal range
- Avoid hyperglycemia in adult patients and maintain serum Ca^{2+} in age-appropriate normal range in children

Renal Osteodystrophy

Definition
- changes to mineral metabolism and bone structure secondary to CKD
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoids
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology
- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)2 vitamin D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features
- soft tissue calcifications, necrotic skin lesions if vessels involved
- osteodystrophy, generalized bone pain, and fractures
- pruritus
- neuromuscular irritability and tetany may occur (with low serum calcium)
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations
- serum Ca^{2+} corrected for albumin, PO_4^{3-}, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy (gold standard; only done if results inform treatment)

Treatment
- prevention
- maintenance of normal serum Ca^{2+} and PO_4^{3-} by restricting PO_4^{3-} intake to 1 g once daily
- Ca^{2+} supplements; PO_4^{3-} binding agents (calcium carbonate, aluminum hydroxide)
- activated vitamin D (calcitriol) with close monitoring to avoid hypercalcemia and metastatic calcification
- bisphosphonates and denosumab are not often used for treatment (can worsen the adynamic components of renal osteodystrophy) as they are contraindicated at low eGFRs; bone biopsy may indicate if there are signs of increased bone turnover amenable to bisphosphonates

Paget's Disease of Bone

Definition
- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
- 3% of the population, 10% of population >80 y/o
- consider Paget's disease of bone in older adults with elevated ALP but normal GGT

Etiology and Pathophysiology
- postulated to be related to a slowly progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis
- osteogenic sarcoma
- multiple myeloma
- fibrous dysplasia
- osteitis fibrosa cystica
- metastases

Clinical Features
- usually asymptomatic (routine x-ray finding or elevated serum ALP with normal LFTs)
- 3 characteristic findings: osteolytic lesions, cortical thickening, pseudofractures (small fissures which develop in the convex surface of long bone)
- most commonly affects: skull, thoracolumbar spine, pelvis, and long bones of lower extremities
- severe bone pain (e.g. pelvis, femur, tibia)
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- increased risk of osteosarcoma and giant cell tumours

Investigations
- laboratory
  - high serum ALP, normal or high Ca^{2+}, normal PO_4^{3-}
  - normal tests LFTs (prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), albumin, bilirubin)
  - elevated procollagen type I N-terminal propeptide (PINP) (bone formation marker)
- imaging
  - plain x-ray of skull and facial bones, abdomen, and tibiae are recommended as initial screening in patients suspected to have Paget's
  - confirmation on x-ray required for diagnosis
    - denser bone with cortical thickening
    - characteristic findings: osteolytic lesions, cortical thickening, and pseudofractures
    - burned-out Paget's disease: when the disease has been present for a long time
  - bone scan, to evaluate the extent of disease and identify asymptomatic sites, in addition to targeted x-ray are recommend to fully and accurately define the extent of metabolically active Paget's disease
  - MRI or CT are not recommended for diagnosis, but can be used to assess disease complications, particularly if malignancy is suspected

Table 37. Paget's Disease-Related Signs

Signs	Descriptions
Tam o'Shanter	Appearance of advanced Paget's disease of the skull – overall enlargement of cranium, skull falling over the facial bones
Blade of grass	Lucent leading edge in a long bone seen in lytic phase of Paget's
Osteoporosis circumscripta	Radiolucent regions of the skull
Jigsaw pattern bone or mosaic pattern bone	Thickened, disorganized trabeculae lead to areas of sclerosis
Picture frame vertebra	Cortex of vertebral body is thickened
Cotton wool appearance of bone	Results from thickened, disorganized trabeculae that lead to areas of sclerosis
Banana fracture	Horizontal pathological fracture seen in bones deformed by Paget's
Looser zones	Wide, transverse lucencies traversing through a bone
Ivory vertebra	Diffuse and homogenous increase in opacity of a vertebral body

Complications

- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions, and suddenly increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output CHF due to increased vascularity

Treatment

- goals: decrease pain, decrease rate of remodelling
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if symptomatic or asymptomatic with ALP >3x normal or planned surgery
  - bisphosphonates, e.g. zoledronic acid 5 mg IV per yr (preferred) OR alendronate 40 mg PO once daily x 6 mo OR risedronate 30 mg PO once daily x 3 mo
  - calcitonin 50-100 U/d SC if unable to tolerate bisphosphonates
- surgery for fractures, deformity, degenerative changes
- joint replacement surgery and osteotomy are recommended for the treatment of osteoarthritis resistant to medical therapy in patients with Paget's

Male Reproductive Endocrinology

Androgen Regulation

- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

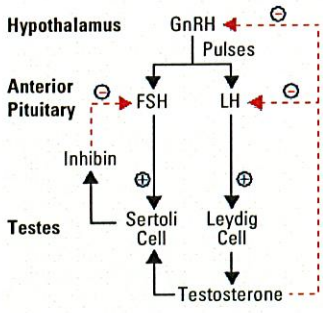


Figure 22. Hypothalamo-pituitary-gonadal axis

Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm in adult)
  - can use orchidometer to measure testicular volume (12-25 mL = adult size)
- LH, FSH, total, bioavailable, and/or free testosterone
- semen analysis
  - semen volume, sperm concentration, morphology, and motility are the most commonly used parameters
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility

- see Urology, U37
- deficiency in gametogenesis or testosterone production

Two Distinct Features of Primary Hypogonadism

The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level

Likely to be associated with gynecomastia

Etiology

- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure), and idiopathic

Diagnosis of Testosterone Deficiency Syndrome (i.e. adult onset primary hypogonadism)

- requires clinical manifestations of testosterone deficiency (see sidebar) AND documented testosterone levels below the laboratory reference range (confirmed on 2 separate analyses, test needs to be done at 8-9 am when testosterone is usually at its peak)
- rule out secondary causes

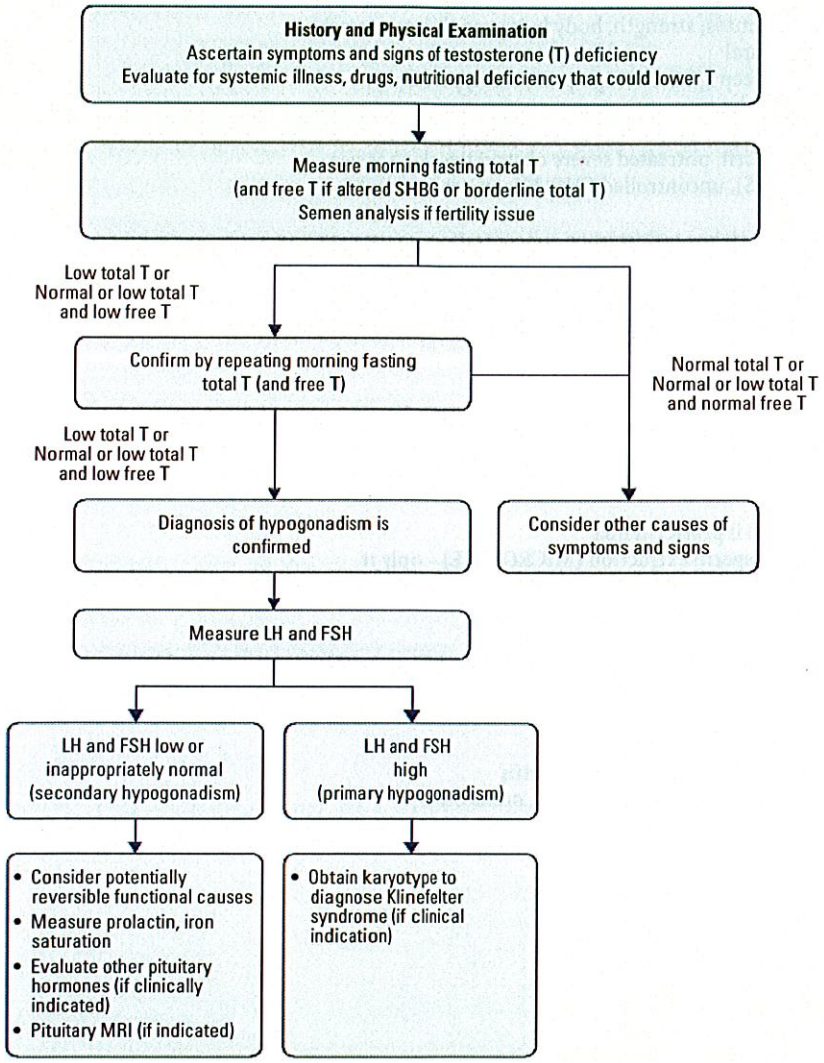


Figure 23. Diagnostic approach to testosterone deficiency

Table 38. Classification and Features of Hypogonadism

	Hypergonadotropic Hypogonadism (Primary Hypogonadism)	Hypogonadotropic Hypogonadism (Secondary Hypogonadism)
Definition	Primary testicular failure ↑ LH and FSH ↓ testosterone and sperm count	Hypothalamic-pituitary axis failure ↓ LH and FSH (LH sometimes inappropriately normal) ↓ testosterone and sperm count
Etiology	Congenital Chromosomal defects (Klinefelter, Noonan) Cryptorchidism Disorders of sexual development (DSD) Bilateral anorchia (vanishing testicle syndrome) Myotonic dystrophy Mutation of FSH or LH receptor gene Disorders of androgen synthesis Germ cell defects Sertoli cell only syndrome Leydig cell aplasia/failure Infection/Inflammation Orchitis – tuberculosis, lymphoma, mumps, leprosy Genital tract infection Physical factors Trauma, heat, irradiation, testicular torsion, varicocele Drugs Cannabis, alcohol, chemotherapy, ketoconazole, glucocorticoid, spironolactone	Congenital Kallman's syndrome Prader-Willi syndrome Abnormal subunit of LH or FSH Infection Tuberculosis, meningitis Endocrine Adrenal androgen excess Cushing's syndrome Hypo or hyperthyroidism Hypothalamic-pituitary disease (tumour, hyperprolactinemia, hypopituitarism) Drugs Alcohol, cannabis, spironolactone, ketoconazole, GnRH agonists, androgen/estrogen/progestin use, chronic narcotic use Chronic illness Cirrhosis, chronic renal failure, AIDS Sarcoidosis, Langerhan's cell histiocytosis, hemochromatosis Critical illness Surgery, MI, head trauma Obesity Idiopathic
Diagnosis	**Testicular size and consistency (soft/firm)** Sperm count LH, FSH, total, and/or bioavailable testosterone hCG stimulation (mainly used in pediatrics) Karyotype	**Testicular size and consistency (soft/firm)** Sperm count LH, FSH, total, and/or bioavailable testosterone Prolactin levels (and pituitary panel - T4/8 AM cortisol) Fe, transferrin MRI of hypothalamic-pituitary region

Approach to Male Infertility

Infertility: failure of a couple to conceive after 12 mo of regular intercourse without use of contraception in women <35 yr of age; after 6 mo of regular intercourse without use of contraception in women ≥35 yr

History
- Partner status regarding infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Previous Surg, Med Hx, STI Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking
- Other: validated questionnaires (e.g. ADAM questionnaire)

Physical Examination
- General (height, weight, gynecomastia, masculine)
- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

Investigations
- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/testicular U/S (look for varicocele)
- Blood work: LH, FSH, testosterone, PRL, thyroid function tests, DNA fragmentation of sperm, karyotype, Y chromosome deletion
- Test female partner (see Gynecology, GY24)

Treatment
- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, in vitro fertilization (IVF), therapeutic donor insemination, testicular aspiration of sperm, adoption

Treatment
- goal: testosterone replacement (improve libido, muscle mass, strength, body hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
  - contraindicated in men with prostate or breast cancer, a palpable prostate nodule, prostate-specific antigen (PSA) >4 ng/mL, elevated hematocrit, untreated severe obstructive sleep apnea (OSA), severe lower urinary tract symptoms (LUTS), uncontrolled CHF, MI, or stroke in last 6 mo, or thrombophilia
  - not suggested in men >65 yr, in men with T2DM with low testosterone concentrations, or in men planning fertility in the near term
  - testosterone therapy only to treat symptoms of hypogonadism, often results in decreased spermatogenesis (and reduced sperm counts) by further suppression of hypothalamic-pituitary-gonadal axis and suppression of endogenous testosterone production
- goal: fertility
  - treat underlying cause
  - GnRH agonist if hypothalamic dysfunction with intact pituitary, administered SC in pulsatile fashion using an external pump
  - hCG ± recombinant follicle stimulating hormone (rFSH) in cases of either hypothalamic or pituitary lesions
  - dopamine agonist (e.g. bromocriptine, cabergoline) if prolactinoma
  - testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

Other Causes of Male Infertility
- hereditary disorders: Kartagener syndrome (primary ciliary dyskinesia), cystic fibrosis (absence of the vas deferens)
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: transurethral resection of the prostate (TURP), radical prostatectomy, orchiectomy

DEFECTS IN ANDROGEN ACTION

Etiology
- complete androgen insensitivity (CAIS)
- partial androgen insensitivity (PAIS)
- 5-α-reductase deficiency
- mixed gonadal dysgenesis
- defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

Clinical Features
- depends on age of onset

Table 39. Effects of Testosterone Deficiency

First Trimester *in utero*	Incomplete virilization of external genitalia (ambiguous genitalia) Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphrodism)
Third Trimester *in utero*	Micropenis Cryptorchidism (failure of normal testicular descent)
Prepuberty	Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair) Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones) Poor muscle development, reduced peak bone mass
Postpuberty	Decrease in energy, mood, and libido Fine wrinkles in corners of mouth and eyes Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD

Adapted from: UpToDate, 2010; Cecil's Essentials of Medicine

Treatment
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)

Erectile Dysfunction

- see Urology, U33

Gynecomastia

Definition

- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- physiologic gynecomastia – trimodal distribution in neonatal, pubertal, and older males
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals



Pubertal Gynecomastia

- This benign condition peaks between ages 13-14 and spontaneously regresses in 90% of cases within 2 yr
- Waiting is often the best approach

Etiology

- physiologic gynecomastia – trimodal distribution in neonatal, pubertal, and older males
- drugs spironolactone, cimetidine, ketoconazole, recombinant human GH, hCG, estrogens, antiandrogens, GnRH agonists, 5-α-reductase inhibitors, androgen deprivation therapy (ADT)
- surgical ADT (orchiectomy) for prostate cancer
- starvation and refeeding
- male hypogonadism
- cirrhosis – due to reduced ability of liver to metabolize and inactivate estrogens
- treatment of HIV infection – due to fat tissue as part of lipodystrophy
- herbal products – plant-derived oils such as lavender and tea tree oil
- idiopathic
- testicular neoplasms
- CKD
- other rare causes: feminizing adrenal tumours, disorders of sex development, ectopic hCG, familial prepubertal gynecomastia
- hyperthyroidism



Causes of Gynecomastia

DOC TECH
Drugs (especially antiandrogens, i.e. spironolactone)
Other
Congenital (Klinefelter syndrome)
Tumour (especially germ cell tumours)
Endocrine (hyperthyroidism)
CHronic disease (cirrhosis, CKD)

Pathophysiology

- hormonal imbalance due to:
  - increased estrogen activity
    - increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen, or decreased metabolism/inactivation
  - decreased androgen activity
    - decreased androgen production, binding of androgen to sex hormone binding globulin (SHBG), or androgen receptor blockage



Drugs Causing Gynecomastia

DISCKO
Digoxin
Isoniazid
Spironolactone
Cimetidine
Ketoconazole
Oestrogen/anti-testosterone

History

- recent change in breast characteristics
- pain
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction



Occurrence of Gynecomastia

3 Peaks	% Affected
Infancy	60-90
Puberty	4-69
Ages 50-80	24-65

Physical Exam

- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard or fixed mass, skin dimpling or retraction, and nipple discharge (especially bloody) or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue
- genito-urinary exam
- stigmata of liver or thyroid disease

Investigations

- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated, need to locate the primary tumour); however not all investigations are required for every case of gynecomastia
- if the differentiation between gynecomastia and breast carcinoma cannot be made on the basis of clinical findings alone, the patient should undergo diagnostic mammography, which has 90% sensitivity and specificity for distinguishing malignant from benign breast diseases
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)

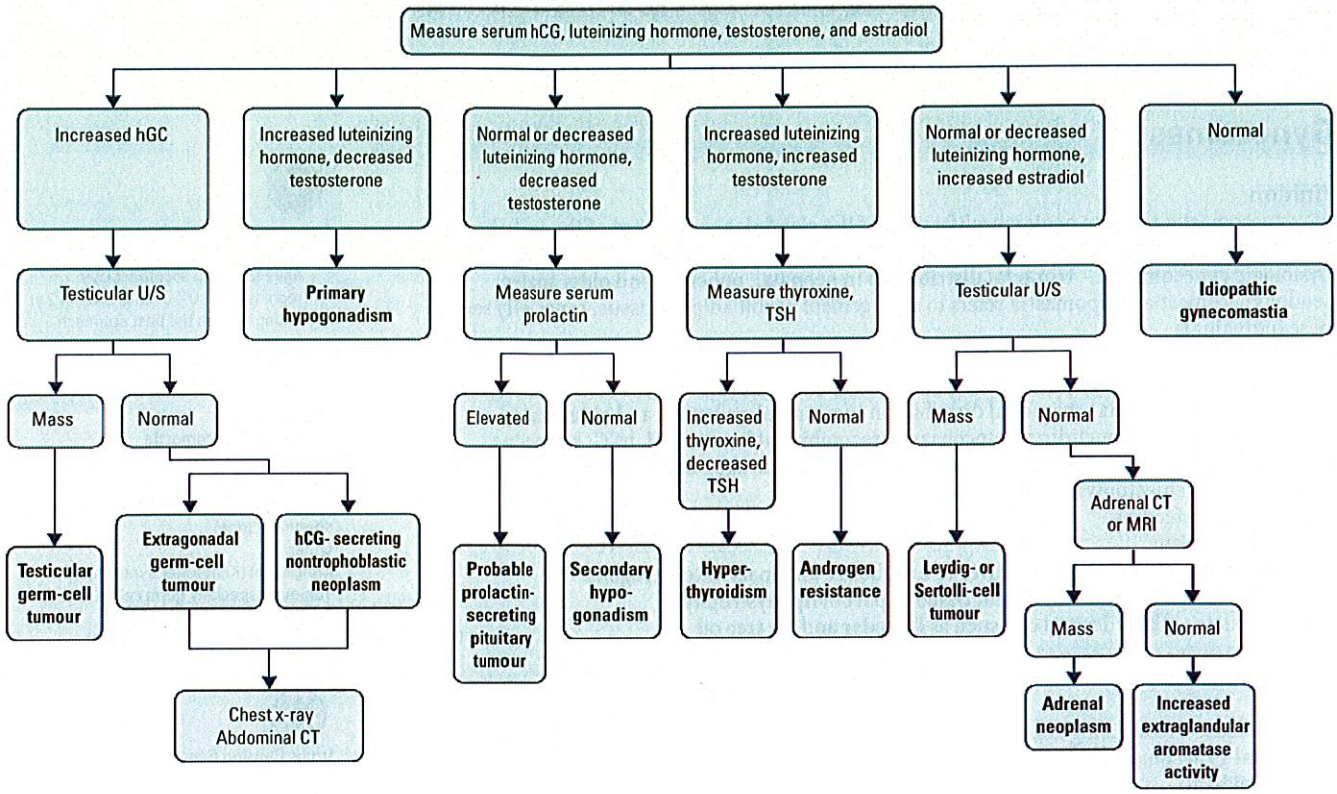


Figure 24. Approach to investigating gynecomastia

Treatment

- initial observation for most men with gynecomastia (after stopping offending medications and treating underlying cause)
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen has most evidence for benefit
- surgical
  - longstanding (>12 mo, fibrotic), discomfort, or causing psychological distress

Female Reproductive Endocrinology

- see Gynecology, GY23

Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

Table 40. Clinical Features

Syndrome Class	Symptoms/Syndrome	Associated Malignancies	Mechanism
Endocrine	Cushing's syndrome Weight gain in trunk/face/between shoulders, stretch marks, easy bruising, slow wound healing, acne, hirsutism, irregular menses, decreased libido	Small-cell lung cancer Pancreatic carcinoma Neural tumours Thymoma	Ectopic ACTH and ACTH-mimicking substance secretion
	Syndrome of inappropriate ADH secretion (SIADH) Oliguria, hyponatremia, nausea/vomiting, headaches, confusion, fatigue, irritability, muscle weakness/cramps, seizures	Small-cell lung cancer CNS malignancies	Antidiuretic hormone secretion
	Hypercalcemia "Stones, bones, abdominal moans, psychic overtones"	Lung cancer Breast carcinoma Renal cell carcinoma Multiple myeloma Ovarian carcinoma	PTH-related protein, transforming growth factor alpha (TGF-α), tumour necrosis factor (TNF) secretion
	Hypoglycemia Tachycardia, headache, tremor, diaphoresis, fatigue, dizziness	Hepatocellular carcinoma Fibrosarcoma insulinoma	Insulin or insulin-like substance secretion
	Carcinoid Flushing, diarrhea, shortness of breath, tachycardia	Gastrointestinal neuroendocrine tumours	Serotonin, bradykinin secretion
Neurologic	Lambert-Eaton myasthenic syndrome (LEMS) Muscle weakness in limbs	Small-cell lung cancer	Ab interferes with acetylcholine (ACh) release
	Myasthenia gravis Fluctuating muscle weakness and fatigability	Thymoma	Ab interferes with ACh release
	Paraneoplastic limbic encephalitis Depression, seizures, short-term memory loss	Small-cell lung cancer	Unknown
Renal	Hypokalemic nephropathy Polyuria, polydipsia, anorexia, nausea/vomiting	Small-cell lung cancer	Ectopic ACTH and ACTH-like substance secretion
	Nephrotic syndrome Edema, hypertension, hematuria, immune impairment, hypercoagulability	Lymphoma Melanomas	Immunocomplex sedimentation in nephrons
GI	Watery diarrhea	MTC VIPoma	Calcitonin, prostaglandin secretion VIP secretion
Hematologic	Erythrocytosis	Renal cell carcinoma Hepatocellular carcinoma	Erythropoietin (EPO) production
Rheumatologic	SLE "SOAP BRAIN MD": serositis (pleuritis, pericarditis), oral ulcers, arthritis, photosensitivity, blood (low counts), renal (protein), ANA+, immunologic (DS DNA, etc.), neurologic (psych, seizures), malar rash, discoid rash	Lymphomas Lung cancer Breast carcinoma Gonadal carcinoma	Anti-nuclear Ab production
	Scleroderma Diffuse thickening of the skin, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)	Breast carcinoma Lung cancer Uterine cancer	Anti-nuclear Ab production

Investigations

- CBC, electrolytes, creatinine, LFTs, ALP, erythrocyte sedimentation rate (ESR), CRP, serum/urine electrophoresis
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, positron emission tomography (PET) scan
- ± endoscopy

Treatment

- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: intravenous immunoglobulin (IVIG), steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)

Common Medications

Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments
Biguanide	Sensitizes peripheral tissues to insulin → increases glucose uptake Decreases hepatic glucose production by simulation of hepatic AMP-activated protein kinase (AMPK)	metformin	Glucophage® Glumetza®		500 mg once daily titrated to 2000 mg/d maximum (split BID unless extended release)	T2DM Improves both fasting and postprandial hyperglycemia Also → TG	ABSOLUTE: Moderate to severe liver dysfunction Moderate renal dysfunction GFR <30 mL/min Cardiac dysfunction	GI upset (abdominal discomfort, bloating, diarrhea) Vitamin B_{12} deficiency	↓ A1c 1.0-1.5% Weight neutral Negligible risk of hypoglycemia as monotherapy
Insulin Secretagogue	Stimulates insulin release from β cells by causing K^+ channel closure → depolarization → Ca^{2+}-mediated insulin release Use in nonobese T2DM	sulfonylureas: glyburide gliclazide glimepiride	 Diabeta® Euglucon® Diamicron® Diamicron® MR Amaryl®	 Micronase® Glynase PreTab® 	 2.5-5.0 mg/d titrated to >5 mg BID Max: 20 mg/d 40-160 mg BID 30-120 mg once daily 1-8 mg once daily	 T2DM, taken with meals	ABSOLUTE: Moderate to severe liver dysfunction RELATIVE (glyburide and glimepiride): Adjust dose in mild to moderate kidney dysfunction and avoid in severe kidney dysfunction Avoid glyburide in the elderly INTERACTIONS: Do not combine with a non-sulfonylurea insulin secretagogue or preprandial insulin	Hypoglycemia Weight gain	↓ A1c 0.8% Gliclazide lowest incidence of hypoglycemia
Meglitinides	Stimulates insulin release from β cells by causing K^+ channel closure → depolarization → Ca^{2+}-mediated insulin release	non-sulfonylureas: repaglinide nateglinide	 GlucoNorm® Starlix®	 Prandin®	 0.5-4 mg TID 60-120 mg TID	 Short t1/2 of 1 h causes brief but rapid ↑ in insulin, therefore effective for postprandial control	ABSOLUTE: Severe liver dysfunction INTERACTIONS: Do not combine with a sulfonylurea or preprandial insulin	Hypoglycemia (less than sulfonylurea) Weight gain	↓ A1c 0.7% for repaglinide and 0.5-1.0% for nateglinide Costly Must be dosed with meals
Insulin Sensitizers (thiazolidinedione)	Sensitizes peripheral tissues to insulin → increases glucose uptake Decreases FFA release from adipose Binds to nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ)	rosiglitazone pioglitazone	Avandia® Actos®		2-8 mg once daily 15-45 mg once daily	T2DM – not as initial therapy	ABSOLUTE: New York Heart Association (NYHA) > class II CHF, bladder cancer INTERACTIONS: Do not combine with insulin	Peripheral edema CHF Anemia Fluid retention and CHF Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing) Increased risk of bladder cancer with pioglitazone Fractures Mild increase in LDL	↓ A1c 0.8% Delayed maximum efficacy (6-12 wk) NOTE: This class of medication is rarely used anymore due to side effects and concerns about potential increased cardiovascular (CV) mortality
α-Glucosidase Inhibitor	↓ carbohydrate GI absorption by inhibiting brush border α-glucosidase	acarbose	Glucobay®	Precose®	25 mg once daily titrated to 100 mg TID	↓ postprandial hyperglycemia	ABSOLUTE: Inflammatory bowel disease Severe liver dysfunction	Flatulence Abdominal cramps Diarrhea	↓ A1c 0.6% Not recommended as initial therapy in patients with HbA1c >8.5%
Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor	Inhibits degradation of endogenous antihyperglycemic incretin hormones Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying	sitagliptin saxagliptin linagliptin	Januvia® Onglyza™ Trajenta®		100 mg once daily 2.5-5 mg once daily 5 mg once daily		ABSOLUTE (sitagliptin): T1DM DKA RELATIVE (sitagliptin and saxagliptin): Use with dose reduction in kidney dysfunction	Nasopharyngitis Upper respiratory tract infection (URTI) Headache Pancreatitis Stevens Johnson syndrome Bullous pemphigoid	↓ A1c 0.7% Weight neutral Expensive Negligible risk of hypoglycemia as monotherapy

Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments
Glucagon-Like Peptide (GLP)-1 Analogue	Binds to GLP-1 receptor to promote insulin release Insulinotropic effect suppressed as plasma glucose <4 mmol/L Slows gastric emptying, suppresses inappropriately elevated glucagon levels Causes β-cell regeneration and differentiation *in vitro*	exenatide	Byetta®		5-10 µg SC BID 1 h before meals		ABSOLUTE: T1DM DKA Acute pancreatitis Hx Multiple endocrine neoplasia syndrome type 2 MTC RELATIVE: Gastroparesis End stage renal disease (ESRD) Personal or family history of MTC	N/V, diarrhea Dizziness, headache Muscle weakness Anti-exenatide antibodies Pancreatitis	↓ A1c 1.0% Weight loss Negligible risk of hypoglycemia as monotherapy Added CV mortality and CV outcomes benefit in patients with known CVD
		liraglutide	Victoza®		0.6-1.8 mg once daily SC				
		semaglutide	Rybelusus PO/ Ozempic SC®		3-14 mg once daily PO, 0.25-1 mg once weekly SC				
		dulaglutide	Trulicity®		0.75-1.5 mg/ wk SC				
Sodium-glucose linked transporter 2 (SGLT2) Inhibitor	Enhances urinary glucose excretion by inhibiting glucose reabsorption in the proximal renal tubule	canagliflozin	Invokana®		100-300 mg once daily before first meal of the day		ABSOLUTE: Severe renal impairment ESRD Patients on dialysis	UTI, genital infections Hypotension caution with concomitant loop diuretic use Caution with renal dysfunction Hyperlipidemia (raises LDL and HDL) Dapagliflozin not to be used in patients with active or history of bladder cancer Rare DKA (may occur with no hyperglycemia)	↓ A1c 0.7-1.0% Negligible risk of hypoglycemia as monotherapy Cause weight loss Added CV mortality, CV outcomes benefit in patients with known prior CVD Renal protection
		dapagliflozin	Forxiga®		5-10 mg once daily in the morning with or without food				
		empagliflozin	Jardiance®		10-25 mg once daily in the morning with or without food				

Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
HMG-CoA Reductase Inhibitor (statins)	Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin simvastatin	Lipitor® Lescol® Mevacor® Pravachol® Crestor® Zocor®		10-80 mg/d 20-80 mg/d 20-80 mg/d 10-40 mg/d 5-40 mg/d 10-80 mg/d	1st line monotherapy Used for ↑ LDL, ↑ TG	Active liver disease	↑ liver enzymes Myositis (↑ risk if combined with fibrates) Rhabdomyolysis
Fibrates	Activate PPAR α, upregulate lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL	bezafibrate fenofibrate gemfibrozil	Bezalip® Lipidil® Lopid®		400 mg/d 48-200 mg/d 600-1200 mg/d	Used for ↑ TG, hyperchylomicronemia	Hepatic disease Renal disease	GI upset Skin rashes ↑ risk of gallstone formation ↑ risk of rhabdomyolysis when combined with statins
Niacin	Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL	nicotinic acid	Niaspan® generic niacin	Niacor®	0.5-2 g/d	Used for severe hypertriglyceridemia not controlled by fibrate	Hypersensitivity Hepatic dysfunction Active peptic ulcer disease (PUD) Hyperuricemia Severe hypotension	Generalized flushing Abnormal liver enzymes Pruritus IGT Watch glucose control with overt DM
Bile Acid Sequestrants	Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL	cholestyramine	Questran®		2-24 g/d	Used for ↑ LDL Use as adjunct with statins or fibrates	Complete biliary obstruction TG >3.5 mmol/L	Constipation, nausea Flatulence Bloating Rise in TG Binds other medications
		colestipol	Colestid®		5-30 g/d			
Cholesterol Absorption Inhibitors	Inhibits cholesterol absorption at the small intestine brush border	ezetimibe	Ezetrol®	Zetia®	10 mg/d	Used for ↑ LDL	Hypersensitivity Hepatic dysfunction (when used with statin) Do not combine with fibrates or bile acid resins	Fatigue Pharyngitis Sinusitis Abdominal pain Diarrhea Arthralgia

Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Anti-PCSK9	Inhibits degradation of the LDL receptor by PCSK9 enzyme LDL clearance	evolocumab alirocumab	Repatha® Praluent®		140 mg q2 wk or 420 mg once monthly 75 mg q2 wk or 300 mg once monthly	Add-on to maximally tolerated statin therapy in heterozygous familial hypercholesterolemia (FH) (evolocumab, alirocumab) and homozygous FH (evolocumab) Consider in patients with atherosclerotic CVD and LDL-C not at target despite maximally tolerated statin ± ezetimibe	Hypersensitivity No studies regarding use in severe hepatic or renal impairment	Nasopharyngitis, URTI, influenza Sinusitis Back pain Myalgia Arthralgia Nausea

Thyroid Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Antithyroid Agent (thionamides)	Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T_4 and T_3 PTU also interferes with conversion of T_4 to T_3	propylthiouracil (PTU)	Propyl-Thyracil®		Start 100 mg PO TID, then adjust accordingly Thyroid storm: start 150-300 PO QID, then adjust accordingly	Hyperthyroidism, thyroid storm	Hypersensitivity PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester Lactation: safe with PTU <300 mg/d and MMI <20-30 mg/d	N/V Rash Drug-induced hepatitis Agranulocytosis Hepatitis with PTU Cholestasis with MMI Vasculitis
		methimazole (MMI)	Tapazole®		Start 5-20 mg PO once daily, then adjust accordingly Up to 60 mg once daily may be required			
Thyroid Hormone	Synthetic form of thyroxine (T_4)	levothyroxine l-thyroxine	Synthroid® Eltroxin®	Levoxyl®	0.05-2.0 mg/d, usually 1.6x weight (kg) is dose in micrograms In elderly patients start at 0.025 mg/d	Hypothyroidism Post thyroidectomy	Recent MI, thyrotoxicosis	If wrong dosing: symptoms of hypothyroidism or hyperthyroidism Skin rash from dye in pill
Antithyroid Agent Radiopharmaceutical	Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue	sodium iodide I-131	Iodotope®		Dose corrected for 24 h radioactive iodine uptake Hyperthyroidism 4-12 millicuries (mCi) Thyroid Ca 50-150 mCi	Hyperthyroidism Thyroid malignancy	Hypersensitivity Concurrent antithyroid medication Pregnancy, lactation	N/V Bone marrow suppression Sialadenitis Thyroiditis

Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Bisphosphonates	Inhibits osteoclast-mediated bone resorption	alendronate	Fosamax®		Osteoporosis: 5-10 mg once daily 70 mg once weekly Paget's: 40 mg once daily for 6 mo	Treaatment of postmenopausal osteoporosis Treatment of osteoporosis Glucocorticoid-induced osteoporosis Paget's disease	Esophageal stricture or achalasia (oral) Unable to stand or sit upright for >30 min (oral) Hypersensitivity Hypocalcemia Renal insufficiency (CrCl <35 mL/min) History or atypical femoral fracture or osteonecrosis of the jaw	GI Musculoskeletal (MSK) pain Headache Osteonecrosis of the jaw Atypical femur fractures
		risedronate	Actonel®		Osteoporosis: 5 mg once daily 35 mg once weekly 150 mg once monthly Paget's: 30 mg once daily for 2 mo	Treatment of postmenopausal osteoporosis Treatment and prevention of glucocorticoid-induced osteoporosis Paget's disease	Same as above	Same as above
		pamidronate	Aredia®		Hypercalcemia of malignancy: 60-90 mg IV over 2-24 h Wait at least 7 d before considering retreatment	Hypercalcemia of malignancy Paget's disease Osteolytic bone metastases of breast cancer Osteolytic lesions of multiple myeloma	Renal insufficiency (CrCl <30 mL/min)	
		zoledronate	Zometa® Aclasta®	Reclast®	5 mg IV once yearly 5 mg IV	Treatment of osteoporosis Hypercalcemia of malignancy Treatment and prevention of skeletal complications related to cancer	Renal insufficiency (CrCl <35 mL/min)	
Selective Estrogen Receptor Modulators	Decreases resorption of bone through binding to estrogen receptors	raloxifene	Evista®		60 mg once daily	Treatment and prevention of postmenopausal osteoporosis (2nd line)	Lactation Pregnancy Active or past history of DVT, PE, or retinal vein thrombosis	Hot flashes Leg cramps Increased risk of fatal stroke, venous thromboembolism
Anti-RANKL Monoclonal Ab	Inhibits RANKL (osteoclast differentiating factor) → inhibits osteoclast formation and decreases bone resorption	denosumab	Prolia™		60 mg SC q6 mo	Treatment for postmenopausal women at high-risk of fracture Prevent skeletal-related events in patients with bone metastasis from solid tumours Also approved for glucocorticoid-induced osteoporosis, and for men	Hypocalcemia Vitamin D insufficiency	Fatigue/headache/GI injection site reaction Hypocalcemia Atypical femur fractures Osteonecrosis of the jaw
PTH analog	Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity	teriparatide	Forteo ® and Osnuvo®		20 µg SC once daily x 18-24 mo	Treatment for postmenopausal women with osteoporosis who are at high-risk for fracture Treatment for men with primary or hypogonadal osteoporosis who are at high-risk for fracture Also approved for glucocorticoid-induced osteoporosis	Paget's disease Prior external beam or implant radiation therapy involving the skeleton Bone metastases Metabolic bone diseases other than osteoporosis	Orthostatic hypotension Hypercalcemia Dizziness Leg cramps
Calcium	Inhibits PTH secretion				1200 mg/d (including diet) Divided in 3 doses	Osteopenia Osteoporosis Prevention of metabolic bone disease	Caution with renal stones	Vomiting Constipation Dry mouth
Anti-sclerostin Monoclonal Ab	Binds to and inhibits sclerostin (inhibitor of Wnt β-Catenin pathway) → increased bone formation and reduced bone resorption	Romosozumab	Evenity®		210 mg SC qMonth x 12 mo	Treatment of osteoporosis in postmenopausal women at high risk for fracture (defined as history of osteoporotic fracture or multiple risk factors for fracture)	Hypocalcemia Hypersensitivity	Headache, joint pain, pain at injection site May increase risk of MI/stroke/CV death Osteonecrosis of jaw Atypical femur fractures

Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Vitamin D	Regulation of calcium and phosphate homeostasis	cholecalciferol (vitamin D_3)			800 -2000 IU/d (higher doses required in Insufficiency or deficiency)	Osteopenia Osteoporosis Prevention of metabolic bone disease	Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)	Hypercalcemia Headache N/V Constipation
		ergocalciferol (vitamin D_2)	Drisdol® Erdol®		50000 IU/wk	Osteoporosis in patients with liver dysfunction, refractory rickets, hypoparathyroidism	Hypercalcemia Malabsorption syndrome Decreased renal function	
		calcitriol ($1,25(OH)_2$-D)	Rocaltrol®		Start 0.25 µg/d Titrate up by 0.25 µg/d at 4-8 wk intervals to 0.5-1 µg/d	Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis Hypoparathyroidism	Hypercalcemia Vitamin D toxicity	
			Calcijex®		Start 0.25 µg/d Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d			

Adrenal Medications

Drug Class	Mineralocorticoid Activity	Generic Drug Name	Potency Relative to Cortisol	Equivalent Dose (mg)	Duration of Action (t1/2 in h)	Dosing	Comments
Glucocorticoid	Yes	Hydrocortisone (cortef, solu-Cortef)	1.0	20	8	Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8 h (continuous infusion x 24-48 h) PO once stable (50 mg q8 h x 48 h, then taper over 14 d) Chronic AI: 15-20 mg PO BID-TID (2/3 AM, 1/3 PM)	In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K^+ metabolic alkalosis)
Glucocorticoid	Yes	cortisone acetate	0.8	25	oral = 8 IM = 18+	Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24 h Chronic AI: 25 mg/d divided BID-TID	Pro-drug which is converted to active form as hydrocortisone High doses can result in mineralocorticoid side effects (see above)
Glucocorticoid	Yes	prednisone	4	5	16-36	Adrenal Crisis:Adrenal Crisis: 15-60 mg/d PO once daily or divided BID/QID Chronic AI: 5 mg daily	Pro-drug which is converted to active form as prednisolone
Glucocorticoid	No	dexamethasone	30	0.75	36-54	Adrenal Crisis: 4 mg IV; repeat q2-6 h if necessary	
Mineralocorticoid	100%	Fludrocortisone (florinef acetate)	—			Chronic: 0.1 mg daily	Replaces aldosterone in primary adrenal insufficiency

Landmark Endocrinology Trials

Trial Name	Reference	Clinical Trial Details
Diabetes Prevention		
DPP Research Group: Lifestyle	NEJM 2002;346:393-403	**Title:** Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin **Purpose:** To investigate whether lifestyle interventions or metformin could prevent or delay the development of T2DM. **Methods:** 3234 nondiabetic persons with elevated fasting and post-load plasma glucose were randomly assigned to placebo, metformin (850 mg BID), or a lifestyle-modification program (min 7% weight loss and 150 min of physical activity/wk). **Results:** Lifestyle interventions and metformin reduced the incidence of T2DM by 58% (95% confidence interval [CI], 48-66%) and 31% (CI, 17-43%), respectively, as compared with placebo. Lifestyle interventions were significantly more effective than metformin. **Conclusion:** Metformin and lifestyle modifications reduced the incidence of diabetes in high-risk individuals but lifestyle modifications were more effective.
Look AHEAD	NEJM 2013;369:145-54	**Title:** Title: Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes Purpose: To investigate if an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among overweight or obese patients with T2DM. **Methods:** 5145 patients were randomly assigned to receive weight loss lifestyle interventions (decreased caloric intake and increased physical activity) or diabetes support and education (control). **Results:** Trial was stopped early on the basis of futility. As compared to control, lifestyle interventions reduced weight, HbA1c and cardiovascular risk factors, but the incidence of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina) was not significantly different between the groups. **Conclusion:** Rate of cardiovascular events in overweight or obese adults with T2DM were not reduced by an intensive lifestyle intervention focusing on weight loss
A1c Targets		
ADVANCE	NEJM 2008;358:2560-72	**Title:** Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes **Purpose:** To investigate the effects of intensive glucose control on vascular outcomes in patients with T2DM. **Methods:** 11140 patients with T2DM received intensive glucose control with modified release gliclazide (and other drugs necessary to reach target HbA1c ≤6.5%) or standard glucose control (target HbA1c defined by local guidelines). **Results:** Intensive glucose control reduced the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% confidence interval [CI], 0.66-0.93; P=0.006), but did not significantly reduce major macrovascular events or death from any cause. Severe hypoglycemia was more common in the intensive control group (2.7%, vs. 1.5%; 1.86 CI [1.42 to 2.40]; P<0.001). **Conclusion:** Intensive glucose control targeting HbA1c ≤6.5% significantly reduces the incidence of nephropathy but not major macrovascular events or death.
ACCORD	NEJM 2008;358:2545-59	**Title:** Effects of Intensive Glucose Lowering in Type 2 Diabetes **Purpose:** To investigate if intensive glucose control targeting normal HbA1c levels reduces cardiovascular events in patients with T2DM with established CVD or CVD risk factors. **Methods:** 10251 patients (mean age 62.2) were randomly assigned to receive intensive therapy targeting a HbA1c level of <6.0% or standard therapy targeting 7.0-7.9%. **Results:** The intensive therapy arm was stopped early due to evidence of increased mortality. There was no difference in cardiovascular events or death from cardiovascular events. There were increased rates of hypoglycemia, fluid retention, and weight gain >10 kg in the intensive therapy group. **Conclusion:** Intensive glucose lowering therapy in T2DM does not improve clinical outcomes and increases mortality with more adverse events.
VADT	NEJM 2009;129-39	**Title:** Glucose Control And Vascular Complications In Veterans With Type 2 Diabetes **Purpose:** To investigate effects of intensive glucose control on cardiovascular events in patients with long-standing T2DM. **Methods:** 1791 military veterans who had suboptimal responses to therapy for T2DM were randomly assigned to intensive control (absolute reduction in HbA1c by 1.5% relative to standard) or standard glucose control. **Results:** Median HbA1c was 6.9% in the intensive-therapy group and 8.4% in the standard-therapy. Risk of major cardiovascular events, microvascular complications, or death from any cause were not significantly different between groups. Adverse events, predominantly hypoglycemia, were more common in the intensive control group. **Conclusion:** Rates of major cardiovascular events, death, or microvascular complications were not reduced by intensive glucose control in patients with poorly controlled T2DM.
Diabetes Treatment		
4T Trial	NEJM 2009;361:1736-1747	**Title:** Three Year Efficacy of Complex Insulin Regimens in T2DM: 4T Trial Study: Randomized Unblinded Trial with 3 yr of Follow-up **Population:** 708 patients with T2DM, not on insulin or thiazolidinedione therapy on maximal metformin and sulfonylurea therapy. **Intervention:** Thrice-daily prandial insulin aspart, vs. twice-daily biphasic insulin aspart, vs. once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regime specific to each arm if there was persistent hyperglycemia. **Primary Outcome:** Three yr HbA1c. **Results:** Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 8.5% basal regimens (P=0.04). There were no significant differences in median HbA1c levels between all three arms from yr 1-3. A smaller proportion of patients reached HbA1c <6.5% or <7.0% in the biphasic arm. The basal arm had the least weight gain and the least weight circumference increase, but the highest rate of secondary insulin requirement. The basal arm had fewest severe hypoglycemic events per patient year, while the biphasic had the most serious adverse effects. **Conclusion:** Basal insulin regimen provides the best glycemic control over a 3 yr study, with better HbA1c control, fewer hypoglycemic events, and less weight gain.
The ACCORD Trial – Blood Pressure Control	NEJM 2010;362:1575-1585	**Title:** Effects of Intensive Blood Pressure Control in T2DM: The ACCORD Trial **Study:** RCT, unblinded with 4.7 yr of mean follow-up. **Population:** 4733 patients with T2DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg. **Intervention:** sBP control <120 mmHg (intensive) or 140 mmHg (standard). **Primary Outcomes:** Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death). **Results:** Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI 3.4-3.5) vs. 2.1 (95% CI 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, P≤0.001); especially bradycardia or arrhythmia (0.5% vs. 0.13%, P=0.02) and hyperkalemia (0.4% vs. 0.04%, P=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, P=0.01) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, P=0.03) in the intensive therapy arm. **Conclusion:** Intensive BP lowering to <120 mmHg vs. 140 mmHg in patients with T2DM and CV risk factors does not reduce major CV event risk except for stroke events.

Trial Name	Reference	Clinical Trial Details
The ACCORD Trial – Combination Lipid Therapy	NEJM 2010;362:1563-1574	**Title:** Effects of Combination Lipid Therapy in T2DM: The ACCORD Trial **Study:** RCT, double-blinded trial with 4.7 yr of mean follow-up. **Population:** 5518 patients with T2DM. Intervention: Statin with or without fibrate therapy. Primary Outcome: Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death). **Results:** No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality between study arms. **Conclusions:** The addition of fibrate therapy to statin therapy in patients with T2DM does not reduce major CV event risk.
DCCT	NEJM 1993;329:977-986	**Title:** The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-term Complications in Insulin-dependent Diabetes Mellitus **Purpose:** To investigate whether intensive treatment to maintain normal blood glucose reduces the frequency and severity of microvascular complications in T1DM. **Methods:** 1441 patients with T1DM received intensive therapy (≥3 daily insulin injections or insulin pump, BG monitoring QID with strict targets) or conventional therapy (1-2 insulin injections daily, BG monitoring daily). **Results:** Intensive treatment of T1DM significantly reduced the risk for the development and progression of retinopathy in primary- and secondary-intervention cohorts, respectively. Intensive therapy also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. Intensive therapy was associated with an increase in the occurrence of severe hypoglycemia. **Conclusion:** Intensive treatment significantly reduces the development and progression of microvascular complications in T1DM.
EDIC	NEJM 2005;353:2644-53	**Title:** Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes **Purpose:** To investigate whether intensive vs. conventional therapy during the DCCT trial influenced the long-term incidence of CVD. **Methods:** The DCCT trial randomly assigned 1441 patients with T1DM to intensive or conventional therapy for a mean of 6.5 years from 1983-1993. 93% were followed until 2005 (EDIC) for cardiovascular events. **Results:** During the mean 17-year follow-up, intensive treatment reduced the risk of any cardiovascular event by 42% (95% confidence interval (CI), 9-63%; P=0.02) and of nonfatal MI, stroke, or death from CVD by 57% (CI, 12-79%; P=0.02). **Conclusion:** Long-term risk of CVD in patients with T1DM is reduced by intensive therapy.
UKPDS 33	Lancet 1998;352:837-53	**Title:** Intensive Blood-Glucose Control With Sulphonylureas or Insulin Compared With Conventional Treatment and Risk of Complications In Patients With Type 2 Diabetes (UKPDS 33) **Purpose:** To investigate the effects of intensive blood-glucose control with sulphonylurea or insulin vs. conventional treatment on the risk of complications in T2DM. **Methods:** 3867 patients with newly diagnosed T2DM received intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L without hyperglycemic symptoms). **Results:** Patients allocated to intensive treatment had lower median HbA1c levels (P<0.0001), and their risk was reduced by 12% for any diabetes-related endpoint (95% confidence interval [CI], 1-21, P=0.029), by 10% for any diabetes-related death (CI, -11-27, P=0.34), and by 6% for all-cause mortality (CI, -10-20, P=0.44). Intensive therapy induced more hypoglycemic episodes and weight gain. **Conclusion:** In T2DM, sulphonylurea or insulin-mediated intensive glucose control reduced microvascular but not macrovascular complications.
UKPDS 34	Lancet 1998;352:854-65	**Title:** Effect of Intensive Blood-Glucose Control With Metformin On Complications In Overweight Patients With Type 2 Diabetes (UKPDS 34) **Purpose:** To investigate the effects of intensive glucose control with metformin on rates of microvascular and macrovascular complications in overweight patients with T2DM. **Methods:** 753 patients were randomized to receive conventional management with diet alone or intensive blood-glucose control regimen with metformin targeting FPG<6 mmol/L. **Results:** Patients allocated metformin had reduced HbA1c (7.4% vs. 8.0%), and risk reductions of 32% for any diabetes-related endpoint (P=0.002), 42% for diabetes-related death (P=0.017), and 36% for all-cause mortality (P=0.011). Among various intensive blood-glucose control regimens, metformin was superior to sulphonylureas or insulin for any diabetes-related endpoint (P=0.0034), all-cause mortality (P=0.021), and stroke (P=0.032). **Discussion:** Metformin decreases risk of diabetes-related endpoints in overweight patients with less weight gain and hypoglycemia than insulin and sulphonylureas. Consider for first line therapy.
UKPDS Extension	NEJM 2008;359:1577-89	**Title:** 10-Year Follow-Up of Intensive Glucose Control in Type 2 Diabetes **Purpose:** Post-trial monitoring of UKPDS to determine whether improved glucose control persisted and if there were long-term effects on macrovascular outcomes. **Methods:** 3277 patients were assessed through annual UKPDS clinics or annual questionnaires for up to 10 yr. **Results:** After 1 yr, between-group differences in HbA1c were lost. Relative risk reductions in the sulfonylurea-insulin group persisted for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), in addition to the emergence of risk reductions for MI (15%, P=0.01) and death from any cause (13%, P=0.007). Risk reductions persisted in the metformin group for any diabetes-related end point (21%, P=0.01), MI (33%, P=0.005), and death from any cause (27%, P=0.002). **Conclusion:** Glycemic differences were lost early, but sustained reductions in microvascular risk and emergent risk reductions for MI and death were evident during 10 years of post-trial follow-up.
Steno-2	NEJM 2008;358:580-91	**Title:** Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes **Purpose:** To investigate if intensified multifactorial interventions would influence rates of death in patients with T2DM and microalbuminuria. **Methods:** 160 patients received either conventional multifactorial treatment or intensified, target-driven therapy involving a combination of medications and focused behaviour modification. **Results:** A lower risk of death from any cause, death from cardiovascular causes, cardiovascular events, and progression to end-stage renal disease was seen in intensive therapy, and fewer patients in this group required retinal photocoagulation. **Conclusion:** Vascular complications and death rates were significantly improved by multifactorial interventions in at-risk patients with T2DM.

Trial Name	Reference	Clinical Trial Details
LIPIDS		
IMPROVE-IT	NEJM 2015;372:2387-97	**Title:** Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes **Purpose:** To assess whether the addition of ezetimibe to statin therapy can further reduce the rate of cardiovascular events. **Methods:** 18144 patients who had been hospitalized within the previous 10 d for acute coronary syndrome (ACS) with LDL cholesterol = 1.3 to 2.6 mmol/L (if on lipid lowering therapy) or 1.3 to 3.2 mmol/L (if not on lipid lowering therapy) were randomly assigned to receive a combination of either simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) or simvastatin (40 mg) and placebo (monotherapy). **Results:** Median time-weighted average LDL cholesterol was significantly lower in the simvastatin-ezetimibe group as compared to monotherapy (1.4 vs. 1.8 mmol/L; P<0.001). At 7 yr, the simvastatin-ezetimibe group was associated with significantly lower Kaplan-Meier event rates of the primary composite outcome (cardiovascular death, nonfatal MI, unstable angina, coronary revascularization, or nonfatal stroke) (32.7% vs. 34.7%; hazard ratio, 0.936; 95% CI, 0.89-0.99; P=0.016). **Conclusion:** Ezetimibe, when added to statin therapy, resulted in lower LDL cholesterol and improved cardiovascular outcomes. Additional benefit was conferred by lowering LDL cholesterol below previous targets.
FOURIER	NEJM 2017;376:1713-22	**Title:** Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease **Purpose:** To assess if the PCSK9 inhibitor evolocumab prevents cardiovascular events. **Methods:** 27564 patients with atherosclerotic CVD and LDL cholesterol ≥1.8 mmol/L who were on statin therapy were randomly assigned to receive evolocumab (140 mg every 2 wk or 420 mg monthly) or matching placebo. **Results:** At 48 wk, evolocumab was associated with a least-squares mean percentage reduction in LDL cholesterol of 59% relative to placebo, from a median baseline of 2.4 mmol/L to 0.78 mmol/L (P<0.001). Patients in the evolocumab group experienced significantly lower rates of the primary composite outcome (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) as compared to placebo (9.8% vs. 11.3%, respectively; hazard ratio, 0.85; 95% CI, 0.79-0.92; P<0.001). **Conclusion:** Evolocumab lowers LDL cholesterol and reduces the risk of cardiovascular events in patients with atherosclerotic CVD.
ODYSSEY OUTCOMES	NEJM 2018;379:2097-107	**Title:** Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome **Purpose:** To determine if the PCSK9 inhibitor alirocumab improves cardiovascular outcomes following acute coronary syndromes (ACS) in patients on high-intensity statin therapy. **Methods:** 18924 patients on high-intensity statin therapy who experienced ACS 1-12 mo prior with LDL cholesterol ≥ 1.8 mmol/L and non-HDL-C ≥ 2.6 mmol/L or ApoB ≥ 80 mg/dL were randomly assigned to receive SC alirocumab (75 mg) or matching placebo every two wk. **Results:** At median follow-up of 2.8 mo, the composite primary outcome (death from coronary heart disease, non-fatal MI, ischemic stroke, or hospitalization for unstable angina) occurred in 9.5% and 11.1% of patients on alirocumab and placebo, respectively (hazard ratio, 0.85; 95% CI 0.78-0.93; P<0.001). Alirocumab was associated with greater absolute benefit with respect to the primary outcome in patients with higher baseline LDL cholesterol. **Conclusion:** Alirocumab reduces the risk of recurrent ischemic cardiovascular events in patients who had a previous ACS on high-intensity statin therapy.
REDUCE-IT	NEJM 2019;380:11-22	**Title:** Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia **Purpose:** To assess the effects of icosapent ethyl on the rate of ischemic events. **Methods:** 8179 patients with established CVD or diabetes and other risk factors, who were on statin therapy with fasting TG 1.52-5.63 mmol/L and LDL cholesterol 1.06-2.59 mmol/L were randomly assigned to receive icosapent ethyl (2 g BID) or placebo. **Results:** At median follow-up of 4.9 yr, the primary composite end point (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) occurred in significantly less patients in the icosapent ethyl group as compared to placebo (17.2% vs. 22.0%, respectively; hazard ratio, 0.75; 95% CI, 0.68-0.83; P<0.001). Icosapent ethyl was associated with significantly higher rates of hospitalization for atrial fibrillation or flutter as compared to placebo (3.1% vs. 2.1%; P=0.004). **Conclusion:** Icosapent ethyl therapy was associated with a significantly lower risk of ischemic events in patients with elevated TGs despite the use of statins.
4S	Lancet 1994;344:1383-1389	**Title:** Randomised Trial of Cholesterol Lowering In 4444 Patients With Coronary Heart Disease: The Scandinavian Simvastatin Survival Study (4S) **Purpose:** To investigate if cholesterol lowering with simvastatin alters mortality and morbidity in patients with coronary heart disease (CHD). **Methods:** 4444 patients with CHD and serum cholesterol 5.5-8.0 mmol/L on a lipid-lowering diet received simvastatin or placebo. **Results:** In the simvastatin group, mean changes in total cholesterol, LDL, and HDL of -25%, -35%, and +8%, respectively, were observed with few adverse effects. The relative risk of coronary events in the simvastatin group was 0.66 (95% confidence interval [CI], 0.59-0.75, P<0.00001) and relative risk of death was 0.70 (CI, 0.58-0.85, P=0.0003). **Conclusion:** In CHD patients, long-term treatment with simvastatin safely improves survival.
HPS	Lancet 2002;360:7-22	**Title:** MRC/BHF Heart Protection Study Of Cholesterol Lowering With Simvastatin In 20536 High-Risk Individuals: A Randomised Placebo-Controlled Trial **Purpose:** To investigate the effects of reducing LDL cholesterol on the development of vascular disease. **Methods:** 20536 adults with coronary disease, other occlusive arterial disease, or diabetes received 40 mg simvastatin daily or placebo. **Results:** As compared to placebo, simvastatin significantly reduced all-cause mortality (12.9% vs.14.7%; P=0.0003), mainly due to an 18% reduction in the coronary death rate (5.7% vs. 6.9%; P=0.0005). There were significant reductions in the first event rate for non-fatal MI or coronary death (8.7% vs. 11.8%; P<0.0001), for non-fatal or fatal stroke (4.3% vs. 5.7%; P<0.0001), and for coronary or non-coronary revascularisation (9.1% vs. 11.7%; P<0.0001). **Conclusion:** Adding simvastatin treatment safely protects against vascular disease in a variety of high-risk patients.
FIELD	Lancet 2005;366:1849-61	**Title:** Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events In 9795 People With Type 2 Diabetes Mellitus (The FIELD Study): Randomised Controlled Trial **Purpose:** To assess the effect of fenofibrate on cardiovascular events in patients with T2DM at high risk for CVD. **Methods:** 9795 patients with T2DM not taking statin therapy were randomly assigned to micronized fenofibrate 200 mg daily or placebo. **Results:** Fenofibrate significantly reduced the relative risk of non-fatal MI (hazard ratio [HR], 0.76, 95% confidence interval [CI], 0.62-0.94; P=0.010) and total cardiovascular events (HR, 0.89; CI, 0.80-0.99; P=0.035), but there was no significant difference in the risk of coronary events or CHD mortality between groups. **Conclusion:** Fenofibrate did not significantly reduce the risk of coronary events, but rates of total cardiovascular events (mainly non-fatal MIs and revascularizations) were reduced.

Trial Name	Reference	Clinical Trial Details
TNT	NEJM 2005;352:1425-35	**Title:** Intensive Lipid Lowering With Atorvastatin In Patients With Stable Coronary Disease **Purpose:** To assess the efficacy and safety of reducing LDL to <2.6 mmol/L in patients with stable coronary heart disease (CHD). **Methods:** 10001 patients with CHD and LDL<3.4 mmol/L were randomly assigned to receive either 10 mg or 80 mg of atorvastatin daily. **Results:** Mean LDL was 2.0 mmol/L and 2.6 mmol/L during treatment with 80 mg and 10 mg of atorvastatin, respectively. Major cardiovascular events occurred in 8.7% receiving 80 mg vs. 10.9% receiving 10 mg, indicating a 22% relative risk reduction (hazard ratio, 0.78; 95% confidence interval, 0.69-0.89; P<0.001). **Conclusion:** In patients with stable CHD, intensive lipid-lowering treatment with 80 mg atorvastatin daily has greater clinical efficacy than 10 mg of atorvastatin daily.
Jupiter	NEJM 2008;359:2195-207	**Title:** Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein **Purpose:** To investigate if statins reduce cardiovascular events in patients with elevated CRP but without hyperlipidemia. **Methods:** 17802 healthy men and women with LDL<130 mg/dL and CRP>2.0 mg/L were randomly assigned to receive rosuvastatin 20 mg daily or placebo. **Results:** Rosuvastatin reduced LDL and CRP levels by 50% and 37%, respectively. In the rosuvastatin and placebo groups, the rates of the primary outcomes (MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CVD) were 0.77 and 1.36 per 100 person-years of follow-up, respectively (P<0.00001). **Conclusion:** Statins reduce the incidence of major cardiovascular events in healthy people without hyperlipidemia but with an elevated CRP.
SGLT2 Inhibitors - Renal		
CREDENCE	NEJM 2019;380:2295-2306	**Title:** Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy **Purpose:** To investigate if an SGLT2i improves renal outcomes in patients with T2DM. **Methods:** 4401 patients with T2DM and chronic kidney disease (CKD) were randomly assigned to receive either 100 mg canagliflozin (oral SGLT2i) daily or placebo. **Results:** Trial was stopped early after median follow-up of 2.6 yr. Canagliflozin significantly lowered the relative risk of the primary composite outcome (end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes) by 30% (hazard ratio, 0.70; 95% confidence interval, 0.59-0.82; P=0.00001). **Conclusion:** Canagliflozin therapy resulted in a lower risk of kidney failure and cardiovascular events in patients with T2DM and CKD.
DAPA-CKD	NEJM 2020;383:1436-46	**Title:** Dapagliflozin in Patients with Chronic Kidney Disease **Purpose:** To assess the effects of SGLT2is in patients with CKD with or without T2DM. **Methods:** 4304 patients with estimated GFR (eGFR) = 25 to 75 mL/min/1.73m^2 and urinary ACR = 200 to 5000 were randomly assigned to receive dapagliflozin (10 mg/d) or placebo. **Results:** Over a median of 2.4 yr, dapagliflozin was associated with significantly lower rates of the primary composite outcome (sustained decline in eGFR ≥50%, end-stage kidney disease, or death from renal or cardiovascular outcomes) as compared to placebo (9.2% vs. 14.5%; hazard ratio, 0.61; 95% CI, 0.51-0.72; P<0.001). Effects were similar in patients with and without T2DM. **Conclusion:** Dapagliflozin therapy resulted in a lower risk of kidney failure and cardiovascular events in patients with CDK, with or without T2DM.
EMPA-KIDNEY	NEJM 2023; 388:117-127	**Title:** Empagliflozin in Patients with Chronic Kidney Disease **Purpose:** To understand empagliflozin's effects on at-risk chronic kidney disease patients. **Methods:** Patients with chronic kidney disease were enrolled based on specific eGFR and urinary albumin-to-creatinine ratio criteria. They were randomly assigned to receive empagliflozin or placebo to evaluate kidney disease progression and cardiovascular-related mortalit. **Results:** Among 6609 patients enrolled, empagliflozin demonstrated benefits in chronic kidney disease. Compared to the placebo group, the empagliflozin group had a lower incidence of kidney disease progression or cardiovascular death (13.1% vs. 16.9%). Similar results were observed across diabetes status and eGFR ranges, with no significant differences in adverse events. Conclusion: Empagliflozin therapy showed lower risk of kidney disease progression or cardiovascular death compared to placebo in at-risk patients with chronic kidney disease.
Additional Trials: see Landmark Clinical Trials C74		
LEADER (GLP-1 Agonists)	NEJM 2016;375:311-22	**Title:** Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
REWIND (GLP-1 Agonists)	Lancet 2019;394:121-30	**Title:** Dulaglutide and Cardiovascular Outcomes in T2DM (REWIND): A Double-Blind, Randomized Placebo-Controlled Trial
AMPLITUDE-O (GLP-1 Agonists)	NEJM 2021; 385: 896-907	**Title:** Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes
HARMONY-OUTCOMES (GLP-1 Agonists)	Lancet 2018; 392: 1519-1529	**Title:** Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomized placebo-controlled trial
SUSTAIN-6 (GLP-1 Agonists)	NEJM 2016; 375: 1834-1844	**Title:** Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
PIONEER 6 (GLP-1 Agonists)	NEJM 2019; 381: 841-851	**Title:** Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
EMPA-REG OUTCOME (SGLT2 Inhibitors)	NEJM 2015;373:2117-28	**Title:** Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
CANVAS (SGLT2 Inhibitors)	NEJM 2017;377:644-57	**Title:** Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
DECLARE-TIMI 58 (SGLT2 Inhibitors)	NEJM 2019;380:347-57	**Title:** Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes
DAPA-HF (SGLT2 Inhibitors)	NEJM 2019;381:1995-2008	**Title:** Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction
DELIVER (SGLT2 Inhibitors)	NEJM 2022; 387:1089-1098	**Title:** Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
EMPEROR-Preserved (SGLT2 Inhibitors)	NEJM 2021;385:1451-1461	**Title:** Empagliflozin in Heart Failure with a Preserved Ejection Fraction
EMPEROR-Reduced (SGLT2 Inhibitors)	NEJM 2020;383:1413-24	**Title:** Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure
PRESERVED-HF (SGLT2 Inhibitors)	Nature 2021; 27: 1954-1960	**Title:** The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial

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FM Family Medicine

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Acronyms

ABG	arterial blood gas
ACR	albumin:creatinine ratio
ACEI	angiotensin converting enzyme inhibitors
AIN	anal intraepithelial neoplasia
AKI	acute kidney injury
AMC	another medical condition
AR	absolute risk
ARB	angiotensin receptor blocker
BPH	benign prostatic hyperplasia
BPPV	benign paroxysmal positional vertigo
BRBPR	bright red blood per rectum
CA	cancer
CABG	coronary artery bypass graft
CAM	complementary and alternative medicine
CANRISK	Canadian Diabetes Risk Questionnaire
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CCS	Canadian Cancer Society
CF	cystic fibrosis
CHEP	Canadian Hypertension Education Program
CK	creatine kinase
CNS	central nervous system
CPAP	continuous positive airway pressure
CRC	colorectal cancer
CrCl	creatinine clearance
CRP	C-reactive protein
CSEP	Canadian Society for Exercise Physiology
CV	cardiovascular
CVA	costovertebral angle
CVD	cardiovascular disease
DASH	dietary approaches to stop hypertension
DHP	dihydropyridine
DKA	diabetic ketoacidosis
DMPA	depot medroxyprogesterone
DRE	digital rectal exam
DS	double strength
EC	emergency contraception
ER	extended release
F/U	follow-up
FAP	familial adenomatous polyposis
FBG	fasting blood glucose
FHT	family health team
FIT	fecal immunochemical test
FOBT	fecal occult blood test
FP	family physician
FRS	Framingham risk score
GAD	generalized anxiety disorder
GERD	gastroesophageal reflux disease
GDS	geriatric depression scale
gFOBT	guaiac fecal occult blood test
GP	general practitioner
HAART	highly active anti-retroviral therapy
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
HEENT	head, ears, eyes, nose, and throat
HF	heart failure
HNPCC	hereditary non-polyposis colon cancer
hs-CRP	high sensitivity C-reactive protein
HSIL	high-grade squamous intraepithelial lesion
HPV	human papillomavirus
HRT	hormone replacement therapy
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICS	inhaled corticosteroid
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IHD	ischemic heart disease
INH	isoniazid
IPT	interpersonal therapy
IUD	intrauterine device
IVP	intravenous pyelogram
KUB	kidney, ureter, bladder
LDCT	low dose computed tomography
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LMWH	low molecular weight heparin
LSIL	low-grade squamous intraepithelial lesion
LV	left ventricle
LVH	left ventricular hypertrophy
MCV	mean corpuscular volume
MMSE	mini mental status examination
MOCA	Montreal cognitive assessment
MS	multiple sclerosis
MSM	men who have sex with men
MUFA	monounsaturated fatty acids
NE	norepinephrine
NHP	natural health product
NNT	number-needed-to- treat
NNH	number-needed-to-harm
NP	nurse practitioner
NPH	neutral protamine hagedorn
NRT	nicotine replacement therapy
NTD	neural tube defect
NTG	nitroglycerin
NYHA	New York Health Association
O&P	ova and parasites
OA	osteoarthritis
OCD	obsessive compulsive disorder
OCP	oral contraceptive pill
OCPD	obsessive compulsive personality disorder
OD	omne in die (i.e. once daily)
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
PCOS	polycystic ovarian syndrome
PCSK9	proprotein convertase subtilisin/kexin 9
PFT	pulmonary function test
PHE	periodic health examination
PHQ	patient health questionaire
PID	pelvic inflammatory disease
PMS	premenstrual syndrome
PND	paroxysmal nocturnal dyspnea
PPD	purified protein derivative
PSA	prostate specific antigen
PTSD	post-traumatic stress disorder
PUD	peptic ulcer disease
PUFA	polyunsaturated fatty acids
PVD	peripheral vascular disease
PVR	post-void residual
QHS	quaque hora somni (i.e. every night at bedtime)
R&M	routine and microscopic
RA	rheumatoid arthritis
RN	registered nurse
ROM	range of motion
RR	relative risk
RSV	respiratory syncytial virus
SAH	subarachnoid hemorrhage
SDRI	serotonin dopamine reuptake inhibitor
SIDS	sudden infant death syndrome
SNRI	serotonin norepinephrine reuptake inhibitor
SOB	shortness of breath
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
TC	total cholesterol
TCA	tricyclic antidepressant
TDEE	total daily energy expenditure
TG	triglyceride
TIA	transient ischemic attack
TM	tympanic membrane
TMJ	temporomandibular joint
TUIP	transurethral incision of the prostate
TURP	transurethral resection of the prostate
UC	ulcerative colitis
URTI	upper respiratory tract infection
VAIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
VBI	vertebrobasilar insufficiency
WC	waist circumference
WSIB	Workplace Safety and Insurance Board

Four Principles of Family Medicine

College of Family Physicians of Canada

1. the family physician is a skilled clinician
   - works with patients to understand their illness experience and collaborate on shared management plans
   - uses expert generalist knowledge to develop a comprehensive approach to the management of undifferentiated disease, multimorbidity, and chronic disease
2. family medicine is a community-based discipline
   - responds/adapts to changing needs and circumstances of the community, with emphasis on injury/disease prevention and health promotion
   - sees patients across their lifespan, with a variety of diseases, in a variety of clinical contexts, collaboratively with a network of multidisciplinary community healthcare providers
3. the family physician is a resource to a defined practice population
   - engages in self-directed, lifelong learning to ensure relevance of practice in maintaining patient health
   - advocates for public policy that promotes health, resource stewardship, and the continuity and coordination of care
4. the patient-physician relationship is central to the role of the family physician
   - commits to the whole person, not just the disease, in the context of the patient's family and wider social environment
   - promotes continuity of patient care, respecting patient privacy and the physician-patient relationship

Experts in Generalism

Generalism is a professional philosophy of care, distinguished by a commitment to holistic, integrated, person-centred care, the broadest scope of practice, and collaboration with the larger health care team in order to respond to patient and community health needs. Family physicians are the quintessential experts in generalism with an emphasis on patient- and family-centred care, community adaptiveness, undifferentiated problems, management of uncertainty, prevention and health promotion, multimorbidity/chronic disease, and longitudinal aspects of health and illness.

Periodic Health Examination

- the Canadian Task Force on Preventive Health Care was established in 1976 to develop and disseminate clinical practice guidelines for primary and preventive care, and provides:
  - recommendations based on systematic analysis of scientific evidence
  - periodic preventive health visits recommended in place of annual physical examinations (sometimes called "yearly physicals")

Purpose of the Periodic Health Examination

- primary prevention: identify risk factors for common diseases; counsel patients on health-promoting practices (e.g. vaccinations)
- secondary prevention: early detection of disease to allow prompt treatment and prevent disease progression (e.g. screening programs)

Classification of Recommendations (GRADE)

Strength of Recommendation

- strong: confidence that desirable effects outweigh undesirable effects (strong recommendation for an intervention) or that the undesirable effects outweigh desirable effects (strong recommendation against an intervention)
  - implies that most individuals will be best served by the recommended course of action
- conditional: desirable effects probably outweigh the undesirable effects (conditional recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (conditional recommendation against an intervention)
  - implies that most people would want the recommended course of action but that many would not
  - different choices will be appropriate for different individuals, patients require support in reaching a management decision consistent with their values and preferences

Quality of Evidence

- high: high level of confidence that true effect lies close to the estimate of the effect
- moderate: true effect likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- low or very low: true effect may be substantially different from the estimate of the effect

Table 1. Periodic Health Exam

	General Population	Special Population
Discussion	Dental hygiene (community fluoridation, brushing, flossing) (A) Noise control and hearing protection (A) Screen for poverty Counsel on smoking cessation and provide nicotine replacement therapy (A), referral to smoking cessation program (B) Dietary advice on leafy green vegetables and fruits (B) Seat belt use (B) Moderate physical activity (B) Avoid sun exposure and wear protective clothing (B) Problem drinking screening and counselling (B) Counselling to protect against STIs (B) Nutritional counselling, dietary advice on fat and cholesterol (B) Dietary advice on calcium and vitamin D requirements (B)	**Pediatrics:** home visits for high-risk families (A), injury prevention (home visits for high-risk families (A), injury prevention (poison control, smoke detectors, non-flammable sleepwear, hot water thermostat settings) (B), inquiry into developmental milestones (B) **Adolescents:** counsel on sexual activity and contraceptive methods (B), counsel to prevent smoking initiation and substance use (B) **Perimenopausal Women (>50):** assess for risk factors for: osteoporosis and fracture (A), counsel on osteoporosis, counsel on risks/benefits of hormone replacement therapy (B) **Adults >65:** follow up on caregiver concern of cognitive impairment (A), multidisciplinary post-fall assessment (A)
Physical	BP measurement, using techniques described in CHEP guidelines (A) Measure height, weight, and calculate BMI for adults ≥18 (B)	**Pediatrics:** repeated examinations of hips, eyes, and hearing (especially in first year of life) (A), serial height, weight, and head circumference (B), visual acuity testing after age 2 (B) **Adults >65:** hearing impairment (inquiry, whispered voice test, audioscope) (B) **First-Degree Relative with Melanoma :** full body skin exam (B)

Classification of recommendation in brackets: A – high quality of evidence; B – moderate quality of evidence. For up-to-date guidelines, see: www.canadiantaskforce.ca.

References:
Guidelines [Internet]. Ottawa (ON): The Canadian Task Force on Preventive Health Care; c2019 [cited 2021].
Available from: https://canadiantaskforce.ca/guidelines/
Zaltzman A, Dubey V, Iglar K. Update to the Preventive Care Checklist Form©. CFP. 2020 Apr 1;66(4):270-2.

Adult Periodic Health Exam
Male and female evidence-based preventive care checklist forms are available online athttp://www.cfpc.ca, most recently updated in 2018, re-endorsed in 2019.

Choosing Wisely Canada
http://www.choosingwiselycanada.org/
"A campaign to help clinicians and patients engage in conversations about unnecessary tests and treatments, and make smart and effective choices to ensure high quality care."

Folic Acid Supplementation in Pregnancy (Joint Society of Obstetricians and Gynecologists of Canada-Motherisk Clinical Guideline May 2015)

- To prevent neural tube defects in all women capable of becoming pregnant
- Low-risk women (no personal health risks, planned pregnancy): diet of folate-rich foods and a daily oral multivitamin supplement containing 0.4-1.0 mg folic acid for at least 2-3 mo before conception, throughout pregnancy, and 4-6 wk postpartum or as long as breast-feeding continues
- High-risk women (health risks including epilepsy, insulin-dependent diabetes, BMI >35, family history of NTD, high-risk ethnic group): diet of folate-rich foods and daily supplementation with multivitamins with 5 mg folic acid at least 3 mo prior to conception until 12 wk post-conception
- From wk 12 post-conception until postpartum period (4-6 wk or as long as breastfeeding continues): 0.4-1.0 mg of folic acid supplementation is sufficient
- Women with additional lifestyle issues (poor compliance with medications, no consistent birth control, taking possible teratogenic substances): higher folic acid dose of 5 mg and counselling about prevention of birth defects

Table 1. Periodic Health Exam

	General Population	Special Population
Tests	See recommendations below for age and gender specific screening for diabetes, dyslipidemia, HTN, and cancer screening (colon, prostate, cervical, lung, and breast) One-time screening ultrasound for abdominal aortic aneurysm in men aged 65–80 yr (B)	**Pediatrics:** routine hemoglobin for high-risk infants (B), blood lead screening of high-risk infants (B) **TB High-Risk Groups:** Mantoux skin testing (A) **STI High-Risk Groups:** voluntary HIV antibody screening (A), gonorrhea screening (A), chlamydia screening in women (B), syphilis screening (A) **Syphilis High-Risk Groups:** VDRL test (A)
Therapy	Folic acid supplementation for women of child-bearing age (A) Pharmacologic treatment of HTN (refer to CHEP Guidelines) (A) Varicella vaccine for children ages 1-12 and susceptible adolescents/adults (A) Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B) Tetanus vaccine: routine booster q10 yr if had 1° series (A) Pertussis vaccine: adults <65 should receive one booster given as Tdap– Adacel® or Boostrix® (A) Herpes zoster vaccine for adults ≥50 (A)	**Pediatrics:** routine immunizations (A) **Influenza High-Risk Groups:** outreach strategies for vaccination (A), annual immunization (B), now recommended for all **HPV High-Risk Groups:** vaccination for males and females from age 9 with no upper age limit, if ongoing risk **TB High-Risk Groups:** INH prophylaxis for household contacts or skin test converters (B), INH prophylaxis for high-risk sub-groups (B) **Immunocompromised/Ages ≥65/COPD/Asthma/CHF/Asplenia/Liver Disease/Renal Failure/DM:** pneumococcal vaccine (Pneumovax®23) for all ≥65 or high-risk, add Prevnar®13 if ≥65 and high-risk (A)

Classification of recommendation in brackets: A – high quality of evidence; B – moderate quality of evidence. For up-to-date guidelines, see: www.canadiantaskforce.ca.

References:
Guidelines [Internet]. Ottawa (ON): The Canadian Task Force on Preventive Health Care; c2019 [cited 2021].
Available from: https://canadiantaskforce.ca/guidelines/
Zaltzman A, Dubey V, Iglar K. Update to the Preventive Care Checklist Form©. CFP. 2020 Apr 1;66(4):270-2.

Breast Cancer Screening Guidelines

2018 Canadian Task Force on Preventive Care Recommendations

- for women ages 50-74, recommend screening with mammography every 2-3 yr; the decision to undergo screening is conditional on the relative value that a woman places on possible benefits and harms from screening (conditional recommendation; very low certainty evidence)
- for women ages 40-49, recommend not screening with mammography; the decision to undergo screening is conditional on the relative value that a woman places on possible benefits and harms from screening (conditional recommendation; low certainty evidence)
- recommend not performing clinical breast examinations to screen for breast cancer (conditional recommendation; no evidence)
- recommend not advising women to practice breast self-examination to screen for breast cancer (conditional recommendation; low certainty evidence)
- recommend not using MRI, tomosynthesis, or U/S to screen for breast cancer in women not at increased risk (strong recommendation; no evidence)
- for more information on benign breast lesions and breast cancer, see General Surgery and Thoracic Surgery, GS66

Lung Cancer Screening Guidelines

2016 Canadian Task Force on Preventive Health Care Recommendations

- for adults ages 55-74 with ≥30 pack-yr smoking history who currently smoke or quit ≤15 yr ago, recommend annual screening with LDCT up to three consecutive times; screening should ONLY be carried out in health care settings with expertise in early diagnosis and treatment of lung cancer (weak recommendation; low quality evidence)
- for all other adults, regardless of age, smoking history, or other risk factors, recommend not screening for lung cancer with LDCT (strong recommendation; very low quality evidence)
- recommend that chest x-ray not be used to screen for lung cancer, with or without sputum cytology (strong recommendation; low quality evidence)

Colorectal Cancer Screening Guidelines

2016 Canadian Task Force on Preventive Health Care Recommendations

- recommend screening adults ages 60-74 for CRC with FOBT (either gFOBT or FIT) q2 yr OR flexible sigmoidoscopy q10 yr (strong recommendation; moderate quality evidence)
- recommend screening adults ages 50-59 for CRC with FOBT (either gFOBT or FIT) q2 yr OR flexible sigmoidoscopy q10 yr (weak recommendation; moderate quality evidence)
- recommend not screening adults ages ≥75 for CRC (weak recommendation; low quality evidence)
- recommend not using colonoscopy as a screening test for CRC (weak recommendation; low quality evidence)

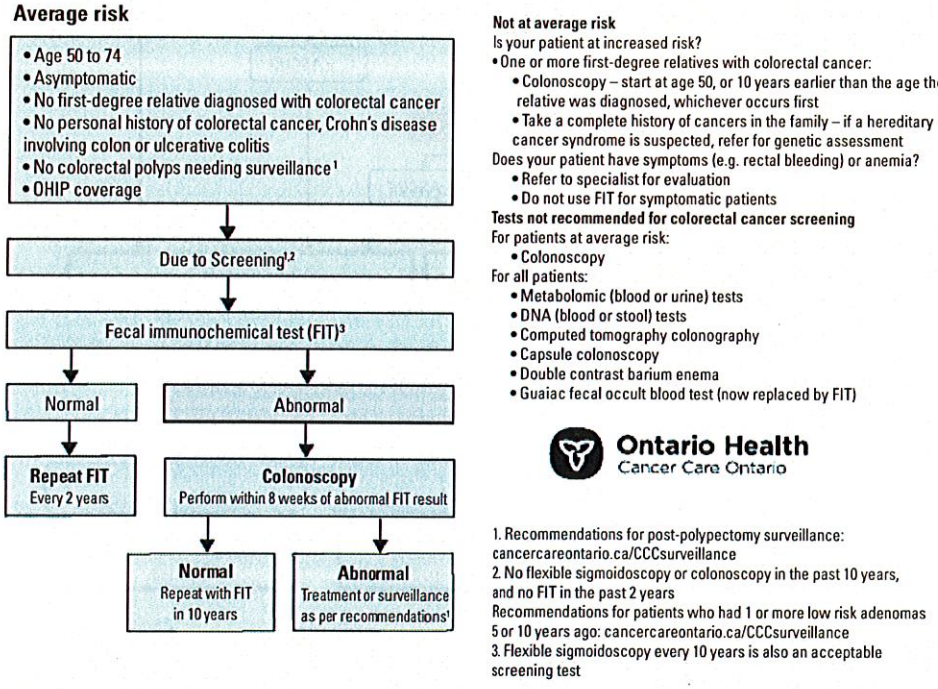


Figure 1. Guide to average risk screening with the fecal immunochemical test (FIT) in Ontario
Colon Cancer Check 2019 Guide to Average Risk Screening with the Fecal Immunochemical Test (FIT) in Ontario. Reproduced with permission from Cancer Care Ontario. Available from https://www.cancercareontario.ca/sites/ccocancercare/files/assets/H-FIT_PCC_2742_ClinicalToolForProviders.pdf

Cervical Cancer Screening Guidelines

2013 Canadian Task Force for Preventive Care Guidelines Recommendations

- for women ages <20, recommend not routinely screening for cervical cancer (strong recommendation; high quality evidence)
- for women ages 20-24, recommend not routinely screening for cervical cancer (weaek recommendation; moderate quality evidence)
- for women ages 25-29, recommend Papanicolaou (Pap) smear or liquid cytology for cervical cancer q3 yr (weak recommendation; moderate quality evidence)
- for women ages 30-69, recommend Pap smear or liquid-based cytology for cervical cancer q3 yr (strong recommendation; high quality evidence)
- for women ages ≥70 who have not been adequately screened, recommend continued screening until 3 negative test results have been obtained (weak recommendation; low quality evidence)
- for women ages ≥70 who have been adequately screened (i.e. 3 successive negative Pap tests in the last 10 yr), recommend that routine screening may cease
- for more information on cervical cancer (see Gynecology, GY47)
- note: provincial/territorial guidelines vary, e.g. Ontario Cervical Screening Program (2022):
  - women ages ≥25 who are or have ever been sexually active, recommend screening q3 yr (if cytology normal);
  - women ages ≥21 may initiate screening if they are immunocompromised and are or have ever been sexually active

The Canadian Task Force on Preventive Health Care is anticipating the publication of new cervical cancer screening guildelines in 2023. Please refer to the published Systematic Review Protocol for the new guidelines: https://canadiantaskforce.ca/wp-content/uploads/2021/11/Task-Force_Cervical-Cancer_SystematicReviewProtocol.pdf

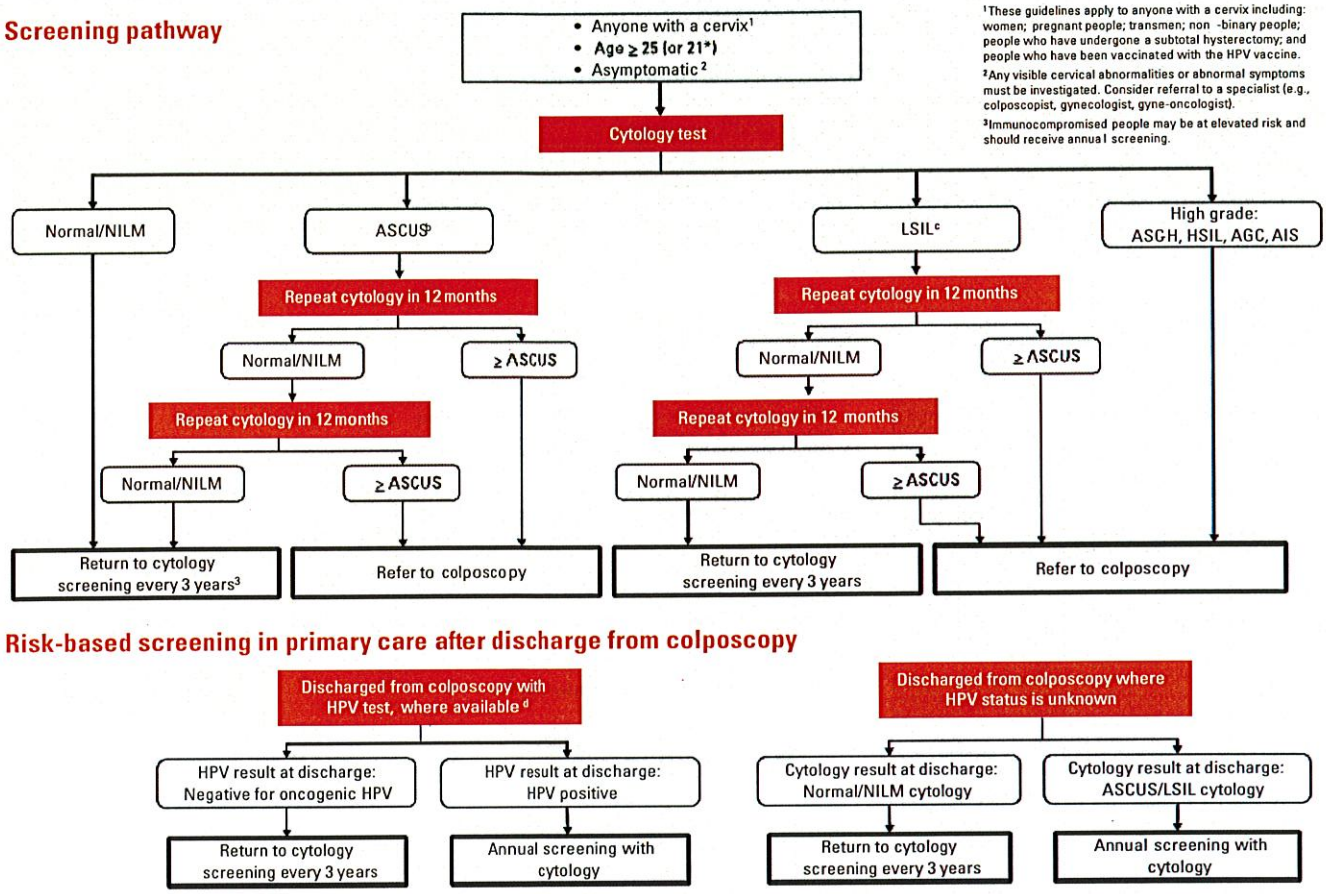


Figure 2. Ontario screening pathway for cervical cancer
AGUS = atypical glandular cells of unknown significance; ASCUS = abnormal squamous cells of unknown significance; ASC-H = abnormal squamous cells cannot rule out HSIL; HSIL = high grade squamous intraepithelial lesion; LSIL = low grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS = adenocarcinoma in-situ; TZ = transitional zone
Adapted from: Ontario Cervical Screening Program 2022 Screening Recommendations Summary. Reproduced with permission from Cancer Care Ontario. Retrieved from https://www.cancercareontario.ca/en/system/files_force/derivative/OCSPScreeningGuidelines.pdf

Prostate Cancer Screening Guidelines

2014 Canadian Task Force for Preventive Care Guidelines Recommendations

- for men ages 55-69, recommend not screening for prostate cancer with the PSA test (weak recommendation; moderate quality evidence); clinicians should discuss the risks and benefits of screening and its potential consequences with each man in the context of his preferences
- for men ages ≤55, recommend not screening for prostate cancer with the PSA test (strong recommendation; low quality evidence)
- for men ages ≥70, recommend not screening for prostate cancer with the PSA test (strong recommendation; low quality evidence)

Basis of Recommendation

- the potential small benefit from PSA screening is outweighed by the potential significant harms of the screening and associated follow-up treatment
  - for men ages ≤55 or ≥70, there is no evidence that screening with the PSA test reduces mortality, whereas there is evidence of harms
  - for men ages 55-69, there is inconsistent evidence of a small potential benefit of screening and evidence of harms

The Canadian Task Force on Preventive Health Care is anticipating the publication of new prostate cancer screening guidelines in 2025/2025. Please refer to the published Systematic Review Protocol for the new guidelines: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-022-02099-9

Health Promotion and Counselling

- health promotion is the most effective preventive strategy
- initial steps should include to respectfully explore the values and purposes of the patient's habits or behaviours
- it is helpful to be guided by a patient's present stage of change when having discussions around healthy behaviours
- for more information, see www.motivationalinterviewing.org

Motivational Strategies for Behavioural Change

Table 2. Motivational Strategies for Behavioural Change

Patient's Stage of Change	Physician's Aim	Physician's Plan
Pre-Contemplation	Encourage patient to consider the possibility of change Assess readiness for change Increase patient's awareness of the problem and its risks	Raise issue in a sensitive manner Offer (not impose) a neutral exchange of information to avoid resistance
Contemplation	Understand patient's ambivalence and encourage change Build confidence and gain commitment to change	Offer opportunity to discuss pros and cons of change using reflective listening
Preparation	Explore options and choose course most appropriate for the patient Identify high-risk situations and develop strategies to prevent relapse Continue to strengthen confidence and commitment	Offer realistic options for change and opportunity to discuss inevitable difficulties
Action	Help patients design rewards for success Develop strategies to prevent relapse Support and reinforce convictions towards long-term change	Offer positive reinforcement and explore ways of coping with obstacles Encourage self-rewards to positively reinforce change
Maintenance	Help patient maintain motivation Review identified high-risk situations and strategies for preventing relapse Increase self-belief in ongoing change	Discuss progress and signs of impending relapse
Relapse	Help patient view relapse as a learning experience Provide support appropriate to re-entry into the change cycle at the patient's present level of readiness, post-relapse	Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future Reassess patient's readiness to change

Adapted from: Hunt P. Motivating Change. Nurs Stand 2001;16:45-52, 54-55

Canadian Cancer Society Recommendations for Vitamin D Use

Based on CCS research on Vitamin D and the prevention of colorectal and breast cancers

In consultation with their healthcare provider, the Society recommends that:

- Adults living in Canada should consider taking Vitamin D supplementation of 1000 IU/d during the fall and winter
- Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1000 IU/d all year round. This includes people: who are older, with dark skin, who do not go outside often, and who wear clothing that covers most of their skin
- Babies who are exclusively breast-fed: 400 IU/d

Nutrition

General Population

- Canada's Food Guide is appropriate for individuals ages ≥2 yr
- counsel on variety, portion size, and plate layout
- guideline 1: nutritious foods are the foundation for healthy eating. Vegetables, fruits, whole grains, and proteins should be consumed regularly. Among protein foods, consume plant-based more often (e.g. legumes, nuts, seeds, tofu, fortified soy beverage). Foods with mostly unsaturated fat should replace those that contain mostly saturated fat. Water should be beverage of choice
  - nutritious foods to consume regularly can be fresh, frozen, canned, or dried
  - consider cultural preferences and food traditions. Traditional food improves diet quality among Indigenous peoples
- guideline 2: processed or prepared foods and beverages that contribute to excess sodium, free sugars, or saturated fat undermine healthy eating, and should not be consumed regularly
- guideline 3: food skills are needed to navigate the complex food environment and support healthy eating. Cooking and food preparation using nutritious foods should be promoted. Food labels should be promoted as a tool to help make informed choices

Energy Content of Food

- Carbohydrates: 4 kcal/g
- Protein: 4 kcal/g
- Fat: 9 kcal/g
- Ethanol: 7 kcal/g

Calculating Total Daily Energy Expenditure

Roughly 35 kcal/kg/d

Varies by age, weight, height, sex, and activity level

Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men

Handy Serving Size Comparisons

85 g meat, fish, poultry → palm of hand

250 ml dairy (milk/yogurt) → size of fist

1 serving of bread/grains → one slice, palm of hand

125 g rice/pasta → one hand cupped

250 g of fruit/vegetables → two cupped hands

28 g cheese → full length of thumb

5 g oil/butter → tip of thumb

28-57 g nuts/chips/snacks→ palm covered

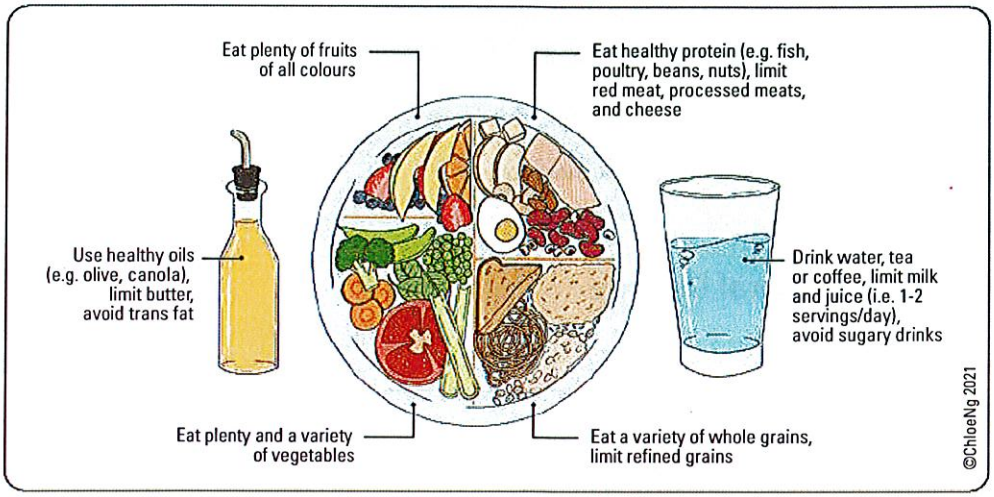


Figure 3. Canada's Food Guide 2019 - plate layout
Source: © All Rights Reserved. Canada's Food Guide. Health Canada, 2019. Adapted and reproduced with permission from the Minister of Health, 2019.

Osteoporosis Canada Recommendations for Calcium and Vitamin D Daily Requirements
Vitamin D: 400-1000 IU for individuals 19-50 yr, 800-2000 IU for individuals ≥50 yr or younger adults at high-risk (osteoporosis, multiple fractures, inadequate vitamin D absorption)
Calcium: 1000 mg daily from all sources for individuals 19-50 yr and pregnant/lactating women; 1200 mg daily for individuals >50 yr (recommended to obtain calcium from diet whenever possible vs. supplementation)

Cardiovascular Disease Prevention

Table 3. Dietary Guidelines for Reducing Risk of Cardiovascular Disease

Carbohydrates	Complex carbs (legumes, whole grains) should be favoured over simple carbs (white flour/rice, table sugar) Eliminate sugar-sweetened beverages in favour of water
Fruits and Vegetables	Consume a higher proportion of whole, fresh fruits and vegetables Consume leafy green vegetables and berries at least 3 times/wk Consume starchy vegetables (white potatoes, corn, green peas) in moderation
Fats	Consume mono- and polyunsaturated fats in moderation (non-tropical vegetable fats, liquid fats) Minimize trans fat intake (processed/snack foods) Limit saturated fats (processed foods, red meat, cheese, whole milk, butter) Olive and canola oil are recommended over butter/margarine/coconut oil Skim or 1% milk is recommended over whole milk
Protein	Consume fish with higher levels of omega-3 fatty acids (salmon, tuna, mackerel) Moderate consumption of lean poultry, seafood, and nuts Limit red meat Minimize consumption of processed meats (deli/cold cuts, sausage, bacon)
Salt	≤2000 mg/d
Alcohol	Recommend limiting drinks to ≤2/wk. There is a continuum of risk associated with alcohol consumption where the risk of harm from alcohol is: Low - ≤2 drinks/wk Moderate - 3-6 drinks/wk High ≥7 drinks/wk
Dietary Approaches	**Mediterranean diet:** High intake of leafy green vegetables, fruits, whole grains, nuts, legumes, extra virgin olive oil Moderate intake of fish, lean meats, low fat dairy, poultry Low intake of red meats and sweets **DASH diet:** High in vegetables/fruits, no or low-fat dairy, whole grains, poultry, fish, beans, seeds, and nuts Low in sodium, sweets, added sugars, sugar-sweetened beverages, fats, and red meats Lower in saturated fat, trans fat, and cholesterol High in potassium, magnesium, calcium, protein, and fibre **Vegetarian diet:** Substitute meat/seafood/poultry with soy products, legumes, nuts, and whole grains

Dietary approaches to stop hypertension (DASH), available from: http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/dash_brief.pdf
Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.
Pallazola VA, et al. A Clinician's Guide to Healthy Eating for Cardiovascular Disease Prevention. Mayo Clin Proc Innov Qual Outcomes 2019;3:251-267.
Anderson TJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2016;32:1263-1282.
Paradis C, et al. Canada's Guidance on Alcohol and Health: Final Report. Canadian Centre on Substance Use and Addiction 2023.

Obesity

Definition

- prevalent, complex, progressive, and relapsing chronic disease that is characterized by abnormal/excessive body fat (adiposity)
- impairs health, increases risk of long-term medical complications, and reduces lifespan

Epidemiology

- in Canada, the prevalence of obesity has tripled and severe obesity has more than quadrupled since 1985
- obesity remains higher in populations which face multiple socioeconomic barriers such as geographic isolation, poverty, and lack of access to nutritious (and more expensive) food
- for example, First Nations living on reserves have higher rates of obesity (30-51%) than non-Indigenous populations (12-31%)
- close to 1/3 of Canadians ages 5-17 yr were identified as having a BMI classified as overweight or obese
- screen time ≥2 h/d (total screen time, television time, and computer time) is likely associated with an increased risk of children having a BMI classified as overweight or obese

2015 Canadian Task Force on Preventive Health Care Recommendations

- for apparently healthy adults ≥18 yr, it is recommended to measure height, weight, and calculate BMI at appropriate primary care visits
  - BMI = weight (kg)/height ^{2}(m ^{2}) = weight (lbs)/height ^{2}(in ^{2}) x 703
  - note: this recommendation does not apply to people with eating disorders or who are pregnant
- for those with increased BMI (25.0-34.9 kg/m ^{2}), WC should be measured regularly to identify patients with increased visceral adiposity and related health risks
- for apparently healthy children and youth ages 0-17 yr, it is recommended to monitor growth at all appropriate primary care visits using the 2014 WHO Growth Charts for Canada (strong recommendation; very low quality evidence). This recommendation does not apply to children and youth with eating disorders, or who are underweight, overweight, or obese

Table 4. Classification of Weight by Body Mass Index and Associated Disease Risks in Adults

	BMI (kg/m^2)	Risk of Developing Health Problems
Underweight	<18.5	Increased
Normal	18.5-24.9	Least
Overweight	25.0-29.9	Increased
Obesity Class I	30.0-34.9	High
Obesity Class II	35.0-39.9	Very high
Obesity Class III (Extreme Obesity)	≥40.0	Extremely high

Body Mass Index (BMI) Nomogram, Government of Canada: Health Canada, available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/healthy-weights/canadian-guidelines-body-weight-classification-adults/body-mass-index-nomogram.html

Management

Canadian Adult Obesity Clinical Practice Guidelines (Obesity Canada, 2020)

- recognize that people with obesity experience weight bias and stigma, which contributes to increased complications and mortality independent of weight or BMI
- **Step 1** - Ask: recognize obesity as a chronic disease and obtain patient permission to discuss and help treat this disease in an unbiased manner
- **Step 2** - Assess: assess the patient using appropriate measures (i.e. height, weight, WC, and BMI calculation) and identify root causes (e.g. biological factors, individual life experiences, psychological factors), complications, and barriers to treatment
- **Step 3** - Advise: discuss treatment options and work with the patient to create individualized care plans that address root causes of obesity and support behaviour change
  - nutrition:
    - all individuals can benefit from adopting a healthy, well-balanced diet
    - weight loss requires long-term reduction in caloric intake, encouraged by a personalized eating pattern that meets the patient's values, preferences, and nutritional needs
    - medical nutrition therapy should not be used in isolation (may promote compensatory mechanisms that promote positive caloric intake by increasing hunger), but instead should be used in combination with other interventions (e.g. psychological, pharmacological, surgical)
  - physical activity:
    - consider aerobic physical activity (30-60 min of moderate to vigorous intensity most d/wk) for adults who wish to achieve small amounts of body weight and fat loss, reduce abdominal visceral fat, maintain weight loss, and/or increase cardiorespiratory fitness
    - resistance training may promote weight maintenance, increased muscle mass, fat-free mass, and mobility in adults who are overweight/obesity
    - regular physical activity can improve cardiometabolic risk factors and improve health-related quality of life
  - psychological and behavioural interventions:
    - multicomponent psychological intervention (behaviour modification, cognitive therapy, and values-based strategies to alter diet/activity) should be incorporated into care plans for weight loss

Treatment for Overweight and Obesity in Adult Populations: A Systematic Review and Meta-analysis
CMAJ Open 2014;2:E306-317
Purpose: To evaluate the effectiveness of behavioural and pharmacological treatments for overweight and obese adults.
Methods: Review of RCTs of primary-care-relevant behavioural (diet, exercise, lifestyle) and pharmacological (orlistat, metformin) treatments with or without behavioural interventions in overweight or obese adults with 12 mo follow-up from baseline for weight outcomes or harms. Secondary health outcomes (TC, LDL, FBG, incidence of T2DM, sBP and dBP) were also studied.
Results: 68 RCTs were included and showed that intervention participants had greater weight loss (-3.02 kg, 95% CI -3.52 to -2.52), waist circumference reduction (-2.78 cm, 95% CI -3.34 to -2.22) and BMI reduction (-1.11 kg/m2, 95% CI -1.39 to -0.84). Relative risk for weight loss of ≥5% body weight was 1.77 (95% CI 1.58 to 1.99; NNT 5, 95% CI 4-7). Relative risk for loss of ≥10% body weight was 1.91 (95% CI 1.69 to 2.16; NNT 9, 95% CI 7-12). Incidence of T2DM was lower among pre-diabetic intervention participants (RR 0.62, 95% CI 0.50 to 0.77; NNT 17, 95% CI 13-29).
Conclusion: Behavioural and pharmacological treatments for overweight and obese adults may lead to clinically important reductions in weight and incidence of T2DM in pre-diabetic populations.

Adverse Medical Consequences of Obesity

- T2DM
- Dyslipidemia
- CAD
- Osteoarthritis
- Stroke
- OSA
- HTN
- Certain cancers
- Gallbladder disease
- CHF
- Low back pain
- Non-alcoholic statohepatitis
- Increased total mortality
- Pregnancy complications

Associations with Low BMI

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications

Pharmacotherapy for Obesity
There are currently 3 prescription medications available in Canada that are approved for use in adult patients with BMI ≥30 kg/m2 or BMI ≥27 kg/m2 and ≥1 weight-related condition (e.g. HTN, T2DM, dyslipidemia)
Note: these medications should be used alongside a reduced-calorie diet and increased physical activity
Contrave® (naltrexone and bupropion): controls hunger and cravings
Saxenda® (liraglutide): decreases appetite and, therefore, food intake
Xenical® (orlistat): reduces dietary fat absorption by 30% through inhibition of pancreatic and gastric lipases

- pharmacotherapy:
  - liraglutide, naltrexone-bupropion combination, or orlistat (see sidebar *Pharmacotherapy for Obesity, FM9*)
  - can be used for patients with BMI ≥30 kg/m2 or ≥27 kg/m2 with adiposity-related complications, in combination with medical nutrition therapy, physical activity, and psychological interventions
  - can be used to maintain weight loss achieved by behaviour changes and to prevent weight regain
- bariatric surgery:
  - consider for patients with BMI ≥40 kg/m2 or BMI ≥35 kg/m2 with ≥1 adiposity-related disease (e.g. T2DM)
  - consider for weight loss and/or to control adiposity-related diseases where optimal medical and behavioural management has been insufficient to produce significant weight loss
  - choice of bariatric procedure should be decided according to the patient's needs, in collaboration with an experienced interprofessional team (suggest against adjustable gastric banding and single anastomosis gastric bypass, due to unacceptable complications and long-term failure)

- **Step 4** - Agree: agree on goals of therapy with the patient, focusing on the patient's values to ensure realistic expectations, sustainable behaviour change, and improved health outcomes
- **Step 5** - Assist: follow up and reassess the patient regularly to assist with drivers/barriers and advocate for improved obesity care

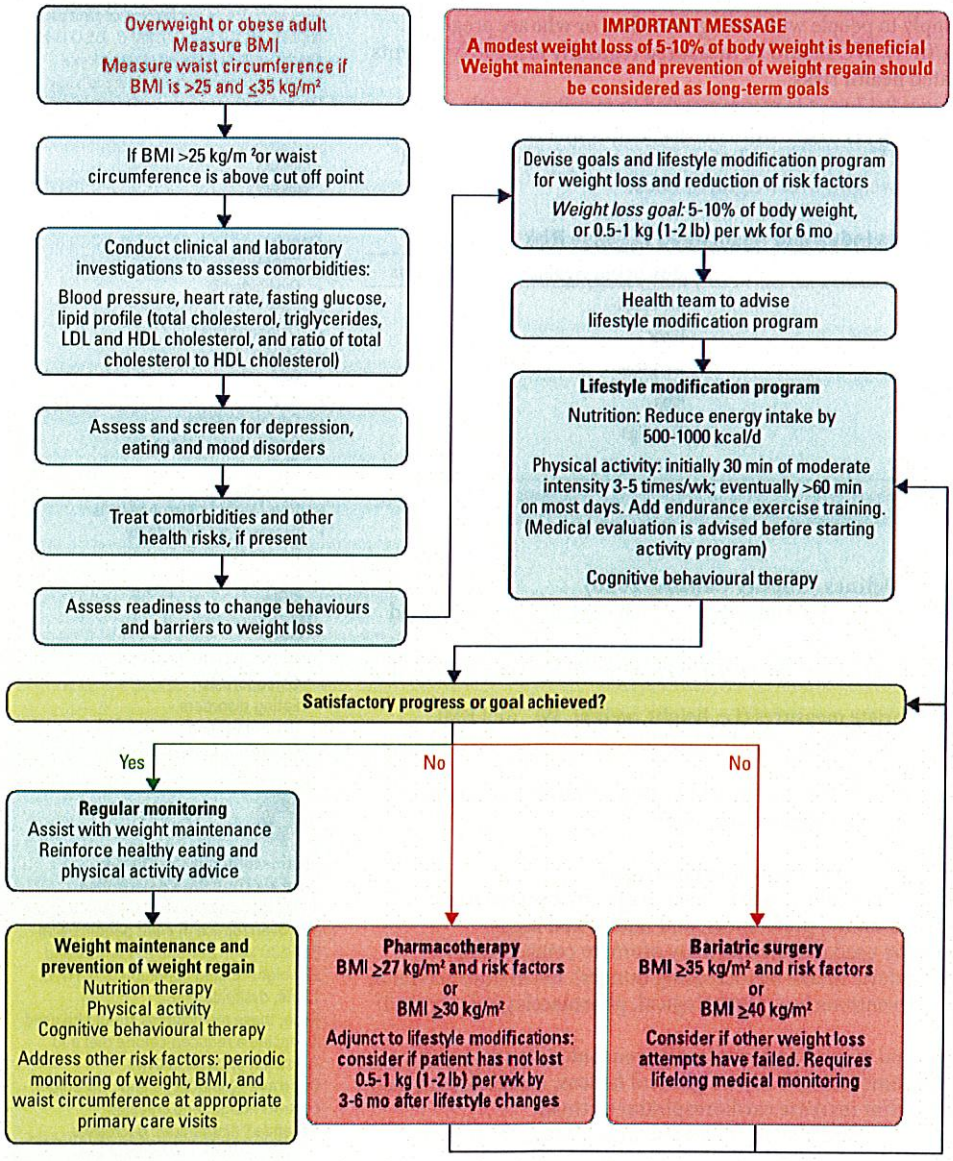


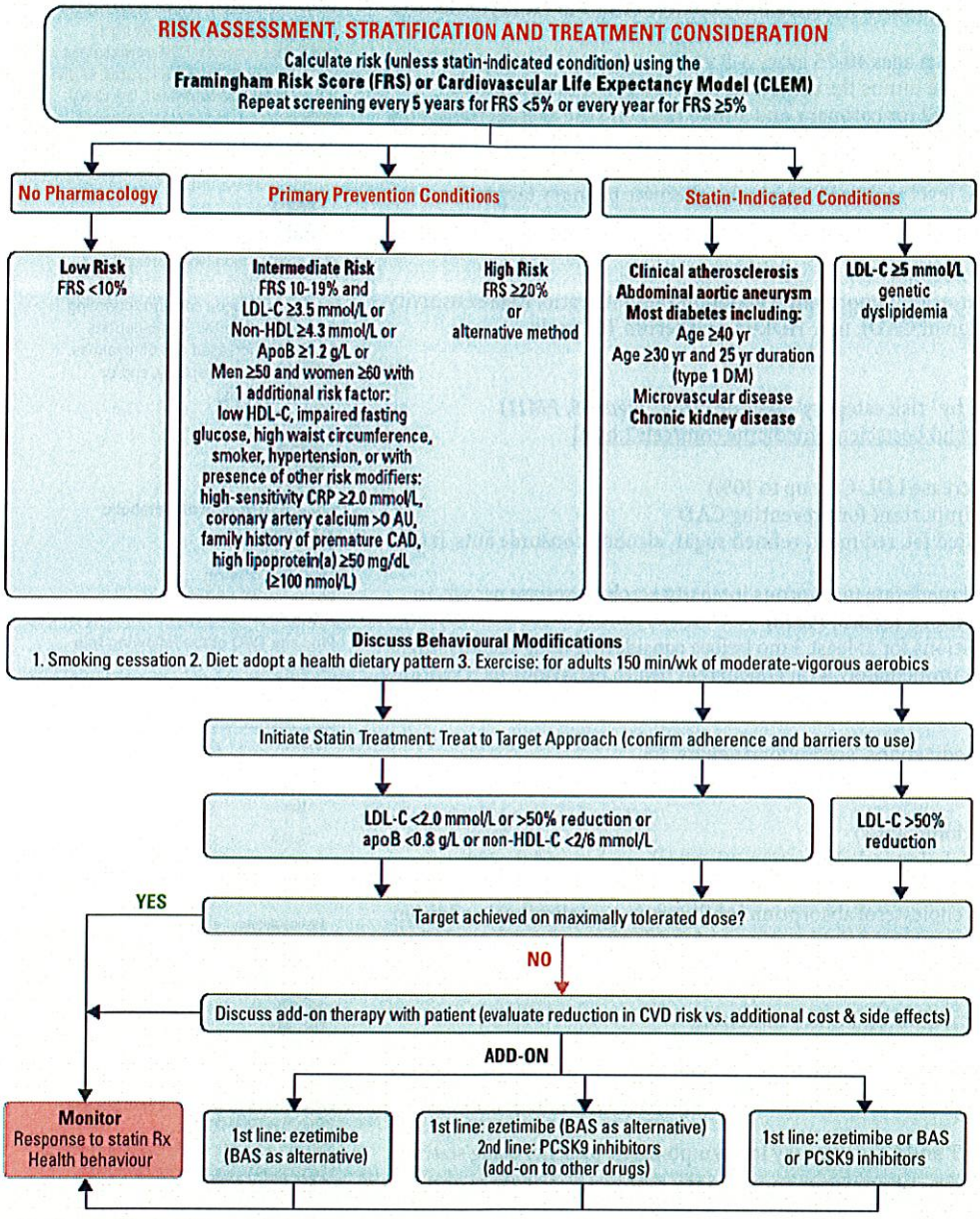
Figure 4. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children

Adapted from: Lau DCW, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. CMAJ 2007;176:S1-S13

Effects of Popular Diets without Specific Calorie Targets on Weight Loss Outcomes: Systematic Review of Findings from Clinical Trials
Nutrients 2017;9:E822
Purpose: To assess the short-term (≤6 mo) and long-term (≥6 mo) weight loss outcomes for current popular diets in overweight and obese adults.
Methods: A systematic review was conducted. All diets in the 2016 U.S. News & World Report Rankings for "Best Weight-Loss Diets" were examined. From the potential 38 diets, eligible studies included trials with a sample size ≥15 per group, interventional clinical trials, intervention periods ≥12 wk, BMI ≥25 mg/m², participants aged ≥18 yr and objective measures of pre- and post-intervention.
Results: Sixteen articles were included in the review. Diets included the Atkins, DASH, Glycemic-Index, Mediterranean, Ornish, Paleolithic, and Zone diets. The Atkins diet showed the most clinically significant reduction in weight loss in both the short-term and long-term.
Conclusion: Other diets had limited evidence supporting their effectiveness in producing clinically significant short-term and long-term weight loss. Future studies are needed to compare and evaluate the efficacy of these other diets.

Effect of Intermittent Energy and Carbohydrate Restriction vs. Daily Energy Restriction on Weight Loss and Metabolic Disease Risk Markers in Overweight Women
Br J Nutr 2013;110:1534-1547
Purpose: To determine if intermittent energy and carbohydrate restriction (IECR) may result in greater improvements in insulin sensitivity and weight control than daily energy restriction (DER).
Methods: Two IECR regimens were tested, including one which allowed ad libitum protein and fat (IECR + PF). Overweight women (n=115) ages 20-69 with a family history of breast cancer were randomized to an overall 25% energy restriction, or a 25% DER, or an IECR + PF for a 3 mo weight-loss period and 1 mo of weight maintenance (IECR or IECR + PF for 1 d/wk).
Results: Insulin resistance reduced with the IECR diets and the IECR + PF diet. Reductions with the IECR diets were significantly greater compared with the DER diet. Both IECR groups had greater reductions in body fat compared with the DER group. During the weight maintenance phase, 1 day of IECR or IECR + PF per week maintained the reductions in insulin resistance and weight.
Conclusion: In the short term, IECR is superior to DER with respect to improved insulin sensitivity and body fat reduction.

Dyslipidemia



ApoB = apolipoprotein B; AU = agatston units; BAS = bile acid sequestrants; PCSK9 = proprotein convertase subtilisin/kexin type 9

Figure 5. Approach to primary prevention of CVD (2021 Canadian Cardiovascular Society Guidelines)
Pearson GJ, Thanassoulis G, Anderson T, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2021 Aug;37(8):1129-1150.

• see Endocrinology, E3

Definition

•abnormal elevation of plasma cholesterol or TG levels

Assessment

•screen with full lipid profile every 1-3 yr in males and females ≥40 yr or who are menopausal, or at any age for adults with additional dyslipidemia risk factors (see Clinical Pearl), and in the late postpartum period for women who have had a pregnancy-related complication (e.g. hypertensive disorders of pregnancy, gestational diabetes, preterm birth, stillbirth, low birthweight infant, placental abruption)
•history and physical examination
•measure standard lipid panel (TC, LDL-C, HDL-C, TG, calculated HDL-C), glucose, and eGFR (optional: apolipoprotein B (ApoB), urine ACR)
•screen for secondary causes: hypothyroidism, CKD, DM, nephrotic syndrome, liver disease

Signs of Hyperlipidemia
Atheromata: plaques in the intimal layer of arterial walls
Xanthelasmata: a sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelid
Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
Eruptive xanthoma: hypertriglyceridemia-induced reddish yellow, pruritic, and painful papular or nodular rash
Lipemia retinalis: characterized by creamy, white-coloured retinal blood vessels, occurs only with extreme hypertriglyceridemia
Corneal arcus (arcus senilis): lipid deposit in cornea

To calculate FRS go to https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/

Risk Factors for Screening for Dyslipidemia
- Men and women ages ≥40 (or postmenopausal)
- Increased incidence in Indigenous individuals or individuals of South Asian ancestry
- Current cigarette smoking
- T2DM
- Arterial HTN
- Family history of premature CVD (men <55 yr, women <65 yr in 1st-degree relative)
- Family history of dyslipidemia
- Erectile dysfunction
- CKD
- Inflammatory disease (lupus, RA, psoriatic arthritis, IBD)
- HIV infection
- COPD
- Clinical evidence of atherosclerosis or abdominal aortic aneurysms
- Stigmata of dyslipidemia (arcus cornea, xanthelasma, or xanthoma)
- Obesity (BMI ≥30 kg/m^2)
- Hypertensive diseases of pregnancy

Non-Fasting Lipids vs. Fasting Lipids
Non-fasting (TC and non-HDL cholesterol) can be used for Framingham Risk Assessment and hold same prognostic value as fasting lipids
In fasted vs. non-fasted samples, HDL-C and TC vary by <2%, LDL-C varies by <10% and TG varies by <20%
Recently, non-fasting LDL-C has the same prognostic value as fasting LDL-C
Ontario Association of Medical Laboratories Guidelines for Lipid Testing in Adults 2013. Accessed from: https://oaml.com/wp-content/uploads/2016/05/OAMLGuidelineforAdultLipidTestingFinal2013.pdf

LDL cannot be calculated when TG ≥4.5 mmol/L

- risk category
  - estimate using the FRS for assessing 10 yr risk of developing CAD
    - FRS is calculated based on gender, age, HDL-C, TC, sBP, smoking, DM
    - family history of premature CVD (<55 in 1st degree male relative or <65 in 1st degree female relative) doubles FRS
    - to be completed for men and women ages 40-75 every 3-5 yr
    - CV age is calculated as patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary and stroke risk) and the average remaining life expectancy of Canadians of the same age and sex
- used to increase adherence to therapy and reaffirm positive effect of following therapy
  - treatment decisions focus on LDL-C level and/or FRS risk; the alternate primary targets are apolipoprotein B and non-HDL-C
  - if moderate risk and LDL-C <3.5, treatment decision thresholds shifted to apolipoprotein B >1.2 g/L or non-HDL-C >4.3 mmol/L
  - other targets include: TC:HDL-C ratio, apolipoprotein B:apolipoprotein A1 ratio, high-sensitivity CRP (used more for risk stratification of CAD), non-HDL-C, and serum TG levels

Management

- intensity and type of treatment is guided by "risk category" assigned (see *Figure 5, FM11*)
- use decision-making aids such as http://chd.bestsciencemedicine.com/calc2.html

1. Health behaviour interventions (can decrease LDL-C by up to 10%)
   - smoking cessation: likely the most important for preventing CAD
   - dietary modification: reduce saturated fat, red meat, refined sugar, alcohol; consume nuts, fruits/vegetables, poultry, fish
   - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per wk, in bouts of ≥10 min to reduce CVD risk (see *Table 5, FM13*)
   - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high-risk patients should start treatment immediately with concurrent health behaviour interventions

2. Pharmacologic therapy
   - for a comparison of dyslipidemia medications, see Endocrinology, E5
   - 1st line monotherapy: statins (β-Hydroxy β-methylglutaryl-CoA, HMG-CoA, reductase inhibitors)
     - risks: myopathy (myalgia, rhabdomyolysis)
     - if severe side effects: ezetimibe (cholesterol absorption inhibitor) can be used for 19% reduction in LDL-C
     - post-acute coronary syndrome: cholesterol absorption inhibitors (e.g. ezetimibe) in addition to simvastatin reduced mortality, attained lipid targets <1.8, and improved outcomes in high-risk individuals

- other agents: bile acid sequestrants, niacin, fibrates, PCSK9 inhibitors
- monitoring
  - ALT, and CK if symptomatic, Cr at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal vs. 2-3 times if symptomatic, or serum Cr rise of ≤25%
  - no routine repeated measures of ALT and CK necessary in asymptomatic patients using statin therapy
  - if adequate response is achieved, evaluate fasting lipids every 6-12 mo
  - a target LDL-C <2.0 mmol/L or >50% reduction of LDL-C is the recommended target for therapy to decrease the risk of CVD events and mortality

Isolated Hypertriglyceridemia

- does not increase cardiovascular risk
- normal HDL-C and TC, elevated TG
- mild ≥2.2 mmol/L (≥200 mg/dL); marked ≥5.6 mmol/L (≥500 mg/dL)
- principal therapy is lifestyle modification
  - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in those with DM, increased omega-3 fatty acid intake
  - severe hypertriglyceridemia (typically >10 mmol/L) is associated with an increased risk of acute pancreatitis
- drug therapy (lowers risk for pancreatitis, not CAD)
  - fibrates



Safety of Statins: An Update
Therapeutic Advances in Drug Safety 2012;3:133-144
Trials have shown that statin therapy slightly increases the incidence of T2DM and hemorrhagic stroke; however, the absolute risk is small. Relative to the reduction in coronary events, their clinical significance is not great enough to recommend against statin use.



Use with caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations (potential increased risk of myalgias, CK elevations, myopathy, and/or rhabdomyolysis)



Clinical Definition of Metabolic Syndrome
Central obesity
Men – WC ≥94 cm
Women – WC ≥80 cm

Plus any TWO of the following four factors

Risk Factor	Defining Level
TG level	≥1.7 mmol/L (150 mg/dL)
HDL-C level:	
Men	<1.0 mmol/L (40 mg/dL)
Women	<1.3 mmol/L (50 mg/dL)
BP	≥130/85 mmHg or taking BP medications
Fasting glucose level	≥5.6 mmol/L (100 mg/dL)



Statin-Related Adverse Events: A Meta-Analysis
Clin Ther 2006;28:26-35
Purpose: To synthesize adverse event data with statin use based on RCT data.
Methods: Meta-analysis of RCTs focused on adverse effects of statins. Eligible patients were those taking statin monotherapy for primary or secondary prevention of CVD, compared to placebo. Adverse events including elevated liver enzymes or myopathy (myalgias, elevated CK, rhabdomyolysis) were the main outcomes.
Results: Statin therapy increased the risk of any adverse event by 39% (OR 1.4; 95% CI 1.09-1.80; P=0.008) compared with placebo. Treating 1000 patients with a statin would cause 5 adverse events. Serious events (CK >10 times the upper limit of normal or rhabdomyolysis) are infrequent (NNH 3400) and rhabdomyolysis, although serious, is rare (NNH 7428).
Conclusion: Statin therapy was associated with greater odds of adverse events compared with placebo but with substantial clinical benefit. Similar rates of serious adverse events were observed between statin and placebo.

Exercise

Table 5. Canadian 24 Hour Movement Guidelines (2020 CSEP Guidelines)

Age Category	Physical Activity Guidelines	Example Activities	Sleep/Sit Guidelines
Infant (<1)	Active several times daily in a variety of ways Accumulate >30 min/d of tummy time while awake	Interactive floor-based play including tummy time, reaching for toys, crawling	**Sleep:** 14-17 h/d (0-3 mo), 12-16 h/d (4-11 mo) of good quality sleep including naps, with consistent bed and wake up times **Sit:** not restrained (i.e. in a stroller) for >1 h, screen time not recommended, engage in reading/storytelling while sedentary
Toddler (1-2)	Accumulate >180 min of physical activity at any intensity spread throughout the day including energetic play	Moving around the home Climbing stairs Exploring environment Brisk walking, running, dancing	**Sleep:** 11-14 h/d of good quality sleep including naps, with consistent bed and wake up times Sit: not restrained (i.e. in a stroller) for >1 h, sedentary screen time not recommended if <2 yr (<1 h screen time for those ages 2 yr), engage in reading/storytelling while sedentary
Preschool (2-4)	Accumulate >180 min in a variety of activities at any intensity, including ≥60 min of energetic play throughout the day	Moving around the home Climbing stairs Exploring environment Brisk walking, running, dancing	**Sleep:** 10-13 h/d of good quality sleep which may include a nap Sit: not restrained (i.e. in a stroller) for >1 h, sedentary screen time <1 h (less is better), engage in reading/storytelling while sedentary
Children (5-11) and Youth (12-17)	Accumulate >60 min/d of moderate to vigorous aerobic physical activity Muscle/bone strengthening exercises 3 d/wk A variety of structured/unstructured light physical activities for several h/d	Moderate: bike riding, playground playing Vigorous: running, swimming	**Sleep:** 9-11 h/d (5-13 yr), 8-10 h/d (14-17 yr) uninterrupted, with consistent bed and wake up times Sit: no more than 2 h/d of recreational screen time, limit sitting for extended periods
Adults (18-64)	Accumulate 150 min/wk of moderate to vigorous intensity aerobic physical activity, in bouts of ≥10 min Muscle/bone strengthening activities using major muscle groups, ≥2 d/wk	Moderate: brisk walking, bike riding Vigorous: jogging, cross country skiing	**Sleep:** 7-9 h/d of good quality sleep, with consistent bed and wake up times **Sit:** limit sedentary time to 8 h or less, no more than 3 h/d of recreational screen time, break up long periods of sitting as often as possible
Older Adults (≥65)	Same as Adults above Physical activities that challenge balance	Same as Adults above Those with poor mobility should perform physical activities to enhance balance and prevent falls	Same as Adults above

Epidemiology

- 25% of the population exercises regularly, 50% occasionally, 25% is sedentary

Management

- assess current level of fitness, motivation, and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, DM (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, T2DM, osteoporosis, and overweight/obesity
  - leads to improved fitness, strength, mobility, functional independence, and mental health (morale and self-esteem)

Smoking Cessation

Epidemiology

- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2012 Canadian Tobacco Use Monitoring Survey on population ages ≥15
  - 16% are current smokers (lowest since 1985)
  - highest prevalence in those ages 20-24 (20%)
  - 11% of youth ages 15-19 smoke (decreased from 25% in 2000): more males (18%) smoke than females (14%); number of cigarettes consumed per day is also decreasing (15.0 per day in 2012 vs. 16.2 per day in 2001)



Doses, Durations, and Modes of Delivery of Nicotine Replacement Therapy for Smoking Cessation

Cochrane DB Syst Rev 2019;4:CD013308

Purpose: NRT helps with smoking cessation but it is unclear what NRT routines and dosages are most helpful. The aim was to establish efficacy of different forms, deliveries, dosages, and duration of treatment.

Methods: Meta-analysis including RCTs.

Results: High-certainty evidence that combination NRT (fast-acting form + patch) results in higher long-term quit rates than single-form NRT. Moderate-certainty evidence that dosages ≥21/22 mg are equally effective. Five studies comparing 4 mg gum to 2 mg gum found a benefit of the higher dose. Nine studies tested the effect of using NRT prior to quit day (preloading) in comparison to using it from quit day onward; there was moderate-certainty evidence of a favourable effect of preloading on abstinence.

Conclusions: There is high-certainty evidence that using combination NRT vs. single-form NRT can increase the chances of successfully stopping smoking. Higher dosed patches and gum result in higher long term quit rates with moderate-quality evidence.

Management

- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts, and results
  - be curious about how the patient relates to smoking. Ask: what purpose does smoking serve in their life at the moment?
  - 2012 Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment (CAN-ADAPTT) Guidelines
    - tobacco use status should be updated for all patients regularly
    - health care providers should clearly advise patients to quit
    - health care providers should assess patient willingness to quit and offer assistance to those who express interest
    - health care providers should conduct regular follow-up to assess response and monitor the patient's mental health status/other addictions while quitting smoking
- willing to quit
  - provision of social support, community resources (self-help, group, helpline, web-based strategies)
- medication dosage should be monitored and adjusted as necessary
  - every smoker should be offered treatment
- educate patient to watch for withdrawal symptoms: low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
- combining counselling/behavioural therapies and smoking cessation medication is more effective than either alone
  - ≥4 counselling sessions, >10 min each, with 6-12 mo follow-up yields better results
  - 14% abstinent with counselling vs. 10% without counselling
  - approach depends on patient's stage of change (see *Motivational Strategies for Behavioural Change, FM7*)
- pharmacologic therapy

1. NRT
   - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
   - no difference in achieving abstinence for different forms of NRT
   - reduces cravings and withdrawal symptoms without other harmful substances contained in cigarettes
   - cost of NRT is comparable, and often lower than cigarettes
   - use with caution: immediately post-MI, worsening angina, arrhythmia
   - advise no smoking while using NRT
   - public reimbursement for smoking cessation treatment varies across Canada – see https://www.helpthemquit.ca/treatment/costs-coverage for more details
2. Antidepressants (mechanism of action appears to be independent of antidepressant effect)
   - bupropion SR (Zyban®)
   - 21% abstinent at 12 mo vs. 8% for placebo
   - bupropion has similar effectiveness to NRT
3. Varenicline (Champix®)
   - partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce response to smoked nicotine)
   - more effective than bupropion (23% abstinent from 9-52 wk with varenicline vs. 16% with bupropion vs. 9% with placebo)
   - significant side effects (including nausea, headache, drowsiness, unusual dreams, neuropsychiatric symptoms) may lower patient compliance

Table 6. Types of Nicotine Replacement Therapy

Type	Dosage	Comment	Side Effects
Nicotine Gum (OTC)	2 mg if <25 cig/d 4 mg if >25 cig/d 1 piece q1-2 h for 1-3 mo (max 24 pieces/d)	Chew until "peppery" taste then "park" between gum and cheek to facilitate absorption Continue to chew/park intermittently for 30 min	Mouth soreness Hiccups Dyspepsia Jaw ache (Most are transient)
Nicotine Patch (OTC)	Use for 8 wk 21 mg/d x 6 wk 14 mg/d x 2 wk 7 mg/d x 2 wk	Start with lower dose if <10 cig/d Change patch q24 h and alternate sides	Skin irritation Insomnia Palpitations Anxiety
Nicotine Inhaler (OTC)	6-16 cartridges/d up to 12 wk	Nicotine inhaled through mouth, absorbed in mouth and throat (not in lungs)	Local irritation Cough
Nicotine Nasal Spray (Rx)		Newer form of NRT	Local irritation Cough



Antidepressants for Smoking Cessation
Cochrane DB Syst Rev 2020;4:CD000031
Purpose: To assess evidence for the efficacy, safety, and tolerability of medications with antidepressant properties in assisting long-term tobacco smoking cessation.
Methods: Meta-analysis of RCTs comparing antidepressant medications to placebo or alternative pharmacotherapy, or the same medication used in a different way for smoking cessation. Safety analyses with any follow-up length was also conducted.
Results: Compared to placebo, bupropion was associated with increased long-term smoking cessation rates (RR 1.64, 95% CI 1.52-1.77), higher risk of reported psychiatric adverse events (RR 1.25, 95% CI 1.15-1.37), and higher dropout rate due to adverse events of the drug (RR 1.37, 95% CI 1.21-1.56). Bupropion resulted in inferior cessation rates to varenicline (RR 0.71, 95% CI 0.64-0.79), however no difference in efficacy between bupropion and NRT was found. Additionally, nortriptyline aided smoking cessation when compared with placebo (RR 2.03, 95% CI 1.48-2.78). There was insufficient evidence to establish whether combination bupropion and NRT resulted in superior quit rates to NRT alone, or whether combination bupropion and varenicline resulted in superior quit rates to varenicline alone.
Conclusion: Evidence suggests that bupropion may be helpful and as successful as NRT and nortriptyline in helping people to quit smoking, but that it is less effective than varenicline.



The 5 A's for Patients Willing to Quit
Ask if the patient currently smokes and is willing to discuss cessation
Advise the patient to quit
Assess willingness to quit
Assist in quit attempt(s)
Arrange follow-up



The 2-3 Pattern of Smoking Cessation
Onset of withdrawal is 2-3 h after last cigarette
Peak withdrawal is at 2-3 d
Expect improvement of withdrawal symptoms at 2-3 wk
Resolution of withdrawal at 2-3 mo
Highest relapse rate within 2-3 mo



Assist Patient in Developing Quit Plan

STAR
Set quit date
Tell family and friends (for support)
Anticipate challenges (e.g. withdrawal)
Remove tobacco-related products (e.g. ashtrays/lighters)

Table 7. Pharmacologic Treatments for Smoking Cessation

Drug	Mechanism	Dosage	Prescribing*	Contraindications
Bupropion	Inhibits re-uptake of dopamine and/or NE Side effects: insomnia, dry mouth	1. 150 mg qAM x 3 d 2. Then 150 mg BID x 7-12 wk 3. For maintenance consider 150 mg BID for up to 6 mo	1. Decide on a quit date 2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk)	Seizure disorder Eating disorder MAOI use in the past 14 d Simultaneous use of bupropion (Wellbutrin®) for depression
Varenicline	Partial nicotinic receptor agonist, and partial competitive antagonist of nicotinic receptor Side effects: nausea, vomiting, constipation, headache, dream disorder, insomnia, increased risk of psychosis, depression, suicidal ideation	1. 0.5 mg qAM x 3 d 2. Then 0.5 mg BID x 4 d 3. Continue 1 mg BID x 12 wk ± additional 12 wk as maintenance	1. Decide on a quit date 2. Continue to smoke for first wk of treatment and then completely stop	Caution with pre-existing psychiatric condition

*Bupropion and varenicline may be used in combination with NRT

Physician Advice for Smoking Cessation
Cochrane DB Syst Rev 2013;5:CD000165
Purpose: To assess the effectiveness of physician advice in promoting smoking cessation, compare minimal physician interventions with more intensive interventions, assess the effectiveness of various aids in smoking cessation, and determine the effect of anti-smoking advice on mortality.
Methods: Systematic review of RCTs of smoking cessation advice from a medical practitioner. Abstinence was assessed ≥6 mo after advice was first provided.
Results: Trials with over 31000 smokers were identified. Most common setting for advice delivery was primary care. A significant increase in quitting rates was noted with advice vs. no advice (RR 1.66, 95% CI 1.42-1.94), which was further increased where the intervention was considered more intensive (RR 1.84, 95% CI 1.60-2.13; n.s.). Intensive advice showed a small, non-significant advantage vs. minimal advice when directly compared (RR 1.37, 95% CI 1.20-1.56). A small benefit with follow-up visits was also noted. No statistically significant difference in mortality at 20 yr follow-up was found.
Conclusion: Simple advice can increase smoking cessation rates by 1-3% on top of the unassisted quit rate. More intensive advice and providing follow-up support may further increase quit rates.

- pregnant patients: counselling is recommended as first line treatment
  - NRT should be made available to pregnant women who are unable to quit using non-pharmacologic methods
  - intermittent NRT use (lozenges, gum) is preferred over continuous dosing of the patch
  - no strong evidence that either major positive or negative outcomes were associated with gestational use of bupropion or varenicline; consider using only if benefits outweigh risks
- unwilling to quit
  - motivational intervention (5 Rs)
    1. Relevance to patient
       - relevance to patient's disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
    2. Risks of smoking
       - short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
       - long-term: MI, stroke, COPD, lung cancer, other cancers
       - environmental: higher risk in spouse/children for lung cancer, SIDS, asthma, respiratory infections
    3. Rewards: (benefits)
       - improved health, save money, food tastes better, good example for children
    4. Roadblocks: (obstacles)
       fear of withdrawal, weight gain, failure, lack of support
    5. Repetition
       - reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)
- recent quitter
  - highest relapse rate within 3 mo of quitting
    - minimal practice: congratulate success, encourage ongoing abstinence, review benefits and risks
    - prescriptive interventions: address problem(s) of weight gain, negative mood, withdrawal, lack of support

Alcohol Use

- see Psychiatry, PS28

Definition
- alcohol use disorder diagnostic categories occur along a continuum

Epidemiology
- 10-15% of patients in family practice misuse alcohol
- 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
- more likely to miss diagnosis in women, elderly, and patients with high socioeconomic status

Assessment
- screen for alcohol dependence with CAGE questionnaire
  - if CAGE is positive, further explore for the possibility of alcohol misuse or dependence
- assess drinking profile
  - setting, time, place, occasion, with whom
  - impact on family, work, social life
  - quantity-frequency history
    - how many drinks per day?
    - how many days per week?
    - maximum number of drinks on any one day in the past month?
- the Alcohol Use Disorders Identification Test (AUDIT) is another useful tool to assess alcohol use, drinking behaviours, and alcohol-related problems
- if identified positive for alcohol use disorder:
  - screen for other drug use
  - identify any medical/psychiatric complications (e.g. delirium tremens or withdrawal seizures)

Standard Drink Equivalents
- One standard drink = 13.64 g of pure alcohol
- Beer/Cider/Cooler (5% alcohol) = 12 oz
- Malt liquor (7% alcohol) = 8-9 oz
- Wine (12-17% alcohol) = 5 oz
- Fortified wine = 3 oz
- Hard liquor (40%) = 1.5 oz

CAGE Questionnaire
Have you ever felt you needed to Cut down on your drinking?
Have people Annoyed you by criticizing your drinking?
Have you ever felt Guilty about drinking?
Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?
Two "yes" responses is considered positive

- ask about drinking and driving
- ask about past recovery attempts and assess current readiness to change

Investigations
- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in persons with alcohol use disorder)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by the liver)

Management
- intervention should be consistent with patient's motivation for change
- individualized counselling and regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-step program
  - outpatient/day programs for those with chronic, resistant alcohol use disorder
  - family treatment (Al-Anon, Alateen, screen for spousal/child abuse)
- refer to specialist or inpatient program if:
  - dangerous or highly unstable home environment
  - severe medical/psychiatric concern
  - addiction to drug that may require in-patient detoxification
  - refractory to other treatment programs
- pharmacologic
  - diazepam for withdrawal
  - disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, N/V, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  - naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
    - may trigger withdrawal in opioid-dependent patients
  - acamprosate: glutamate receptor modulator that also reduces craving
- see Psychiatry, PS29

Some Adverse Medical Consequences of Problem Drinking
GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
Cardiac: HTN, alcoholic cardiomyopathy
Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
Hematologic: anemia, coagulopathies
Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage

Prognosis
- relapse is common and should not be viewed as failure
- monitor regularly for signs of relapse
- 25-30% of persons with alcohol use disorder exhibit spontaneous improvement over 1 yr
- 60-70% of individuals with jobs and families have improved quality of life 1 yr post-treatment

Common Presenting Problems

Abdominal Pain

- see Gastroenterology, G4, General Surgery and Thoracic Surgery, GS4, and Emergency Medicine, ER18

If pain precedes nausea/vomiting, cause of abdominal pain is more likely to require surgery

Epidemiology
- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

Etiology
- most common diagnosis in family medicine at 28% is "nonspecific abdominal pain," which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: DKA, porphyria, hypercalcemia, medications (e.g. NSAIDs), alcohol, toxic ingestion, foreign body, psychogenic

Abdominal Pain Red Flags
- Severe pain
- Signs of shock
- Peritoneal signs
- Abdominal distention
- Pain out of proportion to clinical findings
- New onset pain, change in pain, or altered bowel habits in elderly
- Weight loss
- Blood per rectum/melena
- Anemia
- Supraclavicular lymph nodes
- Family history of serious bowel disease

Pathophysiology
- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain
- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
    - right upper quadrant (RUQ): biliary, hepatic, colonic, pulmonary, renal
    - left upper quadrant (LUQ): cardiac, gastric, pancreatic, renal, vascular
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region
    - right lower quadrant (RLQ): colonic, appendix, gynecological, renal
    - left lower quadrant (LLQ): colonic, gynecological, renal
  - any location: aneurysm, dissection, ischemia, varicella zoster virus, muscle strain, hernia, bowel obstruction, peritonitis, porphyria, DKA

In patients >50, keep a high index of suspicion for AAA – its presentation may mimic renal colic or diverticulitis

Investigations
- guided by findings on history and physical
- possible blood work: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, toxicology screen, β-hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - AXR, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - U/S (renal stones, gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT-scan (AAA, appendicitis), non-contrast helical CT-scan (first choice for renal stones)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - *H. pylori* testing (urea breath test, serology, biopsy)

Allergic Rhinitis

- see Otolaryngology, OT24



Differential Diagnosis
Acute viral infection
Vasomotor rhinitis
Deviated septum
Nasal polyps
Acute/chronic sinusitis
Drug-induced rhinitis



Rhinitis Medicamentosa
Rebound nasal congestion. Occurs with prolonged use (>5-7 d) of vasoconstrictive intranasal medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect

Definition
- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification
  - seasonal
    - symptoms during a specific time of the year
    - common allergens: trees, grass, and weed pollens, airborne moulds
  - perennial
    - symptoms throughout the year with variation in severity
    - common allergens: dust mites, animal dander, moulds
- persistent allergic rhinitis may lead to chronic rhinosinusitis

Epidemiology
- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, eczema, sinusitis, and otitis media

Etiology
- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

Assessment
- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

Management
- conservative
  - minimize exposure to allergens
    - most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral second-generation antihistamines – first-line therapy for mild symptoms
    - e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (expect >1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)
- allergy skin testing
  - for patients with chronic rhinitis whose symptoms are not controlled by conservative and pharmacological therapy
  - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

Amenorrhea

- see Gynecology, GY9
- absence of menses due to dysfunction of the hypothalamus, pituitary, ovaries, uterus, and/or vagina. Classified as either primary (absence of menarche by age 15 or thereafter) or secondary (absence of menses >3 mo in women who previously had regular menstrual cycles)

Anxiety

• see Psychiatry, PS16

Epidemiology

•25-30% of patients in primary care settings have psychiatric disorders
•many are undiagnosed or untreated; hence the need for good screening
•high rate of coexistence of anxiety disorders and depression

Screening

•screening tools such as the GAD-7 tool
• screening questions
  ▪ do you tend to be an anxious or nervous person?
  ▪ have you felt unusually worried about things recently?
  ▪ has this worrying affected your life? How?

Assessment

•identify associated symptoms on history and physical to rule out organic medical causes (e.g. hyperthyroidism, cardiopulmonary disorder, traumatic brain injury)
•risk factors: past history of anxiety, stressful life event, trauma, social isolation, female , LGBTQ2S+, comorbid psychiatric diagnosis (e.g. depression), family history of anxiety or depression
•assess substance misuse, suicidal ideation/self-harm
•to differentiate anxiety disorders, consider symptoms and their duration
•use the GAD-7 tool to assess and monitor levels of anxiety
•ask patients about experiences that may impact current situation and intersectionality

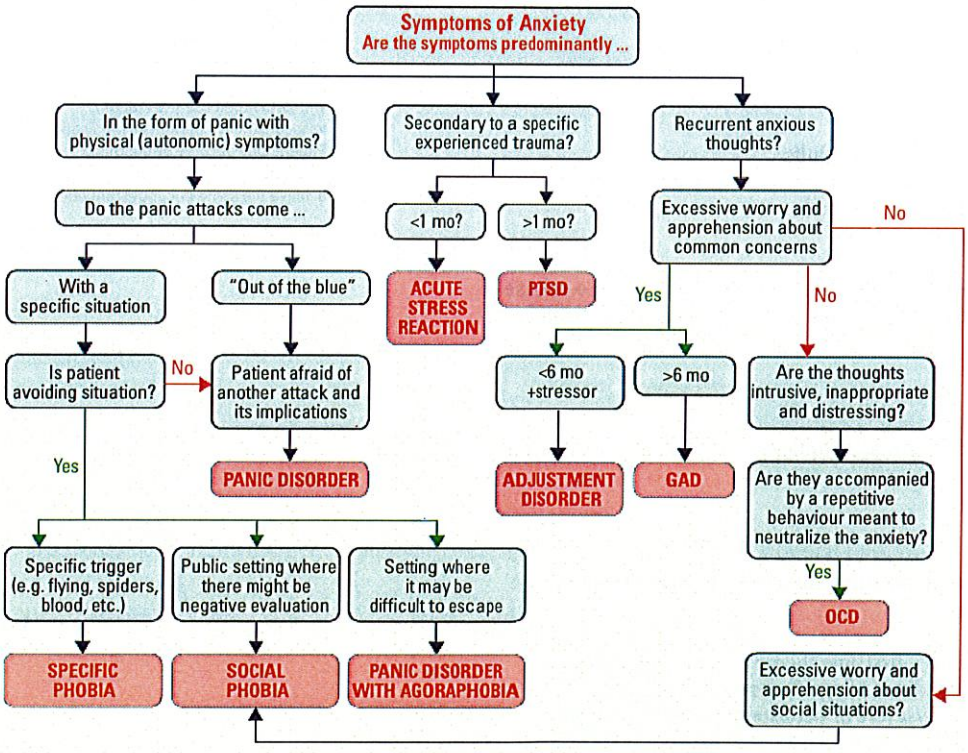


Figure 6. Differentiating anxiety disorders using the DSM-V diagnostic criteria
Adapted from: Evans M, Bradwejn J, Dunn L. Anxiety Review Panel. Guidelines for the treatment of anxiety disorders in primary care. Toronto: Queen's Printer of Ontario, 2000.41

Management

•patient education: emphasize prevalence, good recovery rate of anxiety conditions
•with consent, explore lifestyle habits: exercise, caffeine, alcohol intake, etc. and collaboratively develop a person-centered plan (e.g. reduce caffeine at a particular pace)
•psychological: psychotherapy including CBT, exposure therapy, relaxation techniques, and mindfulness strategies
• pharmacotherapy: see Psychiatry, PS50
•offer self-help materials, connect with community resources (e.g. support groups), and provide support to family and caregivers

Differential Diagnosis of Anxiety Disorders
- Panic disorder
- GAD
- Social anxiety disorder (previously social phobia)
- Agoraphobia
- Specific phobia
- Selective mutism
- Separation anxiety disorder
- Other: general medical condition, AMC, mood disorder, psychotic disorder, OCD, PTSD

Symptoms of GAD

AND I C REST
Anxious, nervous, or worried
No control over the worry
Duration >6 mo
Irritability
Concentration impairment
Restlessness
Energy decreased
Sleep impairment
Tension in muscles
Can Fam Physician 2005;51:1340-42

Rule Out
- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD, avoidant personality disorder)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/ benzodiazepine withdrawal)

Differential Diagnosis of Wheezing
- Allergies, anaphylaxis
- Asthma, reactive airway disease
- GERD
- Infections (bronchitis, pneumonia)
- OSA
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

Self-Management Asthma and COPD Education and Written Action Plan

Education is a key component in management of asthma and COPD

Guided self-management combining education, regular medical review, self-assessment, and written action plans have been shown to reduce hospitalizations, ED visits, and missed days at work or school
Sample action plans available online: https://cts-sct.ca/

Asthma/COPD

- see Respirology, R7

Definition

- asthma
  - chronic, reversible airway inflammation characterized by periodic attacks of wheezing, dyspnea, chest tightness, and coughing
  - airways are hyper-responsive to triggers/antigens leading to acute obstructive symptoms including bronchoconstriction, mucous plugs, and increased inflammation
  - cannot be diagnosed at first presentation
  - PFTs can be done starting at age 6 or when child is able to follow testing instructions
  - peak flow metres are useful in the office and at home for monitoring
- COPD
  - group of chronic, progressive, non-reversible lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms

Table 8. Differentiating COPD from Asthma

	COPD	Asthma
Age of Onset	Usually in 6th decade	Any age (but 50% of cases are diagnosed in children ages <10)
Role of Smoking	>10 pack yr	Not causal, known trigger
Reversibility of Airflow Obstruction	Airflow obstruction is chronic and persistent	Airflow obstruction is episodic and usually reversible with therapy
Evolution	Slow, progressive worsening (with periodic exacerbations)	Stable, episodic, <50% will outgrow
History of Allergy	Infrequent	>50% patients
Precipitators	Environmental irritants (air pollution), cigarette smoking, α-1 antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)	Environmental irritants (dust, pollen), animal fur, cold air, exercise, URTIs, cigarette smoke, use of β-blockers/ASA
Symptoms/Signs	Chronic cough, sputum, and/or dyspnea	Wheeze (hallmark symptom), dyspnea, chest tightness, prolonged expiration, cough which is worse in the cold, at night, and in the early AM
Diffusion Capacity	Decreased (more so in pure emphysema)	Normal (for pure asthma)
Hypoxemia	Chronic in advanced stages	Not usually present Episodic with severe attacks
Spirometry	May have improvement with bronchodilators but not universally seen	Marked improvement with bronchodilators or steroids
Chest X-Ray	Often normal Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae	Often normal or episodic hyperinflation Hyperinflation during asthma attack
Management	**All: Smoking Cessation** **Mild** Step 1: SABA as needed (salbutamol) Step 2: SABA as needed + LAAC (i.e. tiotropium) or + LABA (e.g. salmeterol) **Moderate** Step 3: SABA/SAMA + LABA or SABA + LABA or LAAC; consider inhaled vs. oral steroids **Severe** Step 4: Pneumococcal vaccination, annual influenza immunization	Ongoing patient education, and environmental control SABA taken PRN as rescue medication + maintenance meds Maintenance medications **Mild** Step 1: Low-dose ICS Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LTRA modifier **Moderate** Step 3: Medium/high-dose ICS + either LABA, LT modifier **Severe** Step 4: As above + immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization

ICS = inhaled corticosteroids; LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist, SAMA = short acting muscarinic antagonist

Signs of Poorly Controlled Asthma

β2-agonist use >4x/wk
Asthma-related absence from work/school
Exercise-induced asthma
Night-time symptoms >1x/wk

What Colour is Your Inhaler?

Name	Body/Cap Colour
β2-Agonists	
salbutamol – Ventolin®	Light blue/navy
salmeterol – Serevent®	Teal/light teal
terbutaline – Bricanyl®	Blue/white
ICS	
fluticasone – Flovent®	Orange/peach
budesonide – Pulmicort®	White/brown
Combined Long-Acting β2-Agonist + ICS	
fluticasone/salmeterol – Advair®	Purple discus
budesonide/formoterol–Symbicort®	Red/white
fluticasone/ vilanterol– Breo®	Grey/blue
Anticholinergics	
umeclidinium - Incruse®	White/green
ipratropium – Atrovent®	Clear/green
tiotropium – Spiriva®	White/turquoise

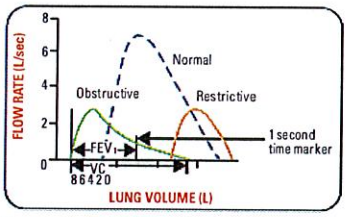


Figure 7. Expiratory flow volume curves (obstructive, normal, and restrictive disease) See Respirology, R4
Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. With permission from Elsevier. ©2008

More About Inhalers

- Aerosols (puffers = MDI, MDI + spacer) MDIs should be used with spacers to:
- Reduce side effects
- Improve amount inhaled
- Increase efficiency of use
- DPI (discuss, turbuhaler, and diskhaler) require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist: recommended for use if contraindications to MDIs
- Currently there is large push in clinical practice to transition away from the use of MDI and to move towards using DPI to reduce the impact of aerosol treatments on the environment - Evohaler MDIs had 20–30 times larger carbon footprints than the Accuhaler and Elipta DPIs (Thorax 2020 Jan;75(1):82-84.)

When prescribing salbutamol, watch out for signs of **hypokalemia**: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, N/V, polyuria

Benign Prostatic Hyperplasia

• see Urology, U7

Definition
•hyperplasia of the stroma and epithelium in the periurethral transition zone

History and Physical
•include current/past health, surgeries, trauma, current medications including OTC
•specific urinary symptoms
•physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth, and rubbery in BPH)

Investigations
•urinalysis to exclude UTI and for microscopic hematuria (common sign)
•serum PSA: protein produced by prostatic tissue
- PSA to screen/test for BPH is no longer used due to the high false positive rate, and is instead used as a marker to guide treatment once diagnosis has been made
- PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
- increased PSA in a younger man is more often due to cancer than other causes
- abnormal DRE or PSA should trigger further assessment
- discuss test with men at increased risk of prostate cancer (FMHx, Black men) or who are concerned about development of prostate cancer
- decision to test PSA in an asymptomatic man (see *Prostate Cancer Screening, FM6*)

• other tests
- Cr, BUN, PVR volume by U/S, urodynamic studies, renal U/S, patient voiding diary

•tests NOT recommended as part of routine initial evaluation include:
- cystoscopy, cytology, prostate U/S or biopsy, IVP, urodynamic studies

Table 9. Symptoms and Complications of BPH

Obstructive Symptoms	Irritative Symptoms	Late Complications
Hesitancy (difficulty starting urine flow)	Urgency	Hydronephrosis
Diminution in size and force of urinary stream	Frequency	Loss of renal concentrating ability
Stream interruption (double voiding)	Nocturia	Systemic acidosis
Urinary retention (bladder does not feel completely empty)	Urge incontinence	Renal failure
Post-void dribbling	Dysuria	
Overflow incontinence		
Nocturia		

Management
• referral to urologist if moderate/severe symptoms
• conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
- fluid restriction (avoid alcohol and caffeine)
- avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
- pelvic floor/Kegel exercises; consider referral to pelvic physiotherapist
- bladder retraining (scheduled voiding)

• pharmacological: for moderate/severe symptoms
- α-receptor antagonists (e.g. terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), alfuzosin (Xatral®))
  - relax smooth muscle around the prostate and bladder neck
- 5-α reductase inhibitors (e.g. finasteride (Proscar®))
  - only for patients with demonstrated prostatic enlargement due to BPH
  - inhibit the enzyme responsible for conversion of testosterone to dihydrotestosterone thus reducing growth of prostate
- antimuscarinic and β-3 agonists
  - recommended for storage symptoms, but avoid in patients with bladder outlet obstruction and/or elevated PVR
- long-acting phosphodiesterase inhibitor
  - recommended in patients with erectile dysfunction
- desmopressin
  - recommended for nocturia as a result of nocturnal polyuria (watch for hyponatremia in older adults)

• surgical
- TURP , TUIP (for prostate <30 g)
- absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
- complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

Bronchitis (Acute)

Definition
- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

Epidemiology
- 5th most common diagnosis in family medicine, and most common is URTI

Etiology
- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, and RSV
- 20% bacterial: *M. pneumoniae, C. pneumoniae,* and *S. pneumoniae*

Investigations
- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not useful
- CXR if suspecting pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or HF
- PFT with methacholine challenge if suspecting asthma

Management
- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics, and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (see *Antimicrobial Quick Reference, FM54*)
  - antibiotics in children show no benefit

Differential Diagnosis of Bronchitis
- URTI
- Asthma
- Acute exacerbation of chronic bronchitis
- Sinusitis
- Pneumonia
- Bronchiolitis
- Pertussis
- Environmental/occupational exposures
- Post-nasal drip
- Others: GERD, CHF, cancer, aspiration syndromes, CF, foreign body

How to Tell if Viral or Bacterial?
Bacterial infections tend to give a higher fever, excessive amounts of purulent sputum production, and may be associated with concomitant COPD

Chest Pain

- see Cardiology and Cardiac Surgery, C5 and Emergency Medicine, ER21

Differential Diagnosis

Table 10. Differential Diagnosis of Chest Pain

Diagnosis	Clinical Findings	LR+	LR−
Acute MI	Chest pain radiates to both arms	7.1	0.67
	Third heart sound on auscultation	3.2	0.88
	Hypotension	3.1	0.96
Chest Wall Pain	>2 of: localized muscle tension, stinging pain, pain reproducible by palpation, absence of cough	3.0	0.47
GERD	Burning retrosternal pain, acid regurgitation, sour or bitter taste in the mouth; 1 wk trial of high-dose proton pump inhibitor relieves symptoms	3.1	0.30
Panic Disorder/Anxiety State	Single question: In the past 4 wk, have you had an anxiety attack (suddenly feeling fear or panic)?	4.2	0.09
Pericarditis	Clinical triad of pleuritic chest pain (increases with inspiration or when reclining, and is lessened by leaning forward), pericardial friction rub, and electrocardiographic changes (diffuse ST segment elevation and PR interval depression without T wave inversion)	N/A	N/A
Pneumonia	Egophony	8.6	0.96
	Dullness to percussion	4.3	0.79
	Fever	2.1	0.71
	Clinical impression	2.0	0.24
Heart Failure	Pulmonary edema on chest radiography	11.0	0.48
	Clinical impression	9.9	0.65
	History of heart failure	5.8	0.45
	History of acute myocardial infarction	3.1	0.69
Pulmonary Embolism	High pretest probability based on Wells criteria	6.8	1.8
	Moderate pretest probability based on Wells criteria	1.3	0.7
	Low pretest probability based on Wells criteria	0.1	7.6
Acute Thoracic Aortic Dissection	Acute chest or back pain and a pulse differential in the upper extremities	5.3	N/A

Adapted from: McConaghy J, Rupal S. Outpatient diagnosis of acute chest pain in adults. Am Fam Physician. 2013 Feb 1; 87(3): 177.182

Risk Factors for CAD
- Major
- Smoking
- Diabetes
- HTN
- Hyperlipidemia
- Family history of early CAD in first degree relative (males <55 yr, females <65 yr)
- Untreated OSA
- CKD

Minor
- Obesity
- Sedentary lifestyle
- Age

Red Flags
- Severe pain
- Pain for >20 min
- New onset pain at rest
- Severe SOB
- Loss of consciousness
- Hypotension
- Tachycardia
- Bradycardia
- Cyanosis

MI in Elderly Women
Elderly women can often present with dizziness, back pain, lightheadedness, or weakness in the absence of chest pain

MI in Diabetics
May present with dyspnea, syncope, and fatigue in the absence of chest pain

Investigations
- ECG, CXR, and others if indicated (cardiac enzymes, d-dimer, LFTs, etc.)
- refer to ED if suspecting serious etiology (e.g. aortic dissection, MI)

Management of Common Causes of Chest Pain
- angina/ischemic heart disease
  - NTG: wait 5 min between sprays and if no effect after 3 sprays, send to ED
- MI
  - ASA (160-325 mg, chewed STAT), clopidogrel (Plavix®) or ticagrelor (Brilinta®), LMWH (enoxaparin), morphine, oxygen, NTG
  - ± reperfusion therapy with fibrinolytics (e.g. tissue plasminogen activator (tPA), reteplase (rPA), tenecteplase (TNK), or streptokinase (SK)) if within 12 h (ideally <30 min) or time from first medical contact to percutaneous intervention (catheter lab) if <30 min
  - start β-blocker (e.g. metoprolol starting dose 25 mg PO q6h or BID, titrating to HR goal of 55-60 bpm)
- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
- GERD: antacids, H2-blockers, PPIs, patient education
- costochondritis: NSAIDs

Ruling Out CAD in Primary Care
CMAJ 2010;182(12):1295-1300
Components of the prediction rule used to determine the presence or absence of CAD in patients with chest pain in primary care:
- Age/sex (female ≥65, male ≥55): 1 pt
- Known clinical vascular disease (coronary artery disease, occlusive vascular disease, or cerebrovascular disease): 1 pt
- Pain worse during exercise: 1 pt
- Pain not reproducible by palpation: 1 pt
- Patient assumes pain is of cardiac origin: 1 pt

Positive result: 3-5 pts; negative result: ≤2 pts (sensitivity: 87.1%, specificity: 80%)

Common Cold (Acute Rhinitis)

- see Infectious Diseases, *Pneumonia*, ID7 and *Influenza*, ID9

Definition
- viral URTI with inflammation

Epidemiology
- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

Risk Factors
- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

Clinical Features
- symptoms
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs
  - erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
- complications
  - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  - asthma/COPD exacerbation

Differential Diagnosis
- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

Management
- patient education
  - symptoms peak at 1-3 d and usually subside within 1 wk
  - cough may persist for days to weeks after other symptoms disappear
  - no antibiotics indicated because of viral etiology
  - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
- prevention
  - frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant
  - yearly influenza vaccination
- symptomatic relief
  - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  - analgesics and antipyretics: acetaminophen, ibuprofen
  - cough suppression: dextromethorphan or codeine if necessary (age <6 should not use any cough/cold medications)
  - decongestants, antihistamines
- patients with asthma will require increased use of bronchodilators and inhaled steroids

Influenza vs. Colds: A Guide to Symptoms

Features	Flu	Cold
Onset of illness	Sudden	Slow
Fever	High fever	None
Exhaustion level	Severe	Mild
Cough	Dry severe or hacking	±
Throat	Fine	Sore
Nose	Dry and clear	Runny
Head	Achy	Headache-free
Appetite	Decreased	Normal
Muscles	Achy	Fine
Chills	Yes	No

Echinacea for Preventing and Treating the Common Cold
Cochrane DB Syst Rev 2014;2:CD000530
Purpose: To assess whether echinacea preparations are effective and safe for the prevention and treatment of the common cold.
Methods: Meta-analysis of RCTs comparing mono-preparations of echinacea with placebo. Primary efficacy outcome was number of individuals with at least one cold in prevention trials and duration of colds in treatment trials. Primary safety and acceptability outcome was the number of participants dropping out due to adverse events.
Results: Twenty-four double-blind trials with 4631 participants were included. No prevention study comparisons comparing echinacea and placebo found a statistically significant difference in terms of number of patients with at least one cold episode, though a relative risk reduction of 10% to 20% was identified. Of treatment trials reporting on duration of colds, only 1 study of 7 showed a significant effect favouring echinacea over placebo. No significant differences were found between echinacea and placebo groups in number of dropouts due to adverse events, though prevention trials showed a trend towards higher dropout numbers due to adverse events in treatment groups.
Conclusions: Echinacea products have not been shown to provide benefits for treating colds, although it is possible there is a weak benefit from some echinacea products. Individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance.

Concussion/Mild Traumatic Brain Injury

- see Neurosurgery, NS36 and Emergency Medicine, ER7
- a useful tool for the assessment of individuals and athletes with concussion is the Sport Concussion Assessment Tool, 5th edition (SCAT5), Br J Sports Med 2017;0:1-8
- Parachute Canada concussion guidelines including return to play/return to sports: https://parachute.ca/en/injury-topic/concussion/

Contraception

- see Gynecology, GY15

Emergency Contraception

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital copper IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- copper IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC

Cough

History and Physical

- duration (chronic ≥8 wk), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis, reflux, post-nasal drip
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, environmental allergies, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACEI, β-blockers), allergies
- PMHx: lung (asthma, COPD, CF), heart (HF, MI, arrhythmias), chronic illness, GI (reflux)
- vitals including O_2 saturation, respiratory exam, HEENT, and precordial exam

Investigations

- guided by findings on history and physical
  - CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

Differential Diagnosis

Common Causes

Upper airway cough syndrome (post-nasal drip)
Asthma/COPD
GERD
Non-asthmatic eosinophilic bronchitis

Other Causes

- ACEI
- Aspiration
- Bronchiectasis
- Cystic fibrosis
- Chronic interstitial lung disease
- CHF
- Lung/laryngeal cancer
- Pertussis
- Psychogenic
- Restrictive lung disease
- TB, atypical mycobacterium, and other chronic lung infections

Dementia (Major Neurocognitive Disorder)

- see Psychiatry, PS24

Epidemiology

- 15% of Canadians ≥65 yr are living with dementia; risk for dementia doubles every 5 yr after age 65
- prevalence of depression in dementia is 20-60%; major depression decreases as dementia severity increases; vascular and mixed dementias have a higher prevalence of depression
- leading types of dementia: Alzheimer's (40-50%), mixed (20-25%), Lewy-Body (5-15%), vascular (5-10%), frontotemporal (5-10%)

Investigations

- history, physical exam, MMSE, MOCA (best screening test), Dementia Quick Screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B12, folate, VDRL, HIV, head CT

Management

- treat and prevent reversible causes
- provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
- family education, counselling, and supports (alternative levels of care)
- pharmacologic therapy: N-methyl-d-aspartate receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose antipsychotics and antidepressants can be used to treat behavioural and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia

Dementia Quick Screen = Mini Cog + Animal Naming

- 3 simple tests, takes about 2 min
- Use when suspecting mild cognitive impairment or when patient is at high-risk
- Mini Cog = 3 words recalled + clock drawing
  - Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing or only minor spacing problems)
  - 0 word recall = impairment
  - 1-2 words and clock drawing abnormal = impairment
  - 3 words recalled = normal
  - Naming animals in 1 min (normal = >15 in 1 min)
- Interpretation: If all 3 results within normal range, cognitive impairment unlikely
- Return for further evaluation if:
  - <15 animals named
  - 0-1 words recalled
  - Clock drawing abnormal

Depression

• see Psychiatry, PS12

Etiology

- often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain); can be associated with triggers (e.g. major life events)
- depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of patients may not receive appropriate treatment for their depression
- early diagnosis and treatment improve outcomes

Screening Questions

- Canadian Task Force on Preventive Health Care (2013) recommends not routinely screening for depression
- if screening indicated, use the PHQ-2
  - "Over the past 2 wk, how often have you been bothered by any of the following problems":
    - little interest or pleasure in doing things?
    - feeling down, depressed, or hopeless?
- the PHQ-2 is scored out of 6, with a score of 3 or more considered positive
  - those who screen positive should be evaluated with the PHQ-9 to determine whether they meet criteria for depression
- PHQ-9 tool is useful to diagnose and monitor depression; use GDS for the geriatric population
- screen all patients presenting with depression for suicidal ideation and behaviour, a positive screen should prompt additional questioning

Assessment

- risk factors: see Psychiatry, PS12
- personal or family history of depression
- medications and potential substance misuse concerns
- high-risk for suicide/homicide
  - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against their will for psychiatric assessment (up to 72 h)
- functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including at least one of anhedonia or depressed mood ≥2 wk for actual diagnosis to be met (see Memory Aid)
- validated depression rating scales: Beck's Depression Inventory, Zung's self-rating depression scale, Children's Depression Inventory, GDS, PHQ-9
- routine medical workup (physical exam, CBC, TSH, ferritin, folate, B12, electrolytes, urinalysis, glucose, etc.)

Treatment

- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
  - acute phase (8-12 wk): relieve symptoms and improve quality of life, counsel patients on risks (e.g. sexual side effects, discontinuation syndrome)
  - maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
- treatment options are pharmacotherapy, psychotherapy, or a combination of both
  - combination therapy is synergistic and most effective (see EBM in sidebar)
- treatment of youth (ages 10-21)
  - for mild depression, a period of active support and monitoring before initiating treatment is recommended
  - fluoxetine is first line among SSRIs (most evidence)
    - monitor closely for adverse effects such as suicidal ideation and behaviour
  - psychotherapy
    - CBT or IPT alone can be used for mild depression
    - psychotherapy plus medication is recommended for moderate to severe depression
  - treatment should continue for at least 6 mo
    - ongoing management should include assessment in key domains (school, home, social setting)
    - reassessment and referral is recommended if there is no improvement after 6-8 wk of treatment
    - consider referral for adolescents with moderate/severe depression and coexisting psychosis and/or substance misuse



Must Ask About/Rule Out

- Suicidal/homicidal ideation
- Psychosis
- Substance use/misuse/withdrawal
- Anxiety
- Bipolar/manic/hypomanic episodes
- Bereavement
- Intimate partner violence
- Postpartum depression
- Organic cause



Differential Diagnosis

- Other psychiatric disorders (e.g. anxiety, personality, bipolar, adjustment disorder, schizoaffective, seasonal affective disorder, substance misuse/withdrawal)
- Cancer (50% of patients with tumours, especially of brain, lung, and pancreas, develop symptoms of depression before the diagnosis of cancer is made)
- Chronic fatigue syndrome
- Early dementia
- Endocrine (e.g. hyper/hypothyroidism, DM, adrenal disorders)
- Infections (mononucleosis)
- Liver failure, renal failure
- Medication side effects (β-blockers, benzodiazepines, glucocorticoids, interferon)
- Menopause
- Neurological (Parkinson's disease, MS)
- Vitamin deficiency (pernicious anemia, pellagra)



Combined Pharmacotherapy and Psychological Treatment for Depression: A Systematic Review
Arch Gen Psychiatry 2004;61:714-719

Purpose: To examine the relationship between adherence and efficacy of antidepressant medications plus psychological treatment vs. medications alone in the management of depressive disorders.

Methods: Systematic review of RCTs comparing antidepressant medications alone vs. combination therapy with psychological intervention included. Efficacy and adherence to therapy were the main outcomes.

Results: Sixteen trials with 1842 patients were included. Patients receiving combination therapy showed significantly greater improvements than those receiving medications alone (OR 1.86, 95% CI 1.38-2.52); dropout and non-responder proportions did not differ in distribution between the two groups (OR 0.86, 0.60-1.24). A significant advantage with combination therapy was noted in studies with follow-up longer than 12 wk (OR 2.21, 1.22-4.03), accompanied by significant reduction in dropout and non-responder proportions.

Conclusion: Combination therapy with psychological treatment and medication is associated with greater improvement rates than medication alone, and may decrease dropout rates with longer therapies.

Table 11. Common Medications

Class	Examples	Action	Side Effects	Notes
SSRI	paroxetine (Paxil®) fluoxetine (Prozac®) sertraline (Zoloft®) citalopram (Celexa®) fluvoxamine (Luvox®) escitalopram (Cipralex®) vortioxetine (Trintellix®)	Block serotonin reuptake	Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested)	First line therapy for youth is fluoxetine; paroxetine is not recommended for youth (controversial)
SNRI	venlafaxine (Effexor®) duloxetine (Cymbalta®) desvenlafaxine (Pristiq®)	Block serotonin and NE reuptake	Insomnia, tremors, tachycardia, sweating	
SDRI	bupropion (Wellbutrin®)	Block dopamine and NE reuptake	Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs	Often chosen for lack of sexual side effects, can be used for augmentation of antidepressant effects with other classes of medication
TCA	amitriptyline (Elavil®)	Block serotonin and NE reuptake	Sexual dysfunction, weight gain, tremors, tachycardia, sweating	Narrow therapeutic window, lethal in overdose

Criteria for Depression
(≥5/9 with at least one of anhedonia or depressed mood for ≥2 wk)

M-SIGECAPS
M Depressed Mood
S Increased/decreased Sleep
I Decreased Interest
G Guilt
E Decreased Energy
C Decreased Concentration
A Increased/decreased Appetite and weight
P Psychomotor agitation/retardation
S Suicidal ideation

Prognosis
- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode, 70% after 2 episodes, 90% after 3 episodes

Diabetes Mellitus

- see Endocrinology, E7
- see 2018 Clinical Practice Guidelines from Diabetes Canada, available from: http://guidelines.diabetes.ca/cpg
- see 2022 Special Article: Remission of Type 2 Diabetes from Diabetes Canada, available from: http://guidelines.diabetes.ca/cpg
- see Diabetes Mellitus Patient Care Flow Sheet from Canadian Diabetes Association, available from: https://guidelines.diabetes.ca/docs/cpg/Appendix-3.pdf

DM Related Symptoms
Hyperglycemia: polyphagia, polydipsia, polyuria, weight change, blurry vision, yeast infections
Diabetic Ketoacidosis (DKA): fruity breath, anorexia, N/V, fatigue, abdominal pain, Kussmaul breathing, dehydration
Hypoglycemia: hunger, anxiety, tremors, palpitations, sweating, headache, fatigue, confusion, seizures, coma

Definition
- metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both

Classification and Diagnosis
- see Endocrinology, E8

Epidemiology
- major health concern, affecting up to 10% of Canadians
- incidence of T2DM is rising due to increasing obesity, sedentary lifestyle, and age of the population
- leading cause of new-onset blindness and renal dysfunction
- Canadian adults with DM are twice as likely to die prematurely compared to persons without DM
- 1 in 5 Indigenous people in Canada has diabetes

Long-Term Complications of DM
Microvascular: nephropathy, retinopathy, neuropathy
- **Macrovascular:** CAD, CVD, PVD

Risk Factors
- T1DM
  - personal or family history of autoimmune disease
- T2DM
  - first degree relative with DM
  - ages ≥40 yr
  - obesity (especially abdominal), HTN, hyperlipidemia, CAD, vascular disease
  - prior gestational diabetes mellitus, macrosomic baby (>4 kg)
  - PCOS
  - history of IGT or IFG
  - presence of complications associated with DM
  - presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  - medications: glucocorticoids, atypical antipsychotics, HAART
- both
  - member of a high-risk population (e.g. Indigenous peoples, Hispanic, Asian, or African descent)

Screening
- T2DM
  - FBG or HbA1c in everyone ≥40 q3 yr, or at high-risk using the CANRISK calculator
  - more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
- gestational diabetes mellitus (see Obstetrics, OB28)
  - all pregnant women between 24-28 wk gestation

A1C Interpretation
- advantages:
  - convenient (measure any time of day)
  - single sample

- predicts microvascular complications
- better predictor of CVD than FBG or two hour plasma glucose in a 75g OGTT
- slow day-to-day variability
- reflects long-term glucose concentration

• disadvantages:
- cost
- misleading in various medical conditions (e.g. hemoglobinopathies, iron deficiency, hemolytic anemia, severe hepatic or renal disease)
- altered by ethnicity and aging
- standardized, validated assay required
- not for diagnostic use in children and adolescents (as the sole diagnostic test), pregnant women as part of routine screening for gestational diabetes, those with CF, or those with suspected T1DM

Goals of Therapy

• see Endocrinology, E9 and Clinical Pearl (SMART Goals)

Assessment and Monitoring

Table 12. Assessment and Monitoring

	Initial Assessment	q2-4mo	Annually
History	Symptoms of hyperglycemia, ketoacidosis, hypoglycemia Past medical history Functional inquiry Family history Risk factors Medications Sexual function Lifestyle	DM-directed history Screen for awareness and frequency of hypoglycemia and DKA Glucose monitoring Use of insulin and oral agents Smoking cessation	DM-directed history Screen for awareness and frequency of hypoglycemia and DKA Glucose monitoring Use of insulin and oral agents Sexual function Lifestyle counselling Screen for depression
Physical Exam	General: height, weight, BMI, BP, WC Head and neck: fundoscopy, thyroid exam Cardiovascular exam: signs of PVD, pulses, bruits Abdominal exam (e.g. for organomegaly) Hand/foot/skin exam Neurological exam	Wt, BP, BMI, WC	Foot exam for sensation (using a 10 g monofilament), ulcers or infection Remainder of exam as per PHE
Investigations	FBG, HbA1c, fasting lipids, Cr, urine ACR Baseline ECG; repeat testing q2 yr for those at high-risk	HbA1c q3 mo FBG as needed	Fasting lipid profile Annual random urine ACR and Cr
Management	Nutritional and physical education Consider referral to DM education program if available Monitoring blood glucose: explain methods and frequency Medication counselling: oral hypoglycemic agents and/or insulin, method of administration, dosage adjustments Pneumococcal vaccination Ophthalmology consult (T1DM within 5 yr T2DM at diagnosis)	Assess progress towards long-term complications Adjust treatment plan if necessary	Calibrate home glucose monitor Arrange annual retinopathy screening Influenza vaccination annually

Nonpharmacologic Management

• diet
- can reduce HbA1c by 1-2%
- moderate weight loss (5%) improves glycemic control and CVD risk factors
- all diabetics should see a registered dietician for nutrition counselling
- decrease combined saturated fats and trans fatty acids to <10% of calories
- avoid simple sugars, choose low glycemic index foods, ensure regularity in timing and spacing of meals

• physical activity and exercise
- at least 150 min of aerobic exercise plus 2 sessions of resistance training per wk is recommended
- encourage 30-45 min of moderate exercise 4-7 d/wk
- promote cardiovascular fitness: increases insulin sensitivity, lowers BP, and improves lipid profile
- if using insulin, may require alterations of diet, insulin regimen, injection sites, and self-monitoring

Self-Monitoring of Blood Glucose

• T1DM: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
• T2DM: recommendations vary based on treatment regimen (e.g. insulin dependent requires more frequent monitoring – refer to 2020 Diabetes Canada Clinical Practice Guidelines)
• if FBG >14 mmol/L, perform ketone testing to rule out DKA
• if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia

Remission of T2DM

• defined as achieving prediabetes or normal HbA1C levels without any antihyperglycemic medications for a minimum of 3 mo
• may be considered for individuals with:
- early T2DM who are overweight or obese



SMART
Diabetes Quick Reference Guide

A A1C: Optimal Glycemic Control (Usually <7%)
B BP: Optimal Blood Pressure Control (≤130/80)
C Cholesterol: LDL-C <2 mmol/L if treating
D Drugs: Consider ACEI/ARB, Statin, and ASA
E Exercise/Eating
S Smoking Cessation



Calculate Total Insulin Required
T1DM: 0.5-0.7 units/kg/d
T2DM: 0.3 units/kg/d
More information on insulin prescription, available at:
1) https://guidelines.diabetes.ca/CDACPG/media/documents/hcp-resources/Insulin_Prescription_Fillable_EN_02_21.pdf
2) https://guidelines.diabetes.ca/docs/resources/in-hospital-management-clinical-order-set-fillable.pdf



Rosiglitazone Revisited: An Updated VertiMeta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality
Arch Intern Med 2010;170:1191-1201
Purpose: To evaluate the effectiveness of rosiglitazone on MIs and mortality.
Methods: Systematic review of RCTs of rosiglitazone, lasting at least 24 wk in duration, and reporting CV adverse events. Main outcomes were MIs, CV-related mortality, and all-cause mortality.
Results: Rosiglitazone significantly increased MI risk (OR 1.28, 95% CI 1.02-1.63, P=0.04) but not CV mortality (OR 1.03, 0.78-1.36, P=0.86).
Conclusion: Rosiglitazone continues to demonstrate increased risk of MIs, though it is not associated with increased risk of CV or all-cause mortality.



Differential Diagnosis of Vertigo

	BPPV	Labyrinthitis	Menière's	Acoustic Neuroma
Onset	Sudden	Sudden	Gradual	Insidious
Duration	Seconds	Days	Min-h	Chronic
Hearing Loss	–	+	+	+
Tinnitus	–	+	+	+
Neuro Symptoms	–	–	–	+

- motivation and ability to pursue weight loss to de-escalate and/or eliminate use of antihyperglycemic agents
- no significant eating or mental health disorders, atherosclerotic CVD, CHF and/or CKD

• sustained weight loss of ≥15 kg of initial body weight is associated with the greatest probability of T2DM remission

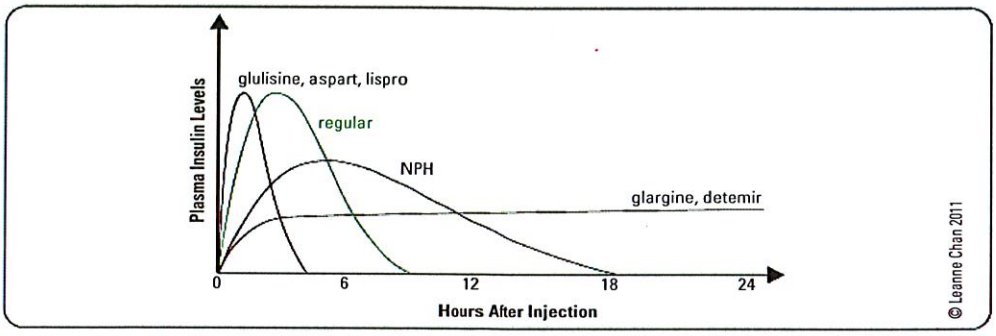
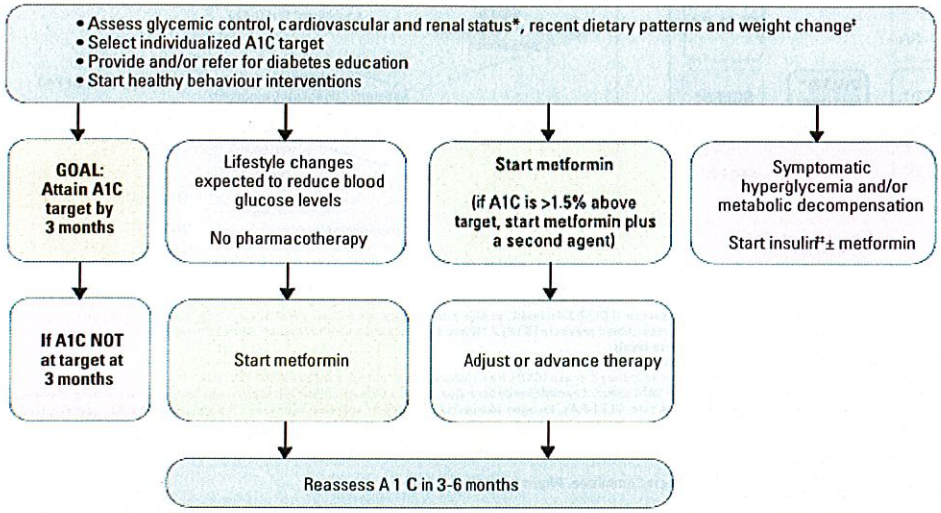


Figure 8. Types of insulin preparation



* In individuals with atherosclerotic cardiovascular disease, history of heart failure (with reduced ejection fraction) or chronickidney disease, agents with cardiorenal benefits (Figures 2A and 2B) may be considered
‡ Unintentional weight loss should prompt consideration of other diagnoses (e.g. type 1 diabetes or pancreatic disease)
‡‡ Reassess need for ongoing insulin therapy once type of diabetes is established and response to health behaviour interventions is assessed.
A1C, glycated hemoglobin; CPG, clinical practice guidelines

Figure 9. Management of hyperglycemia at diagnosis of T2DM
With permission from: Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2018;42(Suppl 1):S1-S325.

Pharmacologic Agents (T2DM)

• oral
- biguanides: metformin (Glucophage®)
- thiazolidinediones: pioglitazone (Actos®), rosiglitazone (Avandia®)
- α-glucosidase inhibitors: acarbose (Precose®)
- non-sulfonylurea insulin secretagogues: repaglinide (Gluconorm®)
- sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicron®)
- DPP-4 inhibitors: sitagliptin (Januvia®), linagliptin (Trajenta®)
- SGLT2 inhibitors: canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®)

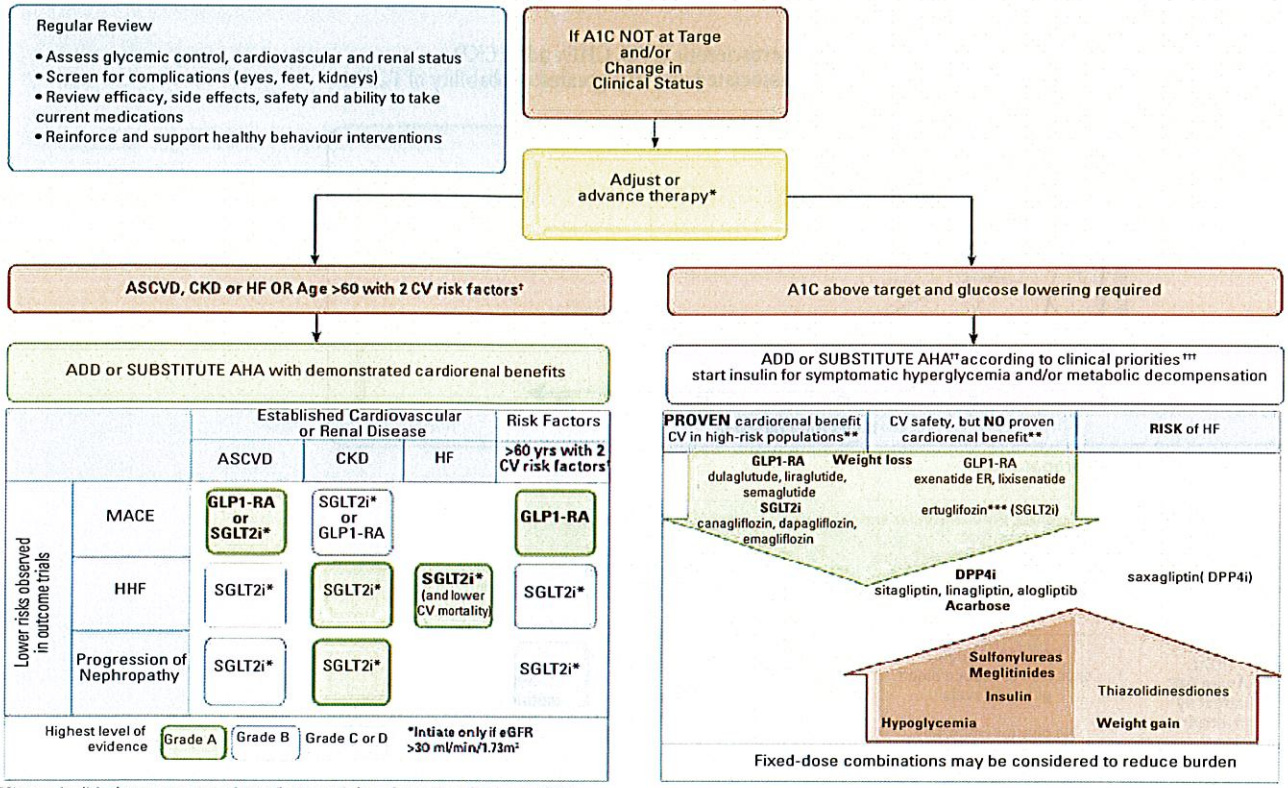
• injectable
- GLP-1 analogues: liraglutide (Victoza®), semaglutide (Ozempic®)

Other Medications Used in DM

•ACEI or ARB in those with any of:
- clinical macrovascular disease
- age ≥55
- age <55 and microvascular complications

•statin in those with any of:
- clinical macrovascular disease
- age ≥40
- age <40 and any of the following:
  - diabetes duration >15 yr and ages >30 yr
  - microvascular complications
  - other cardiovascular risk factors

•low dose ASA (81-325 mg)
- for secondary prevention in people with established CVD (NOT to be used routinely for primary prevention)



*Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing.
†Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides ≥2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥95 mm Hg).
††All antihyperglycemic agents (AHAs) have Grade A evidence for effectiveness to reduce blood glucose levels.
†††Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy.
** In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk.
*** VERTIS (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing.
A1C,g lycated hemoglobin; DPP4i,d ipeptidyl peptidase-4 inhibitors; eGFRe, stimated glomerular filtration rate; GLP1-RAg, lucagon-like peptide-1 receptor agonists; exenatideE R,e xenatide extended-release; HHF, hospitalization for heart failure; SGLT2/s, odium-glucose cotransporter 2 inhibitors; yrs, years.

Figure 10. Reviewing, adjusting, or advancing therapy in T2DM
Reproduced with permission from Diabetes Canada. Diabetes Canada Clinical Practice Guidelines Expert Committee. Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update. Can J Diabetes. 2020 Oct 1;44(7):575-91.

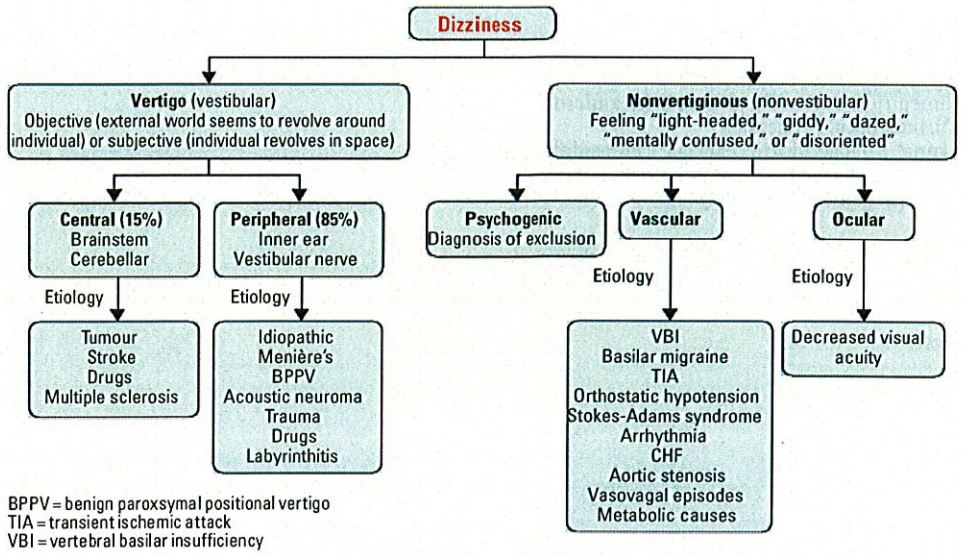
Dizziness

• see Otolaryngology, OT6

Epidemiology

•70% of affected patients see general practitioners initially, 4% are referred to specialists
•frequency is proportional to age; commonest concern of ambulatory patients age >75

Differential Diagnosis



BPPV = benign paroxsymal positional vertigo
TIA = transient ischemic attack
VBI = vertebral basilar insufficiency

Figure 11. Differential diagnosis of dizziness

History
- clarify type of dizziness: vertigo, pre-syncope, disequilibrium, lightheadedness
- duration
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (non-vestibular)
  - worse with exercise (cardiac/pulmonary causes)
- associated symptoms
  - neurologic (central)
    - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
  - audiologic (peripheral)
    - hearing loss, tinnitus, otalgia, aural fullness
  - others
    - N/V (peripheral vestibular disorders)
    - breathlessness, palpitations (hyperventilation, cardiac problem)
- general medical history
  - HTN, DM, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol
  - depression/anxiety: can present with light-headedness

Physical Exam/Investigations
- syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - blood work, ECG, 24 h Holter, treadmill stress test, loop ECG, tilt table testing, carotid and/or vertebral doppler, and EEG
- vertiginous
  - ENT and neurologic exams (head impulse, nystagmus, test of skew, HINTS exam)
  - Dix-Hallpike, consider audiometry, and MRI if indicated
- non-syncopal, non-vertiginous
  - assess gait, vision, and test for neuropathy
  - cardiac and neurologic exams (cerebellar and cranial nerve function)
  - 3 min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG
  - Romberg test: test for disequilibrium due to impaired proprioception

Treatment
- guided by history, physical exam, and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley or Dr. Carol Foster's technique for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy, and surgery
- refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or if atypical presentation



Dix-Hallpike Test

Have the patient seated with legs extended and head at 45° rotation

Rapidly shift patient to supine position with head fully supported in slight extension (for 45 s)

Observe for rotatory nystagmus and ask about sensation of vertigo

Domestic Violence/Elder Abuse/Child Abuse

INTIMATE PARTNER VIOLENCE

Definition
- includes physical, sexual, emotional, psychological, and financial abuse

Epidemiology
- lifetime prevalence of intimate partner violence against women is between 25-30%
- similar prevalence of intimate partner violence against men, who may be less likely to report due to social stigma
- women who experience abuse have increased rates of injury, death, and health consequences including 50-70% increase in gynecological, central nervous system, and stress-related problems
- remember that men can also be victims of abuse
- occurs in all socioeconomic, educational, and cultural groups with increased incidence in pregnancy, disabled women, transgender and non-binary individuals, bisexuality, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs; children exposed to violence in the home are more likely to experience or perpetrate violence later in life (Cycle of Violence)
- physician recognition rates as low as 5%

Presentation
- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

Management
- maintain a high index of suspicion
  - asking about abuse is the strongest predictor of disclosure



Screening Instruments for Domestic Violence

Note: It is important to be mindful that the clinical relevance of the following screening tools may vary. Additionally, should they be relevant, one must take care to reduce distress and maintain patients' trust during these difficult conversations. Helpful strategies include interviewing the patient alone in a safe environment. Consider starting the discussion with "It is important to ask about people's close relationships", or "Do you feel safe in your current relationships?" While domestic violence may seem likely, the patient may not report it during the first encounter. Remember to screen for comorbid depression, anxiety, and substance misuse in suspected victims of domestic violence.

A) Woman Abuse Screening Tool (WAST)-SHORT

1. In general how would you describe your relationship?
   a. A lot of tension
   b. Some tension
   c. No tension
2. Do you and your partner work out arguments with . . .?
   a. Great difficulty
   b. Some difficulty
   c. No difficulty

Endorsing either question 1 ("a lot of tension") or question 2 ("great difficulty") makes intimate partner violence exposure likely

B) HITS

How often does your partner:
1. Physically hurt you?
2. Insult you?
3. Threaten you with harm?
4. Scream or curse at you?

Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)
A total score of 10 or greater is significant

- consider asking if patient feels safe at home or in their relationships; several screening tools (see sidebar) exist to identify victims of intimate partner violence
- make sure to determine the victim's level of immediate and long-term danger and ask if there are weapons in the house

• ensure patient safety
- victim most at risk for homicide when attempting to leave home or following separation
- safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go, and having emergency items prepared should the patient need to leave quickly (including money, clothes, keys, medications, and important documents)

• provide community resources
- shelter or helpline number with legal advocacy and counselling services
- involve social workers or domestic violence advocates with the patient's consent

• appointment for follow-up to assess whether condition is better or worse
• reassure patient is not to blame and that the assault is a crime
• goal is to convey support
- reporting suspected or known child abuse is mandatory
- spousal abuse is a criminal act, but not reportable without the person's permission

• DOCUMENT all evidence of abuse-related visits for medico-legal purposes; aim to provide verbatim quotations, when possible

ELDER ABUSE
• see Geriatric Medicine, GM7

CHILD ABUSE
• see Pediatrics, P18

Dyspepsia

• see Gastroenterology, G10

Definition and Clinical Features
• defined as epigastric pain or discomfort
• can be associated with fullness, belching, bloating, heartburn, food intolerance, N/V

Epidemiology
• annual incidence 1-2%, prevalence 20-40%

Etiology
• common: functional, PUD, GERD, gastritis
• others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

History
• symptoms may not be useful in finding cause
• associated with eating, anorexia, N/V, alcohol, NSAID use
• red flags: vomiting, bleeding/anemia, abdominal mass, dysphagia (VBAD)

Investigations
• for new onset dyspepsia:
- <60 yr without high-risk features, test for *H. pylori* using the urea breath test, stool antigen test, or serology
- ≥60 yr should undergo upper endoscopy to rule out organic pathology

Management
• lifestyle modifications: decrease caffeine and alcohol intake, avoid citrus food, smaller and more frequent meals, avoid supine position right after meals, smoking cessation
• pharmacologic treatment
- gastric acid suppression: H2 blockers, PPIs; both are effective for PUD and GERD
- TCAs or prokinetics: e.g. metoclopramide; effective for functional dyspepsia
• *H. pylori* eradication
- do not keep patients on PPI without at least 1 trial off the medication per year (https://choosingwiselycanada.org/perspective/ppi-toolkit/)
• for non-responders, upper endoscopy should be considered. If endoscopy is negative, defined as functional dyspepsia



Dyspepsia Red Flags
Weight loss
Dysphagia
Persistent vomiting
GI bleeding (hematemesis, hematochezia, melena)
Onset age >50



***H. pylori* Eradication**
Bismuth Quadruple Therapy (PBMT) or Concomitant Non-Bismuth Quadruple Therapy (PAMC) for 14 days

PBMT:
1) PPI standard dose BID
2) Bismuth subsalicylate 524 mg QID
3) Metronidazole 500 mg QID
4) Tetracycline 500 mg QID

PAMC:
1) PPI standard dose BID
2) Clarithromycin 500 mg BID
3) Amoxicillin 1000 mg BID
4) Metronidazole 500 mg BID

Dyspnea

• see Respirology, R3 and Emergency Medicine, ER26

Definition

- uncomfortable, abnormal awareness of breathing, a subjective sensation of shortness of breath, or difficulty breathing
- when discussing dyspnea with patients, consider using language that is easy for patients to understand such as speaking about "feeling breathless" or "having trouble catching your breath"

History and Physical Exam

- history
  - associated symptoms (cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema)
  - constitutional symptoms (night sweats, fever, weight loss)
  - history of asthma, allergies, eczema, ASA/NSAID sensitivity, nasal polyps
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birthplace (considering areas with increased prevalence of TB)
  - family history of atopy
  - previous CXR or PFTs
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

Investigations

- CXR, ECG
- PFTs, ABG acutely if indicated

Management

- dependent on cause
- send to ED if acute presentation with moderate symptoms
- call ambulance if in severe respiratory distress

Differential Diagnosis of Dyspnea

Pulmonary
- COPD
- Asthma
- Restrictive lung disease
- Pneumothorax
- Congenital lung disease
- PE
- Malignancy

Cardiac
- HF
- CAD
- MI (recent or past)
- Cardiomyopathy
- Valvular dysfunction
- Pericarditis
- Arrhythmia
- Hypertrophy

Mixed/Other
- Deconditioning
- Psychological and/or physical trauma
- Pain
- Neuromuscular
- Metabolic condition
- Anemia
- Functional: anxiety, panic attack, hyperventilation

Dysuria

• see Urology, U10

Definition

- the sensation of pain, burning, or discomfort when urinating

Epidemiology

- more common in women than men
- approximately 25% of women report one episode of acute dysuria per yr
- most common in women ages 25-54 and in those who are sexually active
- in men, prevalence of dysuria increases with age

Etiology

- infectious
  - most common cause
  - presents as cystitis, urethritis, pyelonephritis, vaginitis, cervicitis, epididymo-orchitis, or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, radiation, drugs/chemicals, foreign bodies, trauma, neoplasm, kidney stones, inflammatory diseases, endometriosis, psychogenic

Table 13. Etiology, Signs, and Symptoms of Common Causes of Dysuria

Infection	Etiology	Signs and Symptoms
UTI/Cystitis	KEEPS bacteria (*Klebsiella, E. coli, Enterobacter* spp., *P. mirabilis, Pseudomonas* spp., *S. saprophyticus*)	Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)
Urethritis	*C. trachomatis, N. gonorrhoeae, Trichomonas* spp., *Candida* spp., herpes	Initial dysuria, urethral/vaginal discharge, history of STI
Vaginitis	*Candida* spp., *Gardnerella* spp., *Trichomonas* spp., *C. trachomatis*, atrophic, herpes, lichen sclerosis	External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding
Prostatitis	*E. coli, C. trachomatis, S. saprophyticus, P. mirabilis, Enterobacter* spp., *Klebsiella* spp., *Pseudomonas* spp.	Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain
Pyelonephritis	*E. coli, S. saprophyticus, P. mirabilis, Enterobacter* spp., *Klebsiella* spp., *Pseudomonas* spp.	Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, N/V

Investigations

- if history, physical, and urine dipstick are consistent with an uncomplicated UTI, treat empirically with no further investigations
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria

UTI Clinical Decision Aid

Arch Intern Med 2007;67:2201-2206

- Dysuria
- +Leukocytes (on urine dipstick)
- +Nitrites (on urine dipstick)

If 2 or more criteria met, then treat without culture, otherwise culture required prior to treatment.

Risk Factors for Complicated UTI
- Male
- Pregnancy
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- Chronic renal disease
- DM
- Immunosuppression
- Indwelling catheter

Cranberries for Preventing Urinary Tract Infections

Cochrane DB Syst Rev 2023;10:CD001321

Purpose: To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations.

Methods: All RCTs or quasi-RCTs of cranberry products for the prevention of UTIs were assessed and a meta-analysis of 50 RCTs (n=8857) conducted.

Results: Cranberry products reduced the incidence of symptomatic, culture-verified UTIs in women with recurrent UTIs (RR 0.74; 95% CI, 0.55-0.99), in children (RR 0.46; 95% CI, 0.32-0.68), and in people with intervention-related UTI susceptibility (RR 0.47; 95% CI, 0.37-0.61) compared with controls.

Conclusion: Cranberry products reduce the risk of symptomatic UTIs in certain populations.

- urine C&S
- CBC and differential if suspecting pyelonephritis
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomonas, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P69 for UTI

Management

- hospitalize if septic or critically ill, and consider hospitalization if persistently high fever, persistent pain, severe weakness, or inability to maintain hydration or tolerate oral feeds
- first-line treatment of uncomplicated UTI is TMP/SMX (cotrimoxazole) 160/800 mg BID x 3 d or nitrofurantoin 100 mg BID x 5 d
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated (first line: amoxicillin, nitrofurantoin (avoid in third trimester), cephalexin) even if asymptomatic due to increased risk of pyelonephritis, preterm labour, low birth weight, and perinatal mortality. Need to follow with monthly urine cultures and repeat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
- urethritis
  - positive swab or PCR for chlamydia or gonorrhea must be reported to Public Health (see Family Medicine, FM47for management of STIs)
  - all patients should return 4-7 d after completion of therapy for clinical evaluation

Prevention of UTIs
- Maintain good hydration
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse
- Vaginal estrogen therapy for peri- and postmenopausal women with recurrent UTIs

Epistaxis

- see Otolaryngology, OT27

Erectile Dysfunction

- see Urology, U33

Definition

- >3 mo of consistent or recurrent inability to attain and/or maintain sufficient penile erection for sexual performance

Epidemiology

- ~20% of men age 40; ~50% of men age 70

Etiology

- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, DM), anatomic (structural abnormality, e.g. Peyronie's), neurologic (postoperative, DM), medications (clonidine, antihypertensives, SSRIs, tricyclic antidepressants, cimetidine, 5-α-reductase inhibitors)
- psychogenic (10%)

Differential Diagnosis of Erectile Dysfunction

PENIS
Psychogenic
Endocrine (T2DM, testosterone)
Neurogenic (T2DM, postoperative)
Insufficiency of blood (atherosclerosis)
Substances

Table 14. Differentiation Between Organic and Psychogenic ED

Characteristic	Organic	Psychogenic
Onset	Gradual	Acute
Circumstances	Global	Situational
Course	Constant	Varying
Non-Coital Erection	Poor	Rigid
Morning Erection	Absent	Present
Psychosexual Problem	Secondary	Long history
Partner Problem	Secondary	At onset
Anxiety and Fear	Secondary	Primary

Walsh PC, Campbell MF, Retik AB. Campbell's Urology, 8th ed. W.B. Saunders, 2002. Table 46-4

History

- comprehensive sexual, medical, and psychosocial history
  - review medication and substance use
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity
- quantify
  - presence of morning or night time erections
  - stiffness (scale of 1-10)
  - ability to initiate and maintain an erection with sexual stimulation
  - erection stiffness during sex (scale of 1-10)

- qualify
  - partner or situation specific
  - loss of erection before penetration or climax
  - degree of concentration required to maintain an erection
  - percentage of sexual attempts satisfactory to patient and/or their partner
  - significant bends in penis or pain with erection
  - difficulty with specific positions
  - impact on quality of life and relationship

Investigations

- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: FBG, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)

Management

Table 15. Management of Erectile Dysfunction

Nonpharmacologic	Pharmacologic	Surgical
Lifestyle changes (alcohol, smoking, exercise) Relationship/sexual counselling Vacuum devices	Oral agents Suppository Male urethral suppository for erection (MUSE) Injections	Implants Vascular repair Realignment

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors
  - testosterone (currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications))
  - α-adrenergic blockers (e.g. yohimbine); currently limited data for use in erectile dysfunction

Table 16. Phosphodiesterase Type 5 Inhibitors

Examples	Dosing (1 dose/d)	Specifics	Side Effects	Contraindications
sildenafil (Viagra®)	25-100 mg/dose	Take 0.5-4 h prior to intercourse May last 24 h	Flushing, headache, indigestion	Not to be used in patients taking nitrates
tadalafil (Cialis®)	5-20 mg/dose	Effects may last 36 h	As above	As above
vardenafil (Levitra®)	2.5-20 mg/dose	Take 1 h prior to intercourse	As above	As above

The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction
Arch Intern Med 2011;171:1797-1803
Purpose: To evaluate the effectiveness of lifestyle interventions and pharmacotherapy for cardiovascular (CV) risk factors on severity of erectile dysfunction (ED).
Methods: Meta-analysis of RCTs with a follow-up of a minimum of 6 wk, evaluating lifestyle intervention vs. pharmacotherapy for CV risk factor reduction. Main outcome measure was weighted mean differences in the International Index of Erectile Dysfunction (IIEF-5) score.
Results: 6 RCTs with a total of 740 participants were included. Lifestyle modifications and pharmacotherapy for CV risk factor reduction were both associated with significant improvements in sexual function based on IIEF-5 scores (weighted mean difference (WMD) 2.66, 95% CI 1.86-3.47). Excluding statin trials, lifestyle modification interventions were associated with a statistically significant improvement in sexual function (WMD 2.40, 1.19-3.61).
Conclusion: Lifestyle modifications and pharmacotherapy for CV risk reduction are effective in improving male sexual function.

Reasons for Referral to Urology
- Significant penile anatomic disease
- Younger patient with a history of pelvic or perineal trauma
- Cases requiring vascular or neurosurgical intervention
- Complicated endocrinopathies
- Complicated psychiatric or psychosocial problems
- Patient or physician desire for further evaluation

Fatigue

Definition

- can describe difficulty or inability to initiate activity, maintain activity, or difficulty with concentration/memory
- presentation may vary and the patient's specific complaint should be clarified, e.g. excessive sleepiness, muscle weakness, decreased exercise tolerance, mood concerns

Epidemiology

- 25% of office visits to family physicians
  - peaks in ages 20-40
  - F:M=3-4:1
- 50% have associated psychological complaints/problems, especially if <6 mo duration

Differential Diagnosis

Table 17. Differential Diagnosis of Fatigue: PS VINDICATE

P	**Psychogenic**	**Depression, life stresses,** anxiety disorder, chronic fatigue syndrome, fibromyalgia
	Physiologic	Pregnancy, caregiving demands (young children, elderly)
S	Sleep disturbance	**OSA, sleep disorder,** poor sleep hygiene, **BPH,** shift work, pain
	Sedentary	Unhealthy/sedentary lifestyle
V	**Vascular**	Stroke
I	**Infectious**	Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic
N	Neoplastic	Any malignancy
	Nutrition	**Anemia** (Fe^{2}deficiency, B 12deficiency)
	Neurogenic	Myasthenia gravis, multiple sclerosis, Parkinson's disease
D	**Drugs**	β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics, antidepressants
I	Idiopathic	
C	Chronic illnesses	HF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease
A	Autoimmune	SLE, RA, mixed connective tissue disease, polymyalgia rheumatica
T	Toxin	**Substance misuse** (e.g. alcohol), heavy metal
E	Endocrine	**Hypothyroidism, DM,** Cushing's syndrome, adrenal insufficiency, pregnancy

Common causes are in **bold**

Investigations
- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical exam
- investigations are guided by history and physical exam and may include:
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vitamin B12, serum protein electrophoresis, Bence-Jones protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

Treatment
- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - validation and follow-up, especially with fatigue of psychogenic etiology
  - supportive counselling, behavioural, or group therapy
  - encourage patient to stay physically active to maximize function, and consider using motivational interviewing techniques to create person-centred approaches
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
  - prognosis: after 1 yr, 40% are no longer fatigued

CHRONIC FATIGUE SYNDROME

Diagnosis (Institute of Medicine, 2015)
- diagnosis requires the following three symptoms:
  1. a substantial reduction or impairment in the ability to engage in pre-illness levels of activity that is:
     - lasting >6 mo
     - accompanied by fatigue of new onset, not alleviated by rest, and not caused by excessive exertion
  2. post-exertional malaise*
     - worsening of symptoms after physical, mental or emotional exertion that would not have caused a problem before the illness
  3. unrefreshing sleep*
     - even after a full night of sleep despite the absence of specific objective sleep alterations

  AND
  - at least one of the two following manifestations is also required:
    - cognitive impairment*
    - orthostatic intolerance

*The frequency and severity of these symptoms need to be evaluated

Epidemiology
- F>M, more common in White individuals than other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

Etiology
- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency



Exercise Therapy for Chronic Fatigue
Cochrane DB Syst Rev 2019;10:CD003200
Purpose: To determine the effects of exercise therapy for adults with chronic fatigue syndrome (CFS) compared with any other intervention or control.
Methods: Meta-analysis of RCTs involving adults with CFS as a primary diagnosis who were able to participate in exercise therapy. Studies compared exercise therapy to passive control, psychological therapies, adaptive pacing therapy, or pharmacological therapy.
Results: Eight RCTs with 1518 participants were included. Exercise therapy lasted 12 to 26 wk. Moderate quality evidence showed exercise therapy was more effective in reducing fatigue vs. passive or no treatment, and was also associated with a positive effect on daily physical functioning and sleep. It also slightly improved physical functioning, depression, and sleep compared to adaptive pacing.
Conclusion: Exercise therapy may have a positive effect on fatigue in adults with CFS compared to usual care or passive therapies.

Investigations
- no specific diagnostic laboratory tests

Treatment
- promote sleep hygiene
- provide support and education that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy, family therapy, support groups
  - consider using motivational interviewing techniques to create person-centred approaches
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials (if indicated based on investigations), anti-allergy therapy, antihypotensive therapy

Fever

- see Pediatrics, P58

Definition
- oral temperature >37.2°C (AM), >37.7°C (PM), rectal temperature 37.5°C–38.3°C, or axillary temperature >37.2°C
- fever in children <2 yr must be a rectal temperature for accuracy
- TM not accurate for measurement until child is >5 yr

Table 18. Differential Diagnosis of Fever

Infection	Cancer	Medications		Other
Bacterial	Leukemia	Allopurinol	Nifedipine	Inflammatory Bowel Disease
Viral	Lymphoma	Captopril	Phenytoin	Collagen Vascular Disease
TB	Other Malignancies	Cimetidine	Diuretics	DVT
		Heparin	Barbiturates	
		INH	Antihistamines	
		Meperidine		

History
- fever
  - peak temperature, type of thermometer, site of temperature measurement, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - URTI: cough, coryza, ear pain (consider influenza, COVID-19)
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
  - PE/DVT: swollen legs, pain in calf, SOB, pleuritic chest pain
  - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, daycare, contact with TB, foodborne, animals

Possible Investigations
- CBC and differential, blood culture, urine culture, urinalysis
  - viral swab including influenza, COVID-19
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- lumbar puncture

Management
- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

Headache

Definitions
- primary headaches
- see Neurology, N46
  - primary headaches are the most common headaches seen in family medicine including tension headaches, migraines, and cluster headaches
  - secondary causes should be ruled out prior to diagnosing a patient with a primary headache
- secondary headaches
  - caused by underlying organic disease
  - account for <10% of all headaches, may be life-threatening

Etiology of Secondary Headaches
- drug: drug withdrawal, medication overuse, drug side effect, and carbon monoxide
- infectious: meningitis, encephalitis, abscess
- vascular: aneurysm, stroke, SAH, HTN, and temporal arteritis
- endocrine: thyroid disease, pheochromocytoma
- neoplastic: tumour
- trauma: TMJ injury, c-spine injury, head injury, subdural hematoma, and SAH
- other: serious ophthalmological and otolaryngological causes

Investigations
- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR or CRP for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection

Management
- based on underlying disorder
- analgesics may provide symptomatic relief
  - see Neurology, N47

Hearing Impairment

- see Otolaryngology, OT9

Definition
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

Classification
- conductive (external sound does not reach the inner ear)
- sensorineural (involving the inner ear, cochlea, or auditory nerve)
- mixed

Epidemiology
- prevalence increases with age (6% of 35-44 yr, 43% of 65-84 yr)
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people >65 yr

Assessment
- infants: universal newborn hearing screening program
- elderly
- screening tests
  - whispered-voice test
    - examiner stands 0.6 metres (arm's length) behind the patient, whispers a combination of 6 letters/numbers, and asks the patient to repeat the sequence. Test 1 ear at a time while masking the non-test ear simultaneously
  - Rinne and Weber tuning fork tests (to distinguish conductive from sensorineural hearing loss)
- diagnostic tests (formal audiologic assessment)
  - pure tone, air, and bone conduction testing
  - speech audiometry
  - impedance audiometry



Acupuncture for Migraine Prophylaxis
Cochrane DB Syst Rev 2016:6:CD001218
Purpose: To investigate whether acupuncture is more effective than routine care (no prophylaxis), sham acupuncture, or prophylactic pharmacological treatment at reducing episodic migraine frequency in adults.
Methods: Meta-analysis of 22 RCTs (n=4985) with a minimum of an 8 wk duration, comparing acupuncture intervention with a non-acupuncture control (no prophylaxis, routine care, sham, or pharmacological prophylaxis.
Results: Acupuncture moderately reduced headache frequency compared to no acupuncture (standardized mean difference (SMD) -0.56,; 95% CI, -0.65 to -0.48)). Acupuncture showed a small but statistically significant reduction over sham post-treatment (SMD -0.18; 95% CI -0.28 to -0.08) and post-follow-up (SMD -0.19; 95% CI -0.30 to -0.09). Compared to pharmacological prophylaxis, a significant reduction in migraine frequency was noted with acupuncture treatment (SMD -0.25; 95% CI -0.39 to -0.10), but significance was not maintained at follow-up.
Conclusion: Adding acupuncture to symptomatic treatment of attacks reduces frequency of headaches. Acupuncture is more effective than sham, and is similarly effective to pharmacological interventions for migraine prophylaxis.



Migraine Screen

POUND
Pulsatile quality
Over 4-72 h
Unilateral
Nausea and vomiting
Disabling intensity
If ≥4 present then a diagnosis is likely
(Positive likelihood ratio = 24)



Headache Red Flags

SNOOP
Systemic symptoms of illness
- Fever
- Anticoagulation
- Pregnancy
- Cancer

Neurologic signs/symptoms
- Impaired mental status
- Neck stiffness
- Seizures
- Focal neurological deficits

Onset
- Sudden and severe
- New headache after age 50

Other associated conditions
- Following head trauma
- Awakens patient from sleep
- Jaw claudication
- Scalp tenderness
- Worse with exercise, sexual activity, or Valsalva

Prior headache history
- Different pattern
- Rapidly progressing in severity/ frequency

Management
- counsel about noise control and hearing protection programs (high quality evidence)
  - treat patients with unexplained, unilateral, sudden sensorineural hearing loss urgently with steroids
  - consider blood glucose, CBC and differential, TSH, syphilis testing for unexplained sensorineural hearing loss
  - consider a CT/MRI for patients with progressive asymmetric sensorineural hearing loss to exclude vestibular schwannoma (acoustic neuroma)
- refer patients who
  - have an unknown etiology to an ENT specialist
  - experience sudden sensorineural hearing loss to an ENT specialist for ongoing care
- treatment: hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life

Hypertension

- Hypertension guidelines are reviewed and updated annually, for up-to-date recommendations, please see http://guidelines.hypertension.ca/

Definitions
- HTN
  - if diabetic, office BP measurement (OBPM) ≥130/80 mmHg for ≥3 measurements on different days = probable HTN, rule out white coat HTN
  - if not diabetic and automated office BP (AOBP) ≥135/85 mmHg or OBPM ≥140/90 mmHg, rule out white coat HTN
    - ambulatory BP monitoring (ABPM) daytime mean ≥135/85 mmHg OR ABPM 24 hr mean ≥130/80 mmHg = HTN
    - home BP monitoring (HBPM) series mean ≥135/85 mmHg = HTN
    - mean AOBP or OBPM sBP ≥180 mmHg or dBP ≥110 mmHg = HTN
- isolated systolic HTN
  - sBP ≥140 mmHg and dBP <90 mmHg
  - associated with progressive reduction in vascular compliance
  - usually begins in 5th decade
- hypertensive urgency
  - sBP >210 mmHg or dBP >120 mmHg with minimal or no target-organ damage
- hypertensive emergency
  - severe HTN (dBP >120 mmHg) + acute target-organ damage (acute heart failure, MI, aortic dissection, acute kidney injury, hypertensive encephalopathy, hypertensive retinopathy)
  - accelerated HTN
    - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy, but without papilledema
  - malignant HTN
    - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
- white coat HTN
  - high clinic BP with normal home BP and 24 h ambulatory BP, caused by anxiety in clinic
- masked HTN
  - normal clinic BP with high BP in home and/or ambulatory setting, often provoked by anxiety, job stress, exercise



- Symptoms of HTN are usually not present (this is why it is called the "silent killer")
- Patients may have an occipital headache upon awakening or organ-specific complaints if advanced disease



Renovascular HTN Suspected if Patient Presenting with 2 or more of:
- Sudden onset or worsening of HTN and ages >55 or <30
- Presence of abdominal bruit
- HTN resistant to 3 or more drugs
- Rise in Cr of 30% or more associated with use of an ACEI or ARB
- Other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia
- Recurrent pulmonary edema associated with hypertensive surges

Epidemiology
- 22% of Canadian adults suffer from HTN (prevalence is 52% in the 60-70 age group)
- lifetime risk of developing HTN is approximately 90%
- 64% of Canadians who have HTN are treated and controlled, while 17% are unaware that they have HTN
- 3rd leading risk factor associated with death
  - risk factor for CAD, HF, cerebrovascular disease, renal failure, PVD

Etiology
- essential HTN (90%, undetermined cause)
- secondary HTN (10%, known cause)

Predisposing Factors
- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male

- age >30
- excessive salt intake/fatty diet
- Black ancestry
- dyslipidemia

Table 19. Causes of Secondary HTN

	Common Cause		
Renal	Renovascular HTN Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney		
Endocrine	1° hyperaldosteronism Pheochromocytoma Cushing's syndrome Hyperthyroidism/hyperparathyroidism Hypercalcemia of any cause		
Vascular	Coarctation of the aorta Renal artery stenosis		
Other	OSA		
Drug-Induced	Estrogens/OCP MAOIs Cocaine	Steroids Lithium Amphetamines	NSAIDs Decongestants Alcohol

Suspect Hyperaldosteronism when
HTN refractory to treatment with ≥3 drugs
Spontaneous hypokalemia
Profound diuretic-induced hypokalemia (<3.0 mmol/L)
Incidental adrenal adenomas

Hypertensive Emergencies
Malignant HTN
Cerebrovascular
- Hypertensive encephalopathy
- Stroke
- Intracerebral hemorrhage
- SAH

Cardiac
- Acute aortic dissection
- Acute refractory LV failure
- Myocardial infarction/ischemia
- Acute pulmonary edema

Renal failure

Investigations

- for all patients with HTN:
  - electrolytes, Cr, FBG and/or HbA1c, lipid profile, 12-lead ECG, urinalysis
  - self-measurement of BP at home is encouraged (recommended devices listed at www.hypertension.ca)
- for specific patient etiology:
  - DM or chronic kidney disease: urinary protein excretion
  - if suspected renovascular HTN: renal ultrasound, captopril renal scan (if GFR >60 mL/min), MRA/CTA (if normal renal function)
  - if suspected endocrine cause: plasma aldosterone, plasma renin (aldosterone-to-renin ratio)
    - measured from morning samples taken from patients in sitting position after resting 15 min
    - discontinue aldosterone antagonists, ARBs, β-blockers, and clonidine prior to testing
  - if suspected pheochromocytoma: 24 h urine for metanephrines and creatinine
  - if suspected LV dysfunction: echocardiogram
  - if clinically indicated or with refractory hypertension: sleep study

Diagnosis

- all Canadian adults should have BP assessed at all appropriate clinical visits, oscillometric preferred to manual

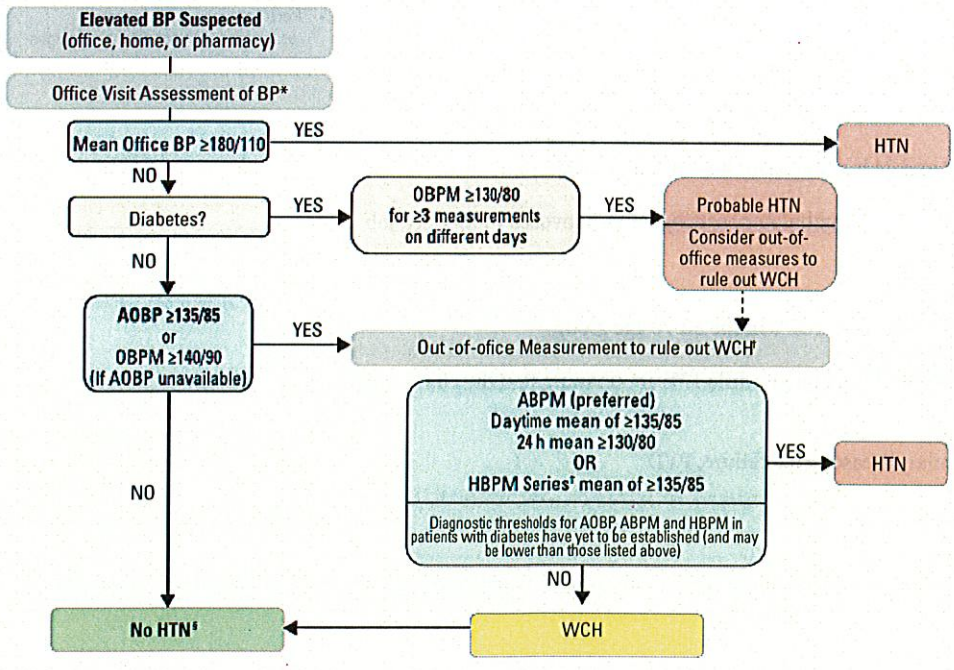


Figure 12. Diagnostic algorithm for HTN in adults
Rabi DM, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol. 2020;36(5):596–624. Reproduced with permission from Hypertension Canada.

Treatment

- hypertension means high pressure/strain. Without increasing a patient's potential distress, consider what may be causing their high pressure or strain. It may be important to support a patient in reducing sources of stress and worry
- treat to target BP: <140/90 mmHg, <130/80 mmHg if DM
- optimum management of HTN requires assessment of overall cardiac risk
- explore adherence to lifestyle modification and pharmacotherapy at each visit
- lifestyle modification (in all HTN patients – may be sufficient treatment in patients with stage 1 HTN (140-159/90-99 mmHg))
  - diet
    - follow Canada's Guide to Healthy Eating (see *Nutrition, FM7*) and DASH
    - limit daily salt intake to 5 g (2000 mg of sodium)
    - potassium/magnesium/calcium supplementations are NOT recommended for HTN, but an increase in dietary potassium may help
  - moderate intensity dynamic exercise: 30-60 min, 4-7x/wk; higher intensity exercise is not more effective
  - smoking cessation
  - low-risk alcohol consumption (see *Alcohol Use, FM15*)
  - work towards a healthy BMI (18.5-24.9 kg/m ^{2}) and waist circumference (<102 cm for men, <88 cm for women)
  - individualized approaches to reduce stress
- pharmacological
  - indications for antihypertensive therapy (caution with elderly patients):
    - sBP ≥140mmHg or dBP ≥90 mmHg with target organ damage or CV risk factors
    - sBP ≥160 mmHg or dBP ≥100 mmHg without target organ damage or CV risk factors
    - sBP ≥130 for high-risk populations (Framingham Risk >20%, ages >50)
    - sBP ≥130 mmHg or dBP ≥80 mmHg for patients with DM
  - first-line antihypertensives (consider a single pill combination therapy)
  - combination therapy principles:
    - if there is an inadequate response to therapy, consider adding another first line antihypertensive
    - avoid combining a non-DHP CCB with a β-blocker or an ACEI with an ARB
    - monitor potassium and creatinine when administering an ACEI/ARB with a potassium-sparing diuretic

Impact of Health Behaviour on Blood Pressure

Intervention	sBP (mmHg)	dBP (mmHg)
Diet and weight control	-6.0	-4.8
Reduced salt/ sodium intake	-5.4	-2.8
Reduced alcohol intake (heavy drinkers)	-3.4	-3.4
DASH diet	-11.4	-5.5
Physical activity	-3.1	-1.8
Relaxation therapies	-3.7	-3.5

CHEP (Canadian Hypertension Education Program) Guidelines 2014. Available from: https://www.onlinecjc.ca/article/S0828-282X(14)00070-1/fulltext

β-blocker
Not recommended as first line for patients of ages ≥60

ACEI
Not recommended as monotherapy in people of African descent

Table 20. Considerations in the Individualization of Pharmacological Therapy in Adults

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended/Notes
Isolated Diastolic HTN with or without Systolic HTN	Monotherapy or single pill combination (SPC) Recommended monotherapy choices include thiazide/thiazide-like diuretics (with longer-acting diuretics preferred), β-blockers, ACEI, ARBs, or long-acting CCBs. Recommended SPC choices include combinations of an ACEI with CCB, ARB with CCB, or ACEI/ ARB with a diuretic. (Consider ASA and statins in selected patients)	Combinations of first-line drugs	Not recommended for monotherapy: α-blockers, β-blocker in those ≥60 yr, ACEI in Black people Hypokalemia should be avoided in those prescribed diuretics. ACEI, ARBs and direct renin inhibitors are potential teratogens, and caution is required if prescribing to women with childbearing potential. Combination of an ACEI with an ARB is not recommended
Isolated Systolic HTN without other compelling indications	Thiazide diuretic, ARB, or long acting DHP CCB	Combinations of first-line drugs	Same as above
CAD	ACEI or ARB; β-blockers or CCB for patients with stable angina	When combination therapy for high-risk patients, ACEI/DHP CCB is preferred	Avoid short-acting nifedipine. Combination of an ACEI with an ARB is specifically not recommended. Exercise caution when lowering sBP to target if dBP is ≤60 mmHg, especially in patients with LVH
Recent MI	β-blocker and ACEI (ARB if cannot tolerate ACEI)	Long-acting CCB if β-blocker contraindicated or not effective	Non-DHP CCBs should not be used with concomitant HF
Left Ventricular Hypertrophy	ACEI, ARB, thiazide/thiazide-like diuretics, or long-acting CCB	Combination of additional agents	Hydralazine and minoxidil can increase LVH, thus not recommended
Cerebrovascular Disease (stroke/TIA)	ACEI and thiazide/thiazide-like diuretic combination	Combination of additional agents	Treatment of HTN should not be routinely undertaken in acute stroke unless extreme BP elevation. ACEI and ARB combination after a stroke is not recommended

2020 Hypertension Highlights, Hypertension Canada.
https://hypertension.ca/wp-content/uploads/2018/07/Hypertension-Guidelines-English-2018-Web.pdf

Calcium Channel Blockers

Dihydropyridine CCBs
Amlodipine
Nifedipine
Felodipine
Non-dihydropyridine CCBs
Diltiazem
Verapamil

How to Combine Antihypertensive Medications (in general)

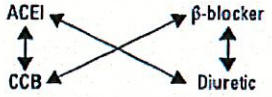


Table 20. Considerations in the Individualization of Pharmacological Therapy in Adults

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended/Notes
Heart Failure	ACEI (ARB if ACEI intolerant) and β-blockers Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent CV hospitalization, acute MI, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms	ARB in addition to ACEI Hydralazine/isosorbide dinitrate combination if ARB or ACEI not tolerated/contraindicated Thiazide/thiazide-like or loop diuretics are recommended as additive therapy. DHP CCB can also be used A combined ARB/neprilysin inhibitor is recommended (in place of an ACEI or ARB) in symptomatic patients with HTN and HFrEF on standard guideline-based therapies	Titrate doses of ACEI and ARBs to those used in clinical trials Carefully monitor potassium and renal function if combining any of ACEI, ARB and/or aldosterone antagonist
Dyslipidemia	Does not affect initial treatment recommendations	Combination of additional agents	
DM with Albuminuria (ACR >2.0 mg/mmol renal disease, CVD or additional CV risk factors)	ACEI or ARB	Addition of a DHP CCB is preferred over a thiazide/ thiazide-like diuretic	A loop diuretic could be considered in hypertensive chronic kidney disease patients with extracellular fluid volume overload
DM without Albuminuria (criteria listed above)	ACEI, ARB, DHP CCB, or thiazide/ thiazide-like diuretics	Combination of first-line drugs If combination with ACEI is being considered, a DHP CCB is preferable to a thiazide/thiazide like diuretic	Normal urine ACR <2.0 mg/mmol
Non-Diabetic Chronic Kidney Disease with Proteinuria (urinary protein >500 mg/24 h or ACR >30 mg/mmol)	ACEI (ARB if ACEI intolerant), if there is proteinuria Diuretics as additive therapy	Combinations of additional agents	Patients on an ACEI or ARB should have careful monitoring of renal function and potassium. ACEI and ARB combinations are not recommended in patients without proteinuria
Renovascular Disease	Does not affect initial treatment recommendations Atherosclerotic renal artery stenosis should be primarily managed medically, while revascularization should be considered for renal fibromuscular dysplasia	Combinations of additional agents	Caution in using ACEI or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney Renal artery angioplasty and stenting could be considered for patients with renal artery stenosis and complicated, uncontrolled HTN

2020 Hypertension Highlights, Hypertension Canada.
https://hypertension.ca/wp-content/uploads/2018/07/Hypertension-Guidelines-English-2018-Web.pdf

Table 21. Common Antihypertensive Medications in Pregnancy and Lactation

Pregnancy			Lactation
First line oral drugs	**Second line oral drugs**	**Medications to avoid**	**Oral drugs**
Labetalol Methyldopa Long-acting oral nifedipine Other β-blockers (acebutolol, metoprolol, pindolol, and propranolol)	Clonidine Hydralazine Thiazide diuretics	ACEIs* ARBs*	Labetalol Methyldopa Long-acting oral nifedipine Enalapril Captopril

* Fetotoxicity of renal system

Follow-Up

- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification q3-6 mo
- pharmacological
  - follow-up q1-2 mo until BP under target for 2 consecutive visits, q3-6 mo once at target BP
  - follow-up frequently for patients with symptomatic/severe HTN, antihypertensive drug intolerance, target organ damage
- referral is indicated for cases of refractory HTN, suspected secondary causes, or worsening renal failure
- hospitalization is indicated for malignant HTN



Systematic Review for 2017 ACC/AHA Guidelines for Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults
Hypertension 2018;71:e116-135
Purpose: Determine evidence for self-measured BP without other augmentation for clinical outcomes and BP control. Determine optimal target for BP lowering during antihypertensive therapy in adults. Determine benefits and harms of different classes of antihypertensive drugs.
Methods: Systematic review and meta-analysis using PubMed and EMBASE.
Results: There is a modest but significant improvement in sBP in RCTs of self-measured BP vs. usual care at 6 but not 12 mo; may be a helpful adjunct to routine office care. sBP lowering to a target of <130 mmHg may reduce risk of several important outcomes including MI, stroke, heart failure, and major CV events. No class of medications (i.e. ACEI, ARBs, CCBs, or β-blockers) was significantly better than thiazides and thiazide-like diuretics as a first-line therapy for any outcome.
Conclusion: Self-measured BP is a useful adjunct in BP control. Target sBP <130. Thiazides, CCBs, β-blockers, ARBs, ACEI are to be used as first-line therapy with patient factors guiding choice.

Joint Pain

• see Rheumatology, RH2

History
•number of joints involved: monoarticular, oligoarticular, polyarticular
•inflammatory vs. non-inflammatory
•pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
•onset: acute vs. chronic (>6 wk)
•morning stiffness (duration) vs. worse at end of day with activity
• PMHx
  - trauma, infection, medications (steroids, diuretics)
  - comorbidities: DM, renal insufficiency (gout), psoriatic arthritis, myeloma, osteoporosis, and OA
  - FMHx of arthritis, autoimmune disease
•ROS: constitutional symptoms (neoplasm, septic arthropathy), myalgia, skin/eye/nail/hand changes, and GI/GU changes



Signs and Symptoms of Inflammatory Arthritis

WARM(S) Joints
Worse with rest, better with activity
Awakening in the latter half of the night
Redness around joint
Morning stiffness (>30 min)
Soft tissue swelling, erythema

Physical Exam
• vitals
•specific joint exams to affected areas
•systemic features (skin, nails, eyes, hands)

Investigations (Guided by the History and Physical Exam)
•general: CBC and differential, electrolytes, Cr
•acute phase reactants: ESR, CRP
•complement (C3, C4)
•urinalysis to detect disease complications (proteinuria, active sediment)
•serology (tailored to clinical suspicion, see Rheumatology, RH4)
  - antinuclear antibody (ANA), negative ANA helps to exclude SLE, positive ANA in subset of RA
  - anti-double stranded DNA (anti-dsDNA), perform anti-dsDNA and anti-smith (anti-Sm) for SLE if positive ANA
  - human leukocyte antigen B27 (HLA-B27), more consistent with reactive arthritis than RA
  - anti-histidyl tRNA synthetase autoantibodies (anti-Jo1), positive in dermatomyositis and polymyositis
  - anti-Sm, positive in SLE
  - anti-La antibodies (anti-La), positive in Sjögren's disease
  - anti-Sjögren's-syndrome-related antigen A (anti-SSA/Ro), positive in Sjögren's disease
  - rheumatoid factor (RhF), positive in RA and other conditions including Sjögren's disease
  - anti-cyclic citrullinated peptide (anti-CCP), positive in RA
•synovial fluid analysis (cell count and differential, culture, Gram stain, microscopy)
•radiology (plain film, CT, MRI, U/S, bone densitometry, bone scan)



Systemic Features
- Fever (SLE, infection)
- Rash (SLE, psoriatic arthritis)
- Nail abnormalities (psoriatic, reactive arthritis)
- Uveitis (psoriatic, reactive arthritis, ankylosing spondylitis)
- Myalgias (fibromyalgia, myopathy)
- Weakness (polymyositis, neuropathy)
- GI symptoms (scleroderma, IBD)
- GU symptoms (reactive arthritis, gonococcemia)

Treatment
•tailor therapy depending on the specific cause; consider referral to rheumatologist
•non-pharmacological: patient education, lifestyle modification, assisted devices, physiotherapy, occupational therapy
•pharmacological: analgesia (acetaminophen, NSAIDs), anti-inflammatory (disease-modifying anti-rheumatic drugs (DMARDs), steroids, antibiotics
  - if OA, consider steroid injections, hyaluronic acid injections

Low Back Pain

• see Orthopedic Surgery, OR27
•Clinically Organized Relevant Exam (CORE) Back Tool: https://cep.health/clinical-products/low-back-pain/

Definition
•acute: <6 wk
•subacute: 6-12 wk
•chronic: >12 wk

Epidemiology
•5th most common reason for visiting a physician
•lifetime prevalence: 90%, peak prevalence: ages 45-60
•largest WSIB category and most common cause of chronic disability for individuals <45 y/o
•90% resolve in 6 wk, <5% become chronic

Etiology

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes (worse with movement, better with rest)
  - soft tissue: sprain (ligament), strain (muscle)
  - spine: facet joint/disc degeneration, disc herniation, spinal stenosis (e.g. spondylosis), spondylolisthesis, compression fracture
  - other: pregnancy
- 2% are non-mechanical causes
  - surgical emergencies
    - cauda equina syndrome (areflexia, lower extremity weakness, saddle anaesthesia, fecal incontinence, urinary retention)
- medical conditions
    - neoplastic: primary, metastatic, multiple myeloma
    - infectious: osteomyelitis, TB
    - metabolic: osteoporosis, osteomalacia, Paget's disease
    - rheumatologic: ankylosing spondylitis, polymyalgia rheumatica
    - referred pain: perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster
    - abdominal aortic aneurysm (pulsatile abdominal mass)

Physical Exam

- inspection: curvature, posture, gait
- palpation: bony deformities/tenderness, paraspinal muscle bulk/tenderness, trigger points
  - percussion of spine to elicit pain due to fracture or infection
- range of motion and peripheral pulses
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- special tests
  - straight leg raise (positive if pain at <70° and aggravated by ankle dorsiflexion), positive test is indicative of sciatica/lumbosacral nerve root irritation
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

Investigations

- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

Table 22. Approach to Non-Traumatic Low Back Pain

	Back Dominant (Pain greatest above gluteal fold)		Leg Dominant (Pain greatest below gluteal fold)	
History	**Pattern 1** Worse with flexion Constant/intermittent	**Pattern 2** Worse with extension Never worse with flexion Always intermittent	**Pattern 3** Pain changes with back movement/position Currently/previously constant	**Pattern 4** Worse with activity Improves with rest and posture change Intermittent/short duration
Physical Exam	Normal neurological exam Fast responder Improves with extension Slow responder No change or worsens with extension	Normal neurological exam ± improves with flexion Worse with extension	Leg pain can improve but not disappear Positive straight leg raise ± conduction loss Fast responder Improves with specific back position Slow responder Not better with position changes	No irritative findings ± conduction loss
Likely Pathology	Disc pain	Facet joint pain	Compressed nerve pain: sciatica	Symptomatic spinal stenosis: neurogenic claudication
Initial Management	Scheduled extension Lumbar roll Night lumbar roll Medication as required: acetaminophen + NSAIDs	Scheduled flexion Limited extension Night lumbar roll Medication as required: acetaminophen + NSAIDs	Prone extension Supine "Z" lie Lumbar roll Night lumbar roll Medication as required: acetaminophen + NSAIDs, may consider opioid therapies if 1st line not sufficient	Abdominal exercises Night lumbar roll Sustained flexion Pelvic tilt Medication as required: acetaminophen + NSAIDs

Adapted from: American Academy of Orthopaedic Surgeons. Acute care: nontraumatic low back pain. Orthopaedic Knowledge Update: Spine 2 2001;153-166
Adapted from: Centre for Effective Practice. Clinically Organized Relevant Exam (CORE) Back Tool. 2016

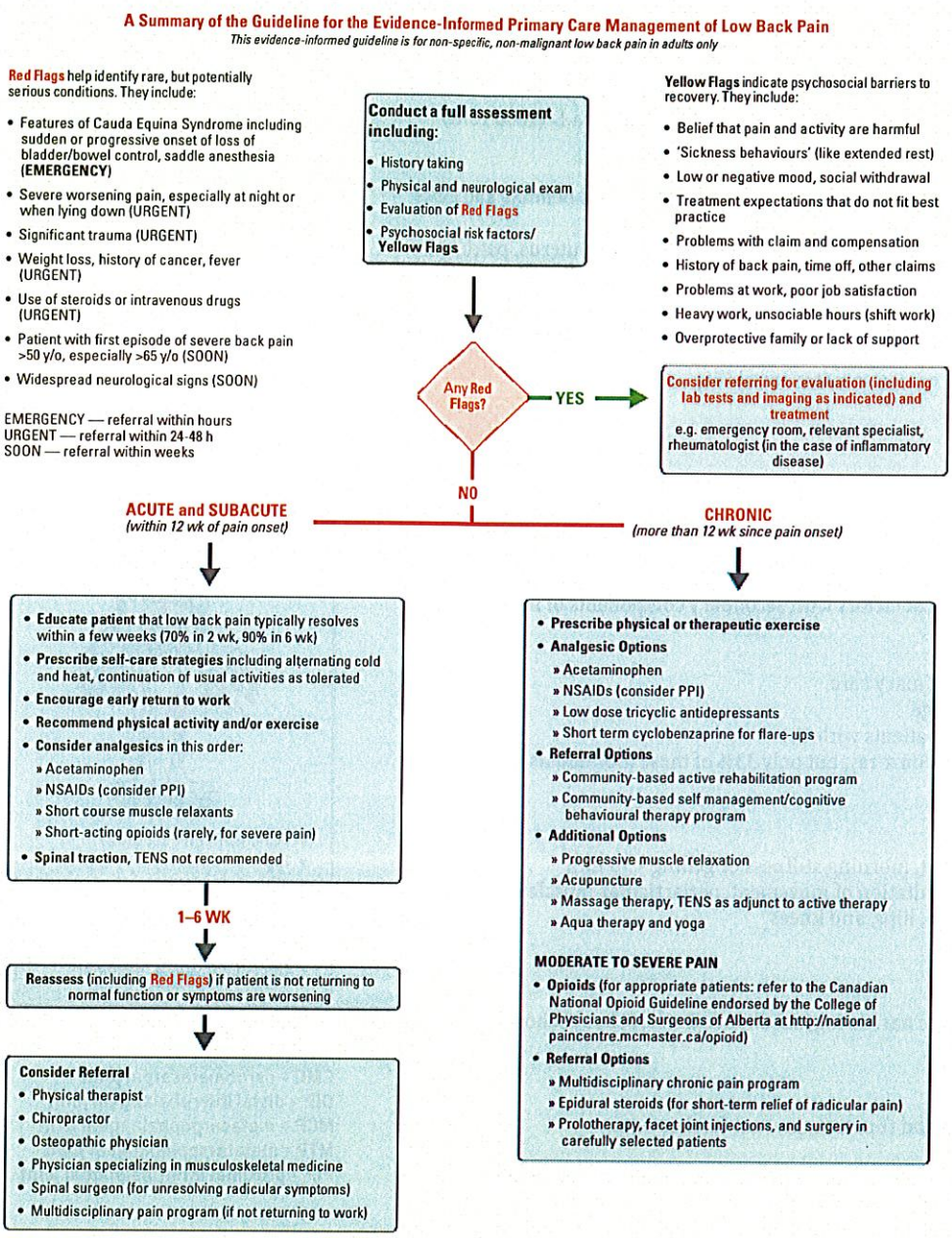


Figure 13. Low back pain treatment
Adapted with permission from Toward Optimized Practice (TOP) Low Back Pain Working Group. 2015 December. Evidence-informed primary care management of low back pain: Clinical practice guideline. Edmonton, AB: Toward Optimized Practice. Appendix I – Summary, p. 43-44. Available from: https://actt.albertadoctors.org/CPGs/Pages/Low-Back-Pain.aspx. Copyright 2015, Toward Optimized Practice.

Massage for Low Back Pain
Cochrane DB Syst Rev 2015;4
Purpose: To evaluate the effect of massage therapy for non-specific low back pain.
Methods: Meta-analysis of randomized or quasi-randomized trials evaluating use of any massage modality (hands or mechanical device) as a treatment for non-specific low back pain.
Results: 13 RCTs were identified, comparing massage therapy to other active or sham treatments. Massage was superior for pain and function on both short- and long-term follow-ups relative to sham treatment. It was similar to exercises, and superior to join mobilization, relaxation therapy, physical therapy, acupuncture and self-care education. Benefits lasted at least 1 yr post-treatment. Acupuncture massage was associated with better results than classic (Swedish) massage, and Thai massage produced similar results to the classic massage.
Conclusions: Massage may be beneficial for subacute and chronic non-specific low back pain, especially in combination with exercise and education.

Association of Spinal Manipulative Therapy with Clinical Benefit and Harm for Acute Low Back Pain
JAMA 2017;317:1451-1460
Purpose: To systematically review studies about the effectiveness and harms of Spinal Manipulative Therapy (SMT) for acute (≤6 wk) low back pain.
Methods: Systematic review and meta-analysis including RCTs and observational studies. Evidence assessed using GRADE criteria. Outcomes such as pain, function, or any harms were measured during 6 wk of SMT.
Results: 15 RCTs provided moderate-quality evidence that SMT has a statistically significant association with improvements in pain (pooled mean improvement in the 100 mm visual analog pain scale, −9.95 (95% CI, −15.6 to −4.3)). 12 RCTs (1381 patients) produced moderate-quality evidence that SMT has a statistically significant association with improvements in function (pooled mean effect size, −0.39 (95% CI, −0.71 to −0.07)). No RCT reported any serious adverse event. Minor transient adverse events such as increased pain, muscle stiffness, and headache were reported 50-67% of the time in large case series of patients treated with SMT.
Conclusion: SMT in acute low back pain was associated with modest improvements in pain and function at up to 6 wk, with transient minor MSK harms. However, heterogeneity in study results was large.

Menopause/Hormone Therapy

• see Gynecology, GY36

Definition
•12 mo of amenorrhea following the final menstrual period

Epidemiology
•mean age of menopause is 51.4 yr

Clinical Features
•associated with estrogen deprivation
•urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
•vascular: vasomotor instability (e.g. hot flashes), increased risk of heart disease
•bones: bone loss, joint/muscle/back pain, fractures, loss of height
•brain: depression, irritability, mood swings, memory loss

Management
- person-specific support and offering of health education about menopause (if desired)
- https://www.menopauseandu.ca
- non-pharmacological management: encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1200 mg/d) and vitamin D (1000 IU/d)
- pharmacological management:
  - hormone therapy (HT)
    - initiation of HT requires a thorough discussion of short- and long-term benefits and risks
o HT should not be initiated if >10y post-menopause
    - regimens: cyclic or continuous estrogen-progestin, estrogen only (if no uterus, patch/gel/cream/ring/vaginal tablet)
    - advantages: decreases risk of osteoporotic fractures, CRC
    - disadvantages: increases risk of DVT and PE. Can increase risk of breast cancer and stroke if HT is initiated >60 yr old or >10 yr from menopause
  - venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

Osteoarthritis

- see Rheumatology, RH5

Definition
- progressive deterioration of articular cartilage and surrounding joint structures caused by genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone >65 yr shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, periarticular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (through occupational therapy/physiotherapy), assistive devices (e.g. canes, orthotics)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs (cyclooxygenase-2 (COX2) selective) in low doses for short durations
  - 3rd line: duloxetine, combination analgesics (e.g. acetaminophen and codeine)
  - other pharmacological adjuncts:
    - intra-articular corticosteroid or hyaluronic acid injections
    - topical NSAIDS (diclofenac)
    - capsaicin cream
    - oral glucosamine (evidence remains inconclusive)
- surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)

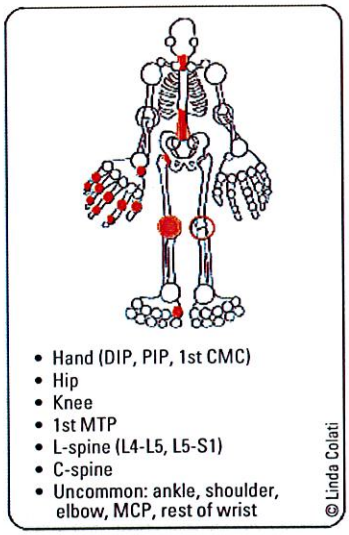


Figure 14. Common sites of involvement in OA
CMC = carpometacarpal joint
DIP = distal interphalangeal joint
MCP = metacarpophalangeal joint
MTP = metatarsophalangeal joint
PIP = proximal interphalangeal joint

Osteoporosis

- see Endocrinology, E46
- for current guidelines and tools see www.osteoporosis.ca

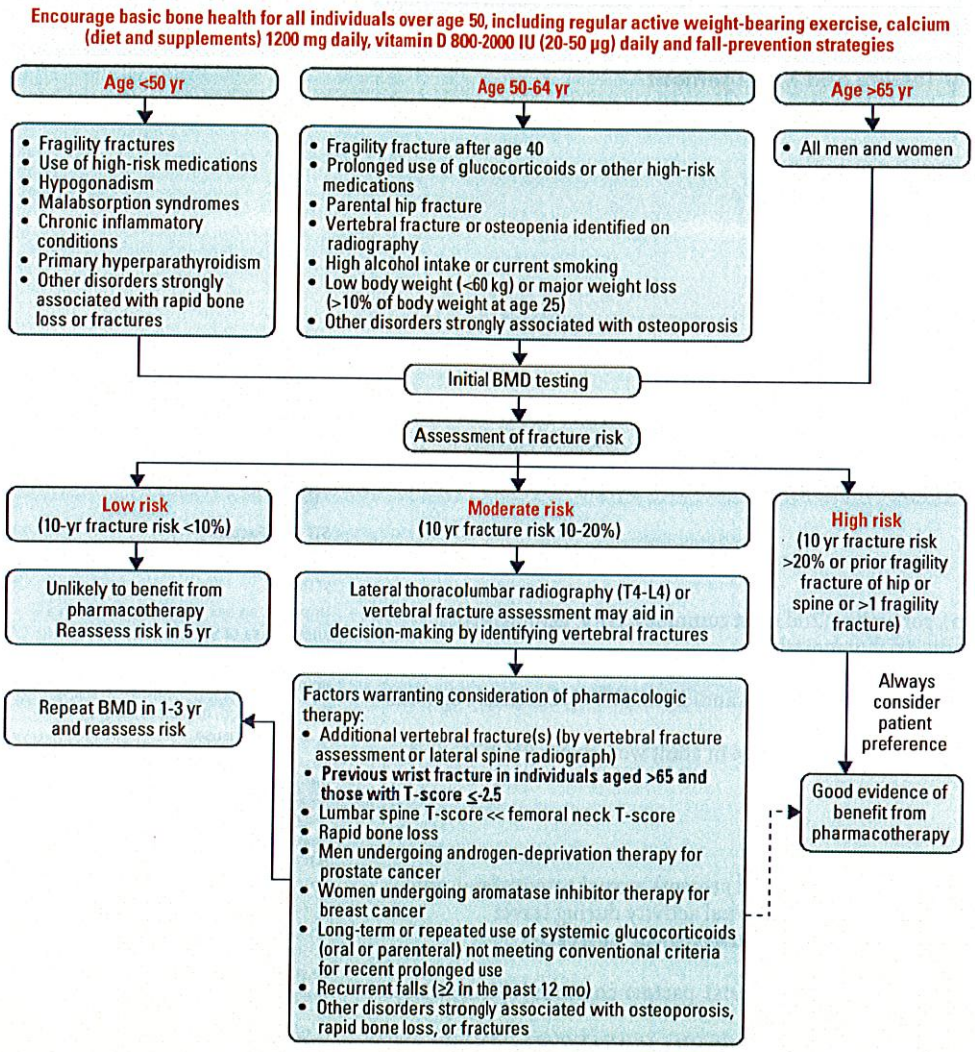


Figure 15. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (integrated management model) Adapted from: CMAJ 2010;182:1864-1873

Definition

•age-related disease characterized by decreased bone mass and increased susceptibility to fractures

Epidemiology

•in Canada, affects 1 in 4 women and 1 in 8 men

Clinical Presentation

•asymptomatic for many years
•fragility or osteoporotic fractures

Approach to Clinical Assessment

•identify risk factors on history and physical examination
• history
  - prior falls, fragility fractures, parental hip fractures, and gait or balance issues
  - glucocorticoid use
  - smoking and alcohol intake (≥3 units/d)
  - RA
• physical examination
  - height annually (prospective loss >2 cm or historical loss >6 cm) and weight (weight loss >10% since age 25)
  - rib-to-pelvis distance ≤2 fingers' breadth

Disorders Strongly Associated with Osteoporosis Include:
Primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. IBD)

10 Yr Fracture Risk Assessment
FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population
FRAX and CAROC are available online from: https://osteoporosis.ca/tools/

How Much Calcium Do We Need?

Age	Amount/day
4-8	1000 mg
9-18	1300 mg
19-50	1000 mg
>50	1200 mg

Calcium Content of Common Foods
1 cup milk = 300 mg
¾ cup yogurt = 332 mg
½ can salmon with bones = 240 mg
½ cup cooked broccoli = 33 mg
1 medium orange = 50 mg

Vitamin D Content in Food
- Milk fortified with vitamin D3 contains 100 IU per 250 mL glass
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish, and fish oils (halibut and cod liver oils) all contain small amounts; supplementation is necessary to obtain adequate levels as dietary intake has minimal impact
- Most multivitamins provide 400 IU of vitamin D3
- Recommended daily intake of vitamin D:
  - adults 19-50 years old, including women who are pregnant or breastfeeding: 400-1000 IU daily
  - individuals over 50 years, or younger people who have risk factors (osteoporosis, multiple fractures, or conditions affecting the absorption of vitamin D): 800-2000 IU daily

- occiput-to-wall distance >5 cm
- assess fall risk by ability to get up from chair without support with arms, and walking several steps and return

Investigations
- CBC, Cr, corrected Ca $^{2+}$, ALP, TSH, 25-hydroxyvitamin D (after 3-4 mo of adequate supplementation), and serum protein electrophoresis if there are vertebral fractures

Indications for Bone Mineral Density Testing and Management
- see Endocrinology, E47
- see *Figure 15, FM45*

Rash

- see Dermatology, D16

Sexually Transmitted Infections

- see Gynecology, GY29

Definition
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

Epidemiology
- high incidence rates worldwide
- canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes
  - less common: hepatitis B, HIV, syphilis, trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

History
- sexual Hx
  - age of first intercourse, gender of sexual partners (past and present), sexual activity (oral, anal, vaginal intercourse, use of sex toys), contraception use, sexual activity during travel
  - total number of partners in the past year and duration of involvement with each
- STI Hx
  - STI awareness, previous STIs and testing (including Pap tests), partner communication/history regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

Investigations/Screening
- individuals at increased risk should be screened for hepatitis B, HIV, and syphilis
- Pap test q3 yr for anyone with a cervix aged 25 to 69 who has ever been sexually active
- annual screening for all sexually active people under 30 for gonorrhea and chlamydia

Management
- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune
- offer Gardasil® to:
  - females between ages of 9 to 27
  - women ≥27 if at risk of ongoing exposure
  - males between ages 9 to 27 to prevent anogenital cancer and genital warts
  - ≥27 years of age and who are at risk of ongoing exposure source
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use barrier contraception or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- a person with an STI is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients diagnosed with bacterial STI or trichomonas infection should abstain from sexual activity until treatment completion and for 7 d after treatment for both partners, or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis, chancroid



When an STI is detected in a child, evaluation for sexual abuse is mandatory



STI Risk Factors

Sexually active males and females <25 yr old

Unprotected sex, sexual contact with a known case of STI, previous STI

New sexual partner or >2 sexual partners in the past 12 mo

Street involved, homeless, and/or substance misuse



Sexual History
5 P's
Partners (numbers, gender)
Practices (vaginal, oral, anal insertive/receptive)
Protection
Past history of STIs
Pregnancy prevention



Efficacy of Human Papillomavirus Vaccines – A Systematic Quantitative Review
Int J Gynecol Cancer 2009;19:1166-1176
Purpose: To evaluate two vaccines for HPV in terms of efficacy, safety and immunogenicity.
Methods: Systematic review of RCTs involving women between the ages of 9 and 26 yr, randomly assigned to receive vaccination with HPV L1 virus-like particle in either quadrivalent (HPV 6, 11, 16, 18), bivalent (HPV 16, 18), or univalent (HPV 16) form or placebo. Main outcomes were prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AIN, adenocarcinoma *in situ* of the cervix, or cancer of the cervix associated with HPV infection).
Results: Six studies involving 47236 women were included. Bivalent and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% (95% CI 87-96%) and 62% (95% CI 27-70%), respectively. More symptoms were found in the bivalent vaccine group (35%, 5-73%) compared to control groups.
Conclusion: Prophylactic vaccination can prevent HPV infection in women ages 9-26 not previously infected with HPV subtypes covered by the vaccines.

Table 23. Diagnosis and Treatment of Common STIs

	Signs and Symptoms	Investigations	Treatment	Complications
Gonococcal Urethritis/ Cervicitis (*Neisseria gonorrhoeae*)	M: urethral discharge, unexplained pyuria, dysuria, irritation, testicular swelling or pain, symptoms of epididymitis F: mucopurulent endocervical discharge, vaginal bleeding, dysuria, pelvic pain, dyspareunia M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex	M: first-void urine nucleic acid amplification test (NAAT), urethral swab for Gram stain and culture F: vaginal swab or urine NAAT, endocervical swab for Gram stain and culture, vaginal swab for wet mount (to rule out trichomonas) M and F: urine NAAT, rectal/pharyngeal swabs if indicated	Ceftriaxone 500 mg IM single dose* Test of cure: cultures 3-7 d post-treatment for pharyngeal infections, ongoing signs or symptoms, treatment failure, or pregnancy Repeat screening in all patients 6 mo post-treatment	M: urethral strictures, epididymitis, infertility F: PID, infertility, ectopic pregnancy, perinatal infection, chronic pelvic pain M and F: arthritis, increased risk of acquiring and transmitting HIV
Non-Gonococcal Urethritis/Cervicitis (Usually *Chlamydia trachomatis*)**	~70% asymptomatic If symptoms appear (usually 2-6 wk after infection) then similar to gonococcal symptoms (see above)	Same as above	Doxycycline 100 mg PO BID x7 d + gonococcal urethritis/cervicitis prescription* Repeat screening in all patients 3 mo post-treatment	Same as above
Human Papillomavirus (genital warts, cervical dysplasia)	Most are asymptomatic M: cauliflower lesions (condylomata acuminata) on skin/mucosa of penile or anal area F: cauliflower lesions and/or pre-neoplastic/neoplastic lesions on cervix/vagina/vulva	None needed if simple condylomata Potential biopsy of suspicious lesions F: screening for cervical dysplasia through regular Pap smears	For condylomata: cryotherapy, electrocautery, laser excision, topical therapy (patient-applied or office-based) For cervical dysplasia: colposcopy and possible excision, dependent on grade of lesion	M and F: anal cancer MSM and F who have receptive anal sex: rectal cancer F: cervical/vaginal/vulvar cancer
Genital Herpes (HSV-1 and -2)	1° episode: painful vesiculoulcerative genital lesions ± fever, tender lymphadenopathy, protracted course Recurrent episodes: less extensive lesions, shorter course may have "trigger factors"	Swab of vesicular content for culture or NAAT	1° Episode Acyclovir 400 mg PO TID daily x7-10 d or Famciclovir 250 mg PO TID x7-10 d or Valacyclovir 1000 mg PO BID x7-10 d Recurrent Episode Acyclovir 800 mg PO TID daily x2 d or 800 mg PO BID x5 d Famciclovir 1000 mg PO BID x 1 d or 125 mg PO BID × 5d or 500 mg PO once followed by 250 mg PO BID x5 d Valacyclovir 500 mg PO BID x3 d or 1000 mg PO once daily x5 d	Genital pain, urethritis, cervicitis, aseptic meningitis, increased risk of acquiring and transmitting HIV
Infectious Syphilis (*Treponema pallidum*)	1°: chancre (painless sore), regional lymphadenopathy 2°: rash and flu-like symptoms, meningitis, headache, uveitis, retinitis, condyloma lata, mucous lesions, alopecia Latent Phase: asymptomatic 3°: neurologic, cardiovascular, and tissue complications	Specimen collection from 1° and 2° lesions, screen high-risk individuals with serologic syphilis testing (VDRL), universal screening of pregnant women	Benzathine penicillin G 2.4 million units IM single dose For late latent, syphilis, 2.4 million units IM penicillin G once a week x3 wk Notify partners (last 3-12 mo) Continuous follow-up and testing until patients are seronegative	Chronic neurologic and cardiovascular sequelae, increased risk of acquiring and transmitting HIV

F = females; M = males
*N.B. if urethritis/cervicitis is suspected, always treat for both gonococcal and nongonococcal types (i.e. ceftriaxone AND azithromycin)
**Most common reportable STI in Canada

Sinusitis

• see Otolaryngology, OT25

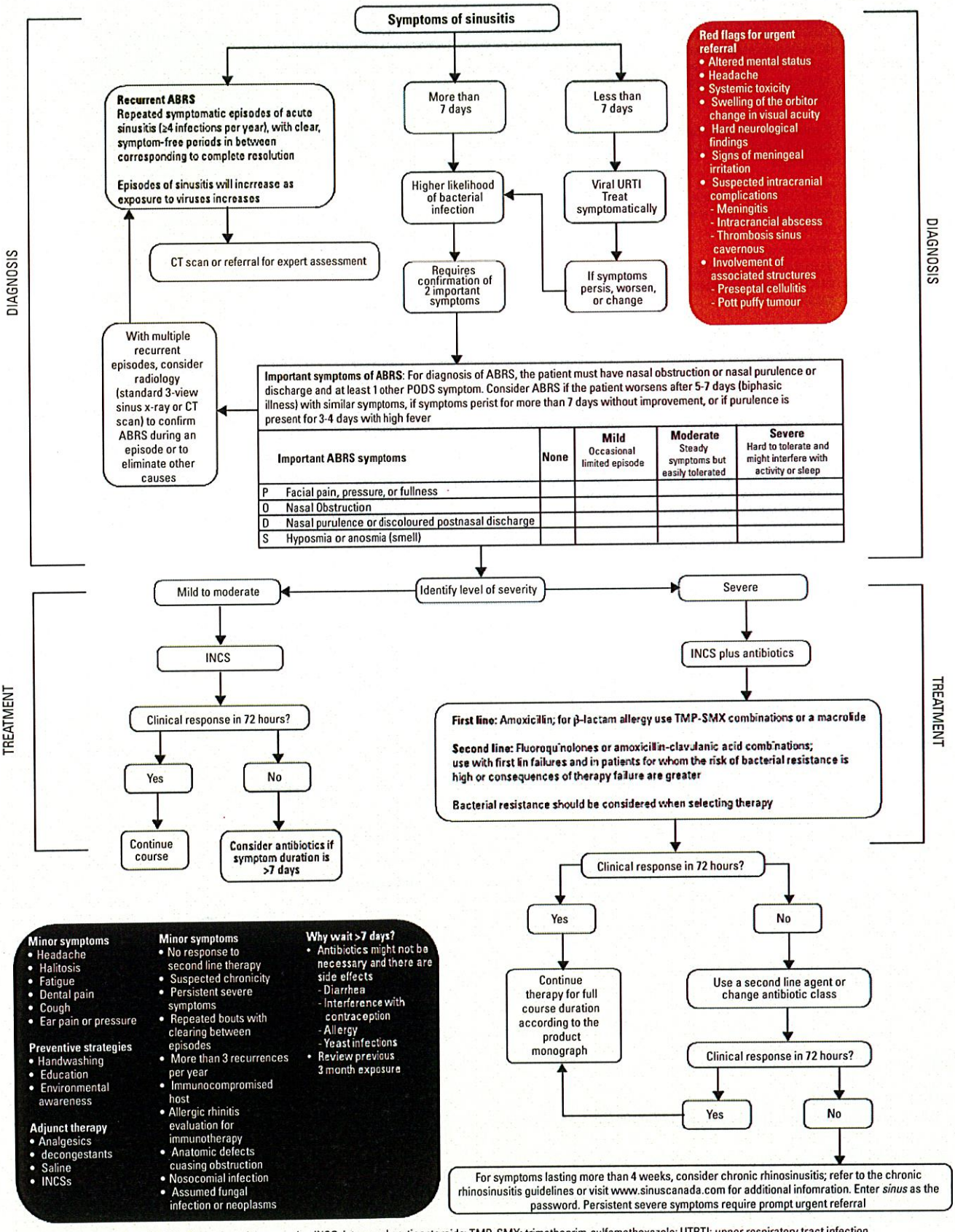
Definition
•acute or chronic inflammation of the sinuses, often also involving the nasal cavities

Etiology
•viral etiology is more common
•viral: rhinovirus, influenza, parainfluenza
• bacterial: *S. pneumoniae, H. influenzae, M. catarrhalis*

Clinical Presentation
•often presents with PODS(facial Pain, pressure, or fullness; nasal Obstruction; nasal purulence or discoloured postnasal Discharge; and Smell disorder), symptoms (see *Figure 16, FM48*)

Management of Acute Sinusitis
•for symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants
•antihistamines are ineffective
•mild to moderate acute bacterial sinusitis: intranasal corticosteroids
•severe acute bacterial sinusitis: antibiotics and intranasal corticosteroids
- first-line antibiotic is amoxicillin, and second line may include amoxicillin-clavulanic acid or a fluoroquinolone
- ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, or ≥4 episodes/yr, refer urgently for the red flags listed in the sidebar

Red Flags for Urgent Referral
- Altered mental status
- Headache
- Systemic toxicity
- Swelling of the orbit or change in visual acuity or extraocular muscles
- Hard neurological findings
- Signs of meningeal irritation
- Suspected intracranial complications (meningitis, intracranial abscess, cavernous sinus thrombosis)
- Involvement of associated structures (periorbital cellulitis, Pott's puffy tumour)



ABRS: acute bacterial rhinosinusitis; CT: computed tomography; INCS: intranasal corticosteroids; TMP-SMX: trimethoprim-sulfamethoxazole; UTRTI: upper respiratory tract infection

Figure 16. Diagnosis and management of sinusitis

ABRS = acute bacterial rhinosinusitis

Adapted from: Kaplan A. Canadian guidelines for acute bacterial rhinosinusitis. Can Fam Physician. 2014 Mar;60(3).

Sleep Disorders

• see Respirology, R29 and Neurology, N48

Definition and Clinical Presentation

•most often characterized by one of three complaints: insomnia, parasomnias, excessive daytime sleepiness
•insomnia: difficulty falling asleep, difficulty maintaining sleep, early morning wakening, non-refreshing sleep
•parasomnias: night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
•excessive daytime sleepiness: abnormal fatigue or tiredness extending into waking hours

Epidemiology

•1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems

Etiology

•primary sleep disorders
  ▪ primary insomnia, narcolepsy, OSA, restless leg syndrome, periodic limb movements of sleep
• secondary causes
  ▪ medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD, pregnancy, neurological disorders
  ▪ drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids, decongestants, amphetamine, cocaine, modafinil, - acetylcholinesterase inhibitors, dopamine agonists, and others
  ▪ psychiatric: mood and anxiety disorders
  ▪ lifestyle factors: shift work, jet lag

Risk Factors for OSA

- Male gender
- Obesity (due to upper airway narrowing). BMI >28 kg/m2 present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroglossia), neuromuscular disease
- FMHx

Investigations

•complete sleep diary every morning for 1-2 wk, see https://app.consensussleepdiary.com/#/
  ▪ record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
•rule out specific medical problems (e.g. CBC and differential, TSH)
•refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

Management of Specific Problems

• primary insomnia
  ▪ person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
  ▪ consider asking the patient if they have questions or fears about sleep that you might be able to address
  ▪ treat any suspected medical or psychiatric cause
  ▪ exercise regularly, avoid heavy exercise within 3 h of bedtime
  ▪ first-line treatment (CBT)
    ◆ sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
    ◆ relaxation therapy: deep breathing, meditation, biofeedback
    ◆ stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
    ◆ sleep restriction therapy: total time in bed should closely match the total sleep time of the patient
    ◆ address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
  ▪ pharmacologic treatment (used to supplement CBT; short-term prescription of <14 d with appropriate follow-up in 7-14 d):
    ◆ short-acting benzodiazepines (e.g. lorazepam) are used cautiously in exceptional circumstances, due to the risk of dependence, to:
      – break the cycle of chronic insomnia
      – manage an exacerbation of previously controlled insomnia
    ◆ non-benzodiazepines: zopiclone, zolpidem, melatonin, sedating antidepressants (e.g. amitriptyline, trazodone)
    ◆ if no progress or limited improvement on pharmacotherapy, consider referral to sleep medicine program
• snoring
  ▪ results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  ▪ physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  ▪ investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)

- treatment
  - sleep on side (position therapy), weight loss
  - nasal dilators, tongue-retaining devices, mandibular advancement devices
- at risk of developing OSA

- OSA
  - apnea (no breathing for ≥10 s) resulting from partial or complete upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present
  - leads to a distinctive snorting, choking, awakening-type pattern as the body rouses itself to open the airway
  - apneic episodes can last from 20-180 s and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes/h of sleep
  - consequences
    - daytime somnolence, non-restorative sleep
    - poor social and work performance
    - mood changes: anxiety, irritability, depression
    - sexual dysfunction: poor libido, impotence
    - morning headache (due to hypercapnia)
    - HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
    - OSA is an independent risk factor for CAD
    - pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
    - memory loss, decreased concentration, confusion
  - investigations
    - evaluate BP, inspect nose, and oropharynx (enlarged adenoids or tonsils)
    - blood gas not helpful, TSH if clinically indicated
    - nocturnal polysomnography
  - treatment
    - modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
    - primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
    - surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy, and adenoidectomy (in children)
    - report patient to Ministry of Transportation if OSA is not controlled by CPAP

Sore Throat (Pharyngitis)

Definition
- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

Etiology
- viral: adenovirus, rhinovirus, influenza virus, RSV, Epstein-Barr virus (EBV), coxsackie virus, herpes simplex virus, cytomegalovirus (CMV), HIV
- bacterial: β-hemolytic *Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae, Fusobacterium necrophorum*

Epidemiology
- viral
  - most common cause (90% in adults is viral), occurs year round
- bacterial
  - Group A β-hemolytic *Streptococcus* (GABHS)
    - most common bacterial cause
    - occurs most often in winter months
    - 5-15% of adult cases and up to 30-40% of all pediatric cases of acute pharyngitis
    - most prevalent between 5-17 yr old

Clinical Presentation
- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - common viral infections
    - EBV (infectious mononucleosis)
      - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
    - coxsackie virus (hand, foot, and mouth disease)
      - primarily late summer, early fall
      - sudden onset of fever, pharyngitis, headache, abdominal pain, and vomiting



Red Flags in Patients with "Sore Throat"
- Persistence of symptoms longer than 1 wk without improvement
- Respiratory difficulty (particularly stridor, croup, etc.)
- Difficulty in handling secretions (peritonsillar abscess)
- Difficulty in swallowing (Ludwig's angina)
- Severe pain in the absence of erythema (supraglottitis/epiglottitis)
- Palpable mass (neoplasm)
- Blood in the pharynx or ear (trauma)

- appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
- ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet

◆ herpes simplex virus
- like coxsackie virus, but ulcers are fewer and larger
- pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash

• bacterial
- symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
- signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
- complications:
  - ◆ suppurative: abscess, sinusitis, otitis media, cervical adenitis, pneumonia
  - ◆ nonsuppurative: acute rheumatic fever, acute glomerulonephritis

Table 24. Modified Centor Score: Approach to Diagnosis and Management of GABHS

Criteria		Points
Cough absent?		1
History of fever >38°C?		1
Tonsillar exudate?		1
Swollen, tender anterior nodes?		1
Ages 5-14		1
Ages 15-44		0
Ages >45		–1
In communities with moderate levels of strep infection (10-20% of sore throats):		
Score	**0-2**	**3 or more**
Risk of GABHS	1-17%	28-53%
Suggested action	No further testing or antibiotics	Perform rapid antigen detection test (RADT) and treat with ABx if positive. For negative RADT and patient <20 yr, perform throat culture and treat with ABx if culture is positive. For negative RADT and patients ≥20 yr, no ABx should be given

Note: Patients who score 2 points should undergo RADT if they are under 18, immunocompromised, frail, or otherwise clinically unwell
Limitations:
*This score is not applicable to patients <5 yr
*If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used
Adapted from: Centor RM, et al. Med Decis Making 1981;1:239-46; Sykes EA, et al. Can Fam Physician. 2020 Apr; 66(4): 251-257.

Investigations

• suspected GABHS
- see *Table 24* for approach to diagnosis and management of GABHS
- gold standard for diagnosis is throat culture
- rapid antigen detection testing: high specificity (95-99%), but moderate sensitivity (85%)
- nucleic acid detection: high sensitivity (92%)
- populations at increased risk of GABHS complications, such as Indigenous peoples in Canada, are more likely to benefit from testing

• suspected EBV (infectious mononucleosis)
- peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")

Management

• viral pharyngitis
- antibiotics not indicated
- symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants

• GABHS
- antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
- 10 d of treatment required
- incidence of glomerulonephritis is not decreased with antibiotic treatment
- no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
- routine F/U and/or post-treatment throat cultures are not required for most patients
- F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier

• infectious mononucleosis (EBV)
- self-limiting course; antibiotics are not indicated
- symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
- avoid heavy physical activity and contact sports for at least 1 mo or until splenomegaly resolves because of risk of splenic rupture
- if acute airway obstruction, give corticosteroids and consult ENT

Palliative Care

Principles and Quality of Life

- early identification of patients who could benefit from a palliative approach to care
- support, educate, and treat both patient and family
- address physical, psychological, social, and spiritual needs
- establish a multidisciplinary team
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End-of-Life Care Discussions

- see Palliative Medicine, PM6

Power of Attorney

- see Ethical, Legal, and Organizational Medicine, ELOM15

Instructional Advance Directives

- see Ethical, Legal, and Organizational Medicine, ELOM19

Symptom Management

- see Palliative Medicine, PM9

Complementary and Integrative Medicine

Prevalence and Use

- 50-75% of Canadians report some use of CAM over their lifetime, but only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy, natural health products
- Indigenous peoples may receive support from a Traditional Healer in addition to receiving allopathic/colonial medical care
- try to be cautious about your own feelings about and experiences with different types of medicine; avoid dismissing or shaming

Natural Health Products (NHPs)

- over 50% of Canadians use NHPs
- most commonly used NHPs include: echinacea, ginseng, ginkgo, garlic, St. John's wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials (though many have been used for millennia)
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - are you allergic to any plant products?
  - are you pregnant or breastfeeding?
- information resources: National Centre for CAM (https://www.nccih.nih.gov/), Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/regulation.html)



Serum Creatinine Does Not Reflect Creatinine Clearance in the Elderly

Instead, use:
CrCl = (weight in kg)(140 – age)(1.23)
(mL/min) (serum creatinine in μmol/L)

Multiply by 0.85 for females

Limitations:
Underestimates CrCl in patients without significant age-related decline in renal function
Overestimates CrCl in patients with muscle mass reduced beyond normal aging



Approach to Medication Review in the Elderly
Ask patient to bring all their current medications:

- Review Beers Criteria (2019) to identify potentially inappropriate medications
- Consider consulting https://deprescribing.org
- Screen for adverse drug effects and drug interactions
- Eliminate unnecessary medications (duplicate therapies or pharmacologic effects)
- Simplify dosing regimen where possible
- Discuss patient's goals of care to guide pharmacologic management of symptoms/disease
- Establish patient's understanding of medications and directions for use
- For tapering off sedatives, consider this tool: http://www.criugm.qc.ca/images/stories/les_chercheurs/risk_ct.pdf



Most Common Uses of CAM

- Back/neck problems
- Gynecological problems
- Anxiety
- Headaches
- Digestive problems
- Chronic fatigue syndromes

Table 25. Common Herbal Products

Common Name	Reported Uses	Possible Adverse Effects	Possible Drug Interactions
Black Cohosh	Menopausal symptoms, PMS, labour induction	Hepatitis, liver failure, GI discomfort, rashes	None reported
Chamomile	Mild sedative, anxiolytic, GI complaints, skin conditions (topical)	Allergic/contact dermatitis, anaphylaxis	Anxiolytics, sedatives, cyclosporine, warfarin
Echinacea	Common cold, flu, wound treatment, URTI, cancer	Hypersensitivity, GI discomfort, avoid use if immunosuppressed	None reported
Evening Primrose	PMS, breast pain, menopausal symptoms, eczema, RA	Headache, nausea, diarrhea, stomach upset, may increase risk of some pregnancy complications	Anticoagulants, antiplatelets
Feverfew	Migraine prevention, headache, RA, anti-inflammatory, fever, menstruation problems, psoriasis, allergies, asthma, tinnitus, dizziness, nausea, vomiting, intestinal parasites	Nausea, GI discomfort, irritation of mouth/skin, miscarriage (may affect uterine contractions), "post-fever few syndrome" (headaches, sleep disturbances, myalgias, arthralgias experienced after discontinuing feverfew)	Anticoagulants
Flaxseed Oil	Laxative, menopausal symptoms, source of omega-3 fatty acids, dietary supplement for DM, cholesterol, cancer	Diarrhea, raw/unripe flaxseeds may contain potentially toxic compounds, can worsen constipation if not taken with plenty of water	Do not take with other medications as fibre content can bind drugs
Garlic	Elevated lipids/cholesterol, atherosclerosis prevention, HTN, common cold, cancer prevention	Breath/body odour, GI irritation, contact dermatitis (raw garlic) May increase postoperative bleeding	Anticoagulants, saquinavir (HIV drug)
Ginger	Nausea, motion sickness, chemotherapy or pregnancy-induced nausea, RA, osteoarthritis	Heartburn, abdominal discomfort, diarrhea, gas, increased flow of bile (use with caution in gallstone disease), not to be used for morning sickness	Anticoagulants
Ginkgo Biloba	Increases peripheral circulation (Alzheimer's disease, dementia, intermittent claudication), eye problems, tinnitus, premenstrual syndrome, vertigo	Headache, stomach upset, bleeding, severe allergic reactions (whole plant/seeds/pulp), poisonous if ingested raw/roasted	Anticoagulants, ASA
Ginseng	Energy enhancer, decreases stress, adjunct support for chemotherapy/radiation	HTN, nervousness, insomnia, breakthrough bleeding, palpitations	Stimulant medications, antihypertensives, hormonal therapies
Glucosamine (Chondroitin)	Osteoarthritis	May cause kidney damage with long-term use, impaired glucose tolerance	Anticoagulants, caution if shellfish allergy
Saw Palmetto	BPH (adjunct to finasteride), chronic pelvic pain, decreased libido, migraine, hair loss	Mild GI distress, headache	None known
St. John's Wort	Mild to moderate depression, dietary supplement for menopausal symptoms, attention-deficit hyperactivity disorder, OCD, bladder problems, anxiety, sleep disorders, wound healing, dermatologic conditions (topical)	Photosensitivity, anxiety, dry mouth, GI symptoms, fatigue, sexual dysfunction, drowsiness, dizziness, headache, confusion	Antidepressants (SSRIs), OCPs, cyclosporine, digoxin, irinotecan (cancer medication), anticoagulants, contraindicated with indinavir
Valerian Root	Sedative, anxiolytic, depression, menopausal symptoms	Drowsiness, dizziness, headache, itching, digestive problems	CNS depressants, antihistamines, other sedatives

Zink T, Chaffin J. Herbal "health" products: What family physicians need to know. American Family Physician 1998;58:1133-1140; NIH National Centre for Complementary and Alternative Medicine website (http://nccam.nih.gov/)

Antimicrobial Quick Reference

Condition	Microorganisms	Antimicrobial
RESPIRATORY/ENT		
Acute Rhinitis (common cold)	Rhinovirus, coronavirus, influenza, RSV, parainfluenza, adenovirus	None
Pharyngitis (sore throat)	Rhinovirus, adenovirus, influenza, parainfluenza, coxsackie virus, coronavirus	None
Streptococcal Pharyngitis	Group A β-Hemolytic *Streptococcus*	**Children:** 1st line: If ≤27 kg, penicillin V 250 mg BID-TID x 10 d; if >27 kg: 500 mg BID-TID x 10 d use amoxicillin 50 mg/kg daily orally (maximum 1000 mg daily) x10 d. May be administered once daily or in 2 equally divided doses penicillin allergy (mild): cephalexin 40 mg/kg/d divided BID for 10 d (maximum 500 mg/dose) penicillin allergy (severe or anaphylaxis): Azithromycin 12 mg/kg/d (maximum 500 mg/dose) for 5 d **Adults:** 1st line: penicillin V 300 mg PO TID or 600 mg BID x 10 d penicillin allergy (mild): Cephalexin 500 mg PO BID x 10 d penicillin allergy (severe or anaphylactic): Azithromycin 12 mg/kg/d (maximum 500 mg/dose) x 5 d
Sinusitis	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *S. aureus*	**Children:** 1st line: amoxicillin/clavulanate 45 mg/kg/d divided BID (max 3 g/d) x 10 d 2nd line: amoxicillin/clavulanate 90 mg/kg/d divided BID (max 3 g/d) x 10 d penicillin allergy (mild): 3rd generation cephalosporin penicillin allergy (severe or anaphylactic): levofloxacin 10-20 mg/kg/d divided every 12 or 24 h **Adults:** 1st line: amoxicillin 500 mg PO TID x 5-10 d penicillin allergy: doxycycline 100 mg PO BID x 5-10d 2nd line or have risk factors for antibiotic resistance: amoxicillin/clavulanate 500 mg PO TID or 875 mg PO BID (7:1 formulation) x 5-10 d or respiratory fluoroquinolone such as levofloxacin 750 mg PO once daily or moxifloxacin 400 mg PO daily x5 d
Acute Otitis Media	*S. pneumoniae* *H. influenzae* *M. catarrhalis* Group A Strep *S. aureus*	**Children:** Treat with antibiotics if under age 6 mo If ages 6-24 mo, watchful waiting appropriate if parents can observe child for 48 h with plan to either reassess the child in 24-48 h; OR have the caregiver return if the child worsens anytime within 48 h OR provide an antimicrobial prescription to be filled if the child does not improve 10 d course if ages <24 mo, 5 d course if ages ≥24 mo 1st line: amoxicillin 75-90 mg/kg/d PO divided BID (max 3 g/d) penicillin allergy: cefuroxime acetil 30 mg/kg/d divided 2-3 times daily 2nd line: amoxicillin/clavulanate 45-60 mg/kg/d PO divided TID (7:1 formulation) x 10 d if under 35 kg amoxicillin/clavulanate 500 mg PO TID (7:1 formulation) x 10 d if over 35 kg Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops BID x 5 d **Adults:** 1st line: amoxicillin 500 mg PO TID x 7-10 d 2nd line: amoxicillin/clavulanate 500 mg PO TID or 875 mg PO BID x 7-10 d Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops BID x 5 d
Otitis Externa	*P. aeruginosa* Coliforms *S. aureus*	With or without tympanic membrane perforation: Ciprodex 4 drop BID x 7 d Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO BID x 4-8 wk
Bronchitis	*H. influenzae*, parainfluenza, coronavirus, rhinovirus, RSV	None
Community Acquired Pneumonia: Outpatient without Comorbidity	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae*	1st line: amoxicillin 1000 mg PO TID x 5-7 d (for patients over age 50 where mycoplasma infection is less likely) if atypical organisms present, add either of the following: clarithromycin 500 mg PO BID or 1000 mg (ER) PO once daily x 5-7 d azithromycin 500 mg PO on 1st d then 250 mg PO once daily x 4 d or 500 mg PO once daily x 3 d 2nd line: doxycycline 200 mg PO on 1st d then 100 mg PO BID x 5-7 d amoxicillin/clavulanate 875 mg PO BID x 5-7 d **PLUS** clarithromycin, azithromycin, or doxycycline as above if treatment failure: levofloxacin 500-750 mg PO once daily x 5 d OR moxifloxacin 400 mg PO once daily x 5 d
Community Acquired Pneumonia: Outpatient with Comorbidity	S. pneumoniae M. pneumoniae C. pneumoniae H. influenzae	
Dental Infections/Periapical and Periodontal Abscesses	Oral Flora	penicillin V potassium 500 mg PO QID x 7-10 d clindamycin 300 mg PO QID or 600 mg BID x 7-10 d
GASTROENTEROLOGY		
Diarrhea – Enteritis	*Enterotoxigenic E. coli* *Campylobacter* *Salmonella* *Shigella* Viruses Protozoa	azithromycin is the preferred agent given growing resistance to quinolones, particularly in Southeast Asia azithromycin 1000 mg PO single dose or 500 mg PO once daily x 1-3 d (children: 10 mg/kg/d x 3 d) ciprofloxacin 750 mg PO single dose or 500 mg PO BID x 1-3 d (prevention: 500 mg PO once daily) levofloxacin 500 mg PO once daily x 1-3 d (prevention: 500 mg PO once daily)
Diarrhea – Post Antibiotics (common with clindamycin)	*C. difficile*	Mild to moderate (WBC <15 x 10^9/L and Cr <1.5 x baseline): vancomycin 125 mg PO QID x 10-14 d (children: vancomycin 40 mg/kg daily divided in 4 doses) Severe (WBC ≥15 x 109/L and Cr ≥1.5 x baseline): vancomycin 125 mg PO QID x 10-14 d (children: vancomycin 40 mg/kg/d PO divided TID-QID x 10-14 d max 500 mg/d)
Peptic Ulcer Disease (non-NSAID related)	*H. pylori*	PPI PO BID + amoxicillin 1000 mg PO BID + clarithromycin 500 mg PO BID + metronidazole 500 mg PO BID x 7 d OR PPI PO BID + bismuth subsalicylate 525 mg PO QID + metronidazole 500 mg PO QID + tetracycline 500 mg PO QID x 7-14 d PPI: lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg or rabeprazole 20 mg

Condition	Microorganisms	Antimicrobial
DERMATOLOGIC		
Head and Pubic Lice (crabs)	*Pediculus humanus capitis* *Phthirus pubis*	permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk
Vulvovaginal Candidiasis	*Candida*	Treat only if patient is symptomatic fluconazole 150 mg PO x 1 dose miconazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally QHS x 7 d Multiple other OTC azole treatments
Bacterial Vaginosis	Overgrowth of: *G. vaginalis* *M. hominis* Anaerobes	If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynaecologic surgery, induced abortion, or upper tract instrumentation 1st line: metronidazole 500 mg PO BID x 7 d metronidazole 0.75% gel: one applicator (5 g) intravaginally QHS x 5 d clindamycin 2% cream: one applicator (5 g) intravaginally QHS x 7 d 2nd line: metronidazole 2 g PO x 1 dose clindamycin 300 mg PO BID x 7 d
Herpes	Herpes simplex virus	1° episode: acyclovir 400 mg PO TID x 5-10 d OR famciclovir 250 mg PO TID x 5 d OR valacyclovir 1000 mg PO BID x 10 d Recurrent Episode: acyclovir 800 mg PO TID x 2 d or 800 mg PO BID x 5 d famciclovir 1000 mg PO BID x 1 d or 125 mg PO BID x 5d or 500 mg PO once followed by 250 mg PO BID x 2 d valacyclovir 500 mg PO BID x 3 d or 1000 mg PO once daily x 5 d Pregnancy: 1° episode: acyclovir 400 mg PO TID TID x 7-10 d OR valacyclovir 1 g PO BID x 7-10 d Prior infection within previous yr: acyclovir 800 mg PO BID x 5 d or 800 mg PO TID x 2 or valacyclovir 500 mg PO BID x 3 d or 1g PO OD x 5 d daily suppressive therapy: acyclovir 400 mg PO TID daily or valacyclovir 500 mg PO BID at 36 wk
Gonorrhea/Chlamydia	*N. gonorrhoeae* *C. trachomatis*	ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO x 1 dose OR doxycycline 100 mg PO BID x 7 d No intercourse for one week after treatment
Mastitis	*S. aureus* *S. pyogenes*	cloxacillin 500 mg PO QID x 7 d cephalexin 500 mg PO QID x 7 d
Tinea Cruris/Pedis (jock itch/ athlete's foot)	*Trichophyton*	clotrimazole 1% cream BID ketoconazole 2% cream BID
Uncomplicated Cellulitis	*S. aureus* Group A Strep.	**Children:** 1st line: cephalexin 50-100 mg/kg/d divided QID x 10-14 d 2nd line: cloxacillin 50 mg/kg/d divided QID x 10-14 d clindamycin 25 mg/kg/d x 10-14 d **Adults:** 1st line: cephalexin 500 mg PO QID x 10-14 d 2nd line: cloxacillin 500 mg PO QID x 10-14 d clindamycin 300 mg PO x 10-14 d

Landmark Family Medicine Trials

Trial Name	Reference	Clinical Trial Details
HYPERTENSION		
DASH	N Engl J Med 1997; 336:1117-1124	**Title:** A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure **Purpose:** To assess the impacts of dietary modifications on blood pressure patterns. **Methods:** RCT involving 459 patients randomized to receive a control diet, a diet rich in fruits and vegetables, or a combination diet rich in fruits, vegetables and low-fat dairy products. **Results:** The combination diet exhibited the most promising results. In normotensive patients the combination diet reduced systolic and diastolic pressure by 5.5 and 3.0 mmHg more than the control diet, respectively. Amongst patients with hypertension the combination diet reduced systolic and diastolic blood pressure by 11.4 and 5.5 mmHg, respectively. **Conclusion:** The combination diet exhibited promising results for the reduction of blood pressure.
Systolic blood pressure intervention trial (SPRINT)	N Engl J Med 2015; 373:2103-2116	**Title:** Intensive vs. Standard Blood Pressure Control **Purpose:** To assess the effectiveness of various targets for systolic BP with regard to lowering CV mortality **Methods:** RCT including 9361 patients with a systolic BP >130 mmHg and high risk for CV events. Patients were randomized to a target BP of 120 mmHg (standard target) or 140mmHg (intensive target). The outcomes of interest were MI, acute coronary syndromes, stroke, HF, or death. **Results:** After 3 yr of follow up the prevalence of cardiovascular complications were significantly reduced within the intensive treatment group when compared to the standard treatment group - 1.65%/yr and 2.19%/yr, respectively. **Conclusion:** With regard to patients who are at high risk for CV events, intensive treatment of their BP resulted in decreased incidence of major CV complications.
Heart outcomes prevention evaluation-3 (HOPE-3)	N Engl J Med 2016; 374:2021-2031	**Title:** Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease **Purpose:** To assess the benefits of statins in intermediate-risk populations without CV disease. **Methods:** RCT consisting of 12705 patients who did not presently have CV disease but were deemed to be at intermediate risk. Patients were randomized to receive either 10mg of rosuvastatin per day or a placebo. The outcome of interest were death by CV cause, non-fatal MI, or non-fatal stroke. **Results:** LDL levels were reduced by 26.5% within the treatment group in comparison to those that received the placebo. The prevalence of vascular events was significantly reduced within the rosuvastatin group (3.7%) when compared to the placebo group (4.8%). **Conclusion:** The use of rosuvastatin in an intermediate-risk group without CV disease reduced the prevalence of vascular events when compared to those that did not receive treatment.

Trial Name	Reference	Clinical Trial Details
Chronic hypertension and pregnancy (CHAP)	N Engl J Med. 2022;386(19):1781	**Title:** Treatment for Mild Chronic Hypertension during Pregnancy **Purpose:** Historically, only severe HTN (BP ≥160/110 mmHg) was treated. This study aims to assess the benefits of treating mild chronic non-severe HTN (BP ≥140/90 mmHg). **Methods:** RCT consisting of 2408 pregnant women with mild chronic HTN and singleton fetuses at a gestational age of less than 23 wk. Patients were randomized to receive the standard medication for severe HTN in pregnant women or no treatment at all. Primary outcomes were preeclampsia, medically indicated preterm birth (<35 wk gestation), placental abruption, or fetal/neonatal death. **Results:** The incidence of the primary outcome was substantially lower within the treatment group as opposed to the control group - 30.2% and 37.0%, respectively. **Conclusion:** Targeting a BP below 140/90 mmHg using anti-HTN medications resulted in improved health and pregnancy outcomes.
MENOPAUSE/HORMONE REPLACEMENT THERAPY		
Women's Health Initiative Trial	JAMA 2002;288:321-333	**Title:** Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women **Purpose:** To assess the impacts of combined hormone therapy in healthy post-menopausal women. **Methods:** RCT consisting of 16608 postmenopausal women with an intact uterus. Participants were randomized to combined estrogen and progesterone, or a placebo. The outcomes of interest were coronary heart disease (CHD) and breast cancer. **Results:** Amongst the treatment group there were 286 cases of CHD, and 290 cases of breast cancer. **Conclusion:** Results show that the overall health risks exceed the benefits of the combined hormone therapy.
HEART FAILURE		
IRONMAN	Lancet 2022;400:2199-2209	**Title:** Intravenous Ferric Derisomaltose in Patients with Heart Failure and Iron Deficiency **Purpose:** To determine the effects of IV ferric derisomaltose on CV events in patients with HF. **Methods:** RCT of 1137 patients with HF (Left ventricular ejection fraction ≤ 45%) and transferrin saturation <20% or serum ferritin <10µg/L who were randomly assigned to receive ferric derisomaltose or standard of care. Primary outcomes were recurrent hospital admissions for HF and CV-related death. **Results:** The ferric derisomaltose-treated group had 336 primary endpoints (22.4 per 100 patient-years) whereas the standard of care group had 411 (27.5 per 100 patient-years) (RR 0.82; 95%CI, 0.66 to 1.02). Fewer serious cardiac adverse events were seen in the ferric derisomaltose group as compared to controls (difference -7.00%; 95% CI, -12.69 to -1.32; p=0.016). **Conclusion:** Ferric derisomaltose is beneficial in patients with HF with reduced ejection fraction and iron deficiency as it is associated with reduced hospital admissions for HF and CV death.

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Dumping Syndrome
- early: 15-30 min postprandial
  - etiology
    - rapid emptying of hyperosmotic chyme leads to jejunal distention, stimulating release of vasoactive hormones
  - clinical features
    - postprandial epigastric cramping, bloating, emesis, nausea, and vasomotor symptoms (dizziness, palpitations, tachycardia, diaphoresis)
  - treatment
    - frequent small meals high in fibre and protein, low in carbohydrates; avoidance of liquids with meals
    - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late: 3 h postprandial
  - etiology: hypoglycemia following postprandial insulin peak
  - treatment: small snack 2 h after meals

Blind-Loop Syndrome
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features
  - anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
- treatment: broad-spectrum antibiotics and surgery (conversion to Billroth I)

Postvagotomy Diarrhea
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine) and surgical (reversed interposition jejunal segment)

SMALL INTESTINE

Small Bowel Obstruction

Mechanical Small Bowel Obstruction

Pathophysiology
- obstruction → gas and fluid (swallowed or GI secretions) accumulate proximal to site of obstruction and distal decompression → intestinal activity increases to overcome obstruction → colicky pain and diarrhea (initially)

Etiology

Table 14. Common Causes of SBO

Intraluminal Foreign Body	Intramural	Extramural (>85% of causes)
Intussusception	Crohn's	Adhesions from previous surgeries (75% SBO)
Gallstones (gallstone ileus)	Radiation stricture	Incarcerated hernia
Bezoars	Neoplasm (adenocarcinoma, carcinoid, lymphoma, sarcoma)	Peritoneal carcinomatosis
Foreign body		

- AAST grading system for severity (Grade - "Operative Criteria")
  - partial SBO - minimal intestinal distension with no evidence of obstruction
  - complete SBO with viable bowel - intestinal distension with transition point: no bowel compromise
  - complete SBO with compromised but viable bowel - intestinal distension with impending bowel compromise
  - complete SBO with nonviable bowel or perforation and localized spillage - intestinal distension with localized perforation or free fluid
  - small bowel perforation with diffuse peritoneal contamination - intestinal distension with perforation, free fluid, and diffuse peritonitis
- closed-loop obstruction is when a segment is obstructed in two separate locations, creating a segment with no proximal or distal outlet and can rapidly progress to complications and require immediate abdominal exploration

Risk Factors
- prior abdominal or pelvic surgery (adhesions)
- abdominal wall or groin hernia
- personal history or increased risk of malignancy
- prior radiation

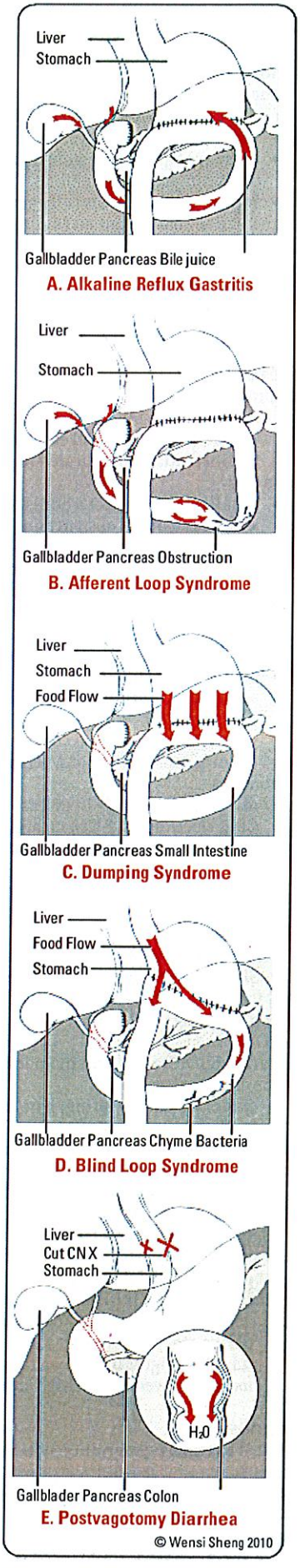


Figure 10. Complications of gastric surgery

- IBD
- history of foreign body ingestion

Clinical Features

- symptoms: colicky periumbilical abdominal pain, N/V, obstipation, delayed passage/inability to pass flatus, inability to tolerate an oral diet
  - more feculent vomitus suggests more established obstruction because of bacterial overgrowth
  - passage of gas and/or stool that continues 6-12 h after onset of symptoms suggests partial rather than complete obstruction
  - inability to pass flatus is the most useful indicator
- signs: abdominal distention (most prominent if obstruction at distal ileum), hyperactive proceeding to minimal bowel sounds, bloating, hypovolemia, hyperresonance with percussion
- strangulated obstruction: abdominal pain disproportionate to physical exam findings suggest intestinal ischemia
  - may have tachycardia, localized abdominal tenderness, fever, marked leukocytosis, and lactic acidosis

Investigations

- approach
  1. distinguish mechanical obstruction from ileus
  2. determine likely and easily reversible etiology of obstruction
  3. differentiate complicated (e.g. strangulated) obstruction
- imaging
  - usually if you suspect a bowel obstruction, a CT scan is the first line. Further, once CT scan confirms a bowel obstruction,, we perform 6 and 12 hour X-rays after giving water soluble contrast which is diagnostic for obstruction and often therapeutic
  - CT with IV contrast: discrete transition zone/point with proximal bowel dilation, distal bowel decompression, and intraluminal contrast does not pass the transition zone
    - most importantly to rule out ischemic bowel/strangulation: pneumatosis intestinalis (free air in bowel wall) and thickened bowel wall, air in portal vein, free intraperitoneal fluid, and differential wall enhancements (poor uptake of IV contrast into the wall of the affected bowel)
  - other (less common)
    - upper GI series/small bowel series (if no cause apparent, i.e. no hernias, and no previous surgeries)
    - serial CTs with oral contrast
    - may consider U/S or MRI in pregnant patients
- laboratory
  - may be normal early in disease course
  - CBC, electrolytes, BUN, creatinine, lactate
  - creatinine and hematocrit to assess degree of dehydration
  - may have fluid and electrolyte abnormalities with metabolic alkalosis due to frequent emesis
  - if strangulation: leukocytosis with left shift, elevated lactate (late signs)

Treatment

- IV isotonic fluid resuscitation and urine output monitoring with catheter
  - SBO related vomiting and decreased PO intake leads to volume depletion
- NG tube in the stomach for gastric decompression; decrease nausea, distention, and risk of aspiration from vomiting
- NPO
- if partial SBO/Crohn's/Carcinomatosis: conservative management with fluid resuscitation and NG tube decompression
  - 48 h of watchful waiting; if no improvement or develops complications, surgery
  - for Crohn's patients, consider GI consult for steroid management
- if no clinical features of ischemia: short course of conservative management with fluid resuscitation and NG tube decompression with frequent re-examination by surgical team
  - duration of observation varies from hours to a few days
  - if SBO fails to resolve, or if symptoms of ischemia develop, then surgery
- if high-risk for ischemia based on clinical symptoms: urgent surgery to prevent irreversible ischemia
  - early postoperative SBO: if bowel function does not return within 3-5 d after surgery; usually partial, extended conservative therapy (2-3 wk) with bowel rest, fluids, and TPN is appropriate
- immediate surgery if ischemia, necrosis, and perforation
  - clinical signs: fever, leukocytosis, tachycardia, worsening pain, metabolic and lactic acidosis, and tachypnea
  - radiologic signs: free air on radiographs or CT, closed-loop obstruction, abnormal course of a mesenteric vessel, and high-density free fluid

Prognosis

- related to etiology; mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%
- surgical intervention associated with a lower risk of recurrence

Prevention

- open surgery has four-fold increase in risk of SBO in 5 yr compared to laparoscopic surgery



Increased Risk of Perforation with Distention as seen on Abdomen Imaging
Small bowel ≥3 cm
Distal colon ≥6 cm
Proximal colon ≥9 cm
Cecum ≥12 cm



Important to know if chronic vs. acute. Chronic distention is more likely to be tolerated without perforation



Patients with NO Abdominal Surgery History ("Virgin Abdomen")
Presenting with a SBO should have surgery ASAP (EXCEPTION: malignant obstruction from history and imaging)

Patients with Abdominal Surgery History ("Non-virgin Abdomen")
Adhesional SBOs resolve spontaneously with NG tube decompression 70% of time



Top 3 Causes of SBO (in order)

ABC
Adhesions
Bulge (hernias)
Cancer (neoplasms)



Causes of SBO

SHAVING
Stricture
Hernia
Adhesions
Volvulus
Intussusception/IBD
Neoplasm
Gallstones

Paralytic Ileus

Pathogenesis
- temporary, reversible impairment of intestinal motility; most frequently caused by:
  - abdominal operations, infections and inflammation, medications (opiates, anesthetics, psychotropics), and electrolyte abnormalities
  - often seen for patients in the postoperative setting from intra-abdominal sepsis (perforated appendicitis, diverticulitis, etc.)
  - pathophysiology related to inhibitory splanchnic reflexes, inhibitory sympathetic activity, inflammatory stress response, peptides (VIP, substance P, Calcitonin gene-related peptide (CGRP))
- NOT the same as intestinal pseudo-obstruction
  - chronic pseudo-obstruction refers to specific disorders that affect the smooth muscle and myenteric plexus, leading to irreversible intestinal dysmotility

Clinical Features
- symptoms and signs of intestinal obstruction without mechanical obstruction
  - bowel sounds are diminished or absent (in contrast to initial hyperactive bowel sounds in SBO)
  - pain is often diffuse and less frequently has the colicky pattern present in mechanical obstruction
  - passing gas is the most useful indicator
- postoperative: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d

Investigations
- routine postoperative ileus: expected, no investigation needed
- if ileus persists or occurs without abdominal surgery
  - review patient medications (especially opiates)
  - measure serum electrolyte to monitor for electrolyte abnormalities (including extended electrolytes like Mg^{2+}, Ca^{2+}, PO_4^{3-})
  - creatinine and BUN
  - LFTs
  - CT scan to rule out abscess or peritoneal sepsis, or to exclude mechanical obstruction

Treatment
- address underlying cause
- most important initial treatment: NPO + fluid resuscitation
- for prolonged ileus: NG tube decompression, TPN, and pain management

Intestinal Ischemia

Etiology
- acute
  - arterio-occlusive mesenteric ischemia (AOMI)
    - thrombotic, embolic, and extrinsic compression (e.g. strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
    - mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  - mesenteric venous thrombosis (MVT)
    - consider hypercoagulable state (i.e. rule out malignancy) and DVT (prevents venous outflow)
- chronic: usually due to atherosclerotic disease – look for cardiovascular risk factors
- can lead to occlusion in vessels that supplies the small intestine and the large intestine



Pain "out of keeping with physical findings" is the hallmark of early intestinal ischemia

Clinical Features
- acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, and sepsis
- chronic: postprandial pain (from mesenteric angina), fear of eating, and weight loss
- common sites: SMA supplied territory, "watershed" areas of colon – splenic flexure, left colon, and sigmoid colon

Investigations
- laboratory: leukocytosis (non-specific) and lactic acidosis (late finding)
  - lactate used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, and free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, and pneumatosis
- CT angiography is the gold standard for acute arterial ischemia



An acute abdomen + metabolic acidosis is bowel ischemia until proven otherwise

Treatment
- fluid resuscitation, correct metabolic acidosis, NPO, NG tube decompression of stomach, and prophylactic broad-spectrum antibiotics; avoid vasoconstrictors and digitalis
- exploratory laparotomy/laparoscopy to assess extent of viability ± segmental resection of necrotic intestine
  - if extent of bowel viability is uncertain, a second-look laparotomy 12-24 h later is mandatory
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, and percutaneous transluminal angioplasty ± stent

Tumours of Small Intestine

BENIGN TUMOURS

- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum and proximal jejunum
- polyps
  - adenomas
  - hamartomas
  - FAP (see *Familial Colon Cancer Syndromes, GS42*)
  - juvenile polyps
- other: leiomyomas, lipomas, and hemangiomas

Table 15. Malignant Tumours of the Small Intestine

	Adenocarcinoma	Carcinoid/GI NET-Neuroendocrine Tumour	Lymphoma	Metastatic
Epidemiology	Usually 50-70 yr M>F	Increased incidence 50-60 yr	Highest incidence in 70s M>F Usually non-Hodgkin's lymphoma	Most common site of GI metastases in patients with metastatic melanoma
Risk Factors	Crohn's, FAP, history of CRC, HNPCC		Crohn's, celiac disease, autoimmune disease, immunosuppression, radiation therapy, and nodular lymphoid hyperplasia	Melanoma, breast, lung, ovary, colon, and cervical cancer
Origin/Location	Usually in proximal small bowel, incidence decreases distally	Classified based on embryological origin (foregut, midgut, and hindgut) Originate from gut enterochromaffin cell Appendix 46%, distal ileum 28%, rectum 17%	Usually distal ileum Proximal jejunum in patients with celiac disease	Hematogenous spread from breast, lung, and kidney Direct extension from cervix, ovaries, and colon
Clinical Features	Early metastasis to lymph nodes 80% metastatic at time of operation Abdominal pain (common)	N/V, anemia, GI bleeding, jaundice, and weight loss (less common) Often slow-growing Usually asymptomatic, incidental finding Obstruction, bleeding, crampy abdominal pain, and intussusception Carcinoid syndrome (<10%) Hot flashes, hypotension, diarrhea, bronchoconstriction, and right heart failure Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver)	Fatigue, weight loss, fever malabsorption, abdominal pain, anorexia, vomiting, constipation, and mass Rarely perforation, obstruction, bleeding, and intussusception	Obstruction and bleeding
Investigations	CT abdomen/pelvis Endoscopy	Most found incidentally at surgery for obstruction or appendectomy CT thorax/abdomen/pelvis Consider small bowel enteroclysis to look for primary Serum chromogranin A as a tumour marker Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood Some nuclear medicine testing available but should be done by endocrine oncologist. Testing includes Galium DOTATATE PET scans and octreotide scans	CT abdomen/pelvis	CT abdomen/pelvis
Treatment	Surgical resection ± chemotherapy	Surgical resection ± chemotherapy Carcinoid syndrome treated with octreotide Metastatic risk 2% if size <1 cm, 90% if >2 cm	Low-grade: chemotherapy with cyclophosphamide High-grade: surgical resection, and radiation Palliative: somatostatin, doxorubicin	Palliation
Prognosis	5 yr survival 25% (if node positive)	5 yr survival 70%; 20% with liver metastases Based on the Ki67 index	5 yr survival 40%	Poor
Staging System	TNM	TNM	Ann Arbor	

Carcinoid Syndrome Symptoms

FDR
Flushing
Diarrhea
Right-sided heart failure

Indirect Inguinal Hernias: Rule of 5s

5% lifetime incidence in males
5x more common than direct inguinal hernias
5-10x more common in males than females
Generally occur by **5**th decade of life

Short Gut Syndrome

Definition
- reduced surface area (length) of small bowel causing insufficient intestinal absorption leading to diarrhea, malnutrition, and dehydration

Etiology
- due to surgical resection
  - large amount of bowel at once (acute mesenteric ischemia, trauma, malignancies)
  - cumulative resections (Crohn's disease)
- in infant and pediatric patients, the most common causes are necrotizing enterocolitis, abdominal wall defects, jejunal ileal atresia, and midgut volvulus

Prognostic Factors
- residual small bowel length, residual colon length (reabsorption of water and electrolytes and some reabsorption of nutrients), condition of the remnant small bowel (healthier bowel facilitate better reabsorption), presence of ileocecal valve (delay transition into colon leading to more reabsorption)
- resection of ileum is less tolerated than resection of jejunum (ileum reabsorbs bile salt and vitamin B_{12})

Therapy
- medical
  - IV fluids in acute management (initial 3-4 wk following resection) and TPN once stabilized to replenish lost fluid and electrolytes in diarrhea
  - histamine 2-receptor antagonist or PPI to prevent gastric acid secretion
  - antimotility agent to prolong transit time in the small intestine
  - consider octreotide to decrease GI secretion and cholestyramine for bile acid absorption
- surgical: non-transplant
  - to slow transit time: small bowel segmental reversal, intestinal valve construction, or electrical pacing of small bowel
  - to increase intestinal length:
    - LILT (longitudinal intestinal lengthening and tailoring) procedure
    - STEP (serial transverse enteroplasty procedure) in dilated small bowels
- surgical: small bowel transplant
  - indication: life-threatening complication from intestinal failure or long-term TPN, including liver failure, thrombosis of major central veins, recurrent catheter-related sepsis, and recurrent severe dehydration

Abdominal Hernia

- see *Hiatus Hernia, GS23*

Definition
- defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

Epidemiology
- M:F=9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, and 3-8% umbilical
- most common surgical disease in males

Risk Factors
- activities which increase intra-abdominal pressure
  - obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, and heavy lifting
- congenital abnormality (e.g. patent processus vaginalis and indirect inguinal hernia)
- previous hernia repair, especially if complicated by wound infection
- loss of tissue strength and elasticity (e.g. hiatal hernia, aging, and repetitive stress)
- family history

Clinical Features
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

Investigations
- physical examination usually sufficient
- U/S ± CT (CT required for obturator hernias, internal abdominal hernias, and Spigelian and/or femoral hernias in obese patients)



Inguinal Hernias

MD's don't LIe
MD: Medial to the inferior epigastric a. = Direct inguinal hernia
LI: Lateral to the inferior epigastric a. = Indirect inguinal hernia
Inguinal Canal Walls = MALT x 2

2 M Roof	2 muscles (internal oblique, transversus abdominis)
2 A Ant. wall	2 aponeuroses (external and internal oblique)
2 L Floor	2 ligaments (inguinal and lacunar)
2 T Post. wall	2T (transversalis fascia, conjoint tendon)



Borders of Hesselbach's Triangle
- Lateral: inferior epigastric artery
- Inferior: inguinal ligament
- Medial: lateral margin of rectus sheath



Shouldice Technique vs. Other Open Techniques for Inguinal Hernia Repair
Cochrane DB Syst Rev 2012;4:CD0001543
Purpose: To evaluate the efficacy and safety of the Shouldice technique compared to other non-laparoscopic techniques.
Results/Conclusions: 16 RCTs or quasi-randomized RCTs with 2566 hernias (1121 mesh; 1608 non-mesh). The recurrence rate with Shouldice was higher than mesh (OR 3.80, 95% CI 1.99-7.26) but lower than non-mesh (OR 0.62, 95% CI 0.45-0.85). There was no difference in chronic pain or complications. In conclusion, with respect to recurrence rates, Shouldice herniorrhaphy is the best non-mesh technique, although inferior to mesh. However, it is also more time consuming and results in slightly longer postoperative hospital stays.



Long-Term Results of a Randomized Controlled Trial of a Nonoperative Strategy (Watchful Waiting) for Men with Minimally Symptomatic Inguinal Hernias
Ann Surg 2013;258:508-514
Purpose: Ascertaining the long-term crossover (CO) rate in patients with asymptomatic or minimally symptomatic inguinal hernias undergoing watchful-waiting (WW) as their primary treatment modality.
Background: A 2006 RCT comparing WW with routine inguinal hernia repair, concluded that WW was an acceptable option in the management of male patients with minimal symptoms (JAMA 2006;295(3):285-292). This study analyzes the WW group after 7 yr of follow-up.
Conclusions: The estimated CO rate for the WW cohort was 68%, while men older than 65 had a rate of 79%. Therefore, while WW is a safe strategy, it is likely that symptoms will progress, and definitive surgical management will be indicated.



Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias
JAMA Surg 2013;148:1043-1048
See Landmark General and Thoracic Surgery Trials table for more information on outcomes of patients electively undergoing laparoscopic ventral hernia repair (LVHR) vs. open ventral hernia repair (OVHR)

Classification
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires emergency repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter's hernia: only part of bowel circumference (usually antimesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter's hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
- sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

Anatomical Types
- groin
  - indirect and direct inguinal, femoral
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre's (involving Meckel's), Amyand's (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications
- incarceration
- strangulation
  - small, new hernias more likely to strangulate
  - femoral > indirect inguinal > direct inguinal
  - intense pain followed by tenderness
  - intestinal obstruction, gangrenous bowel, sepsis
  - surgical emergency
  - DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous. This will result in reduction of gangrenous contents and subsequent need for laparotomy

Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, or for cosmesis; if asymptomatic, can delay surgery. Data has shown that prophylactic surgery does not affect rate of strangulation in ASYMPTOMATIC patients
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Postoperative Complications
- recurrence (15-20%)
  - risk factors: recurrent hernia, ages >50, smoking, BMI >25, poor preoperative functional status (ASA ≥3 – see Anesthesia, A4), associated medical conditions: T2DM, hyperlipidemia, immunosuppression, and any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/"tension-free" repair
- scrotal hematoma (3%)
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein
  - acute leg swelling
- ischemic colitis
- minimally invasive repair for ventral and umbilical hernia

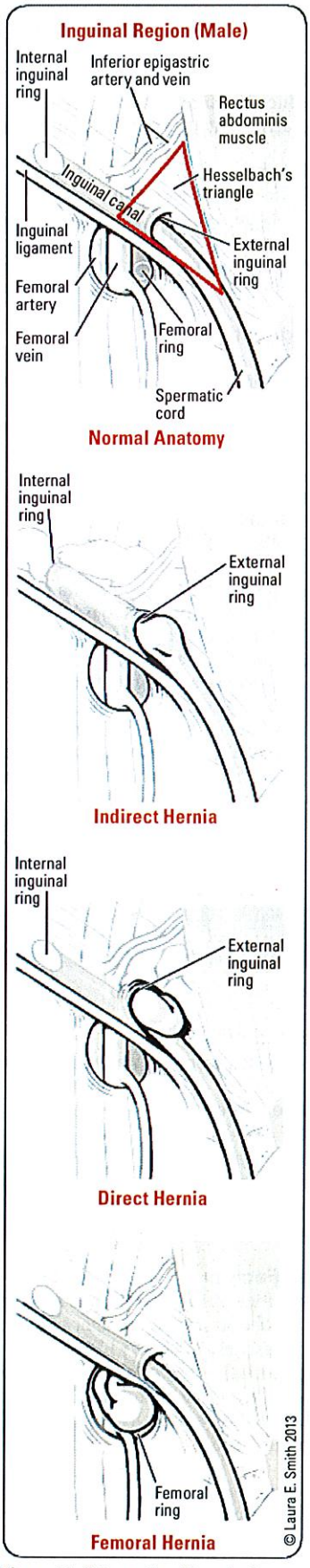


Figure 11. Schematic of inguinal (direct and indirect) and femoral hernias

Groin Hernias

Table 16. Groin Hernias

	Direct Inguinal	Indirect Inguinal	Femoral
Epidemiology	1% of all men	Most common hernia in men and women M>F	Affects mostly females
Etiology	Acquired weakness of transversalis fascia "Wear and tear" Increased intra-abdominal pressure	Congenital persistence of processus vaginalis in 20% of adults	Pregnancy weakness of pelvic floor musculature Increased intra-abdominal pressure
Anatomy	Through Hesselbach's triangle **Medial** to inferior epigastric artery Usually does not descend into scrotal sac	Originates in deep inguinal ring Lateral to inferior epigastric artery Often descends into scrotal sac (or labia majora)	Into femoral canal, below inguinal ligament but may override it Medial to femoral vein within femoral canal
Treatment	Surgical repair	Surgical repair	Surgical repair
Prognosis	3-4% risk of recurrence	<1% risk of recurrence	

Table 17. Superficial Inguinal Ring vs. Deep Inguinal Ring*

Superficial Inguinal Ring	Deep Inguinal Ring
Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle	Opening in transversalis fascia: palpable superior to mid-inguinal ligament
Medial border: medial crus of external oblique aponeurosis	Medial border: inferior epigastric vessels
Lateral border: lateral crus of external oblique aponeurosis	Superior-lateral border: internal oblique and transversus abdominis muscles
Roof: intercrural fibres	Inferior border: inguinal ligament

*see *Basic Anatomy Review, Figure 2, GS3*

Robotic Inguinal vs. Transabdominal Laparoscopic Inguinal Hernia Repair: The RIVAL Randomized Clinical Trial
JAMA Surg. 2020;155(5):380-387
Purpose: To determine whether a robotic approach to inguinal hernia repair results in improved postoperative outcomes compared with the traditional laparoscopic inguinal hernia repairs.
Results: At preoperative, 1 wk and 30 d assessments there were no differences between the groups on wound events, readmissions, pain, or quality of life. However, the robotic approach was associated with increased cost, operative time, and surgeon frustration compared to the laparoscopic approach.
Conclusions: There is no benefit of the robotic approach compared with the laparoscopic approach.

Appendix

Appendicitis

Epidemiology
- 6% of population, M>F (1.4:1)
- 80% between ages 5-35

Pathogenesis
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecalith, or obstructing neoplasm
  - other causes: parasites or foreign body

Clinical Features
- most reliable feature is progression of signs and symptoms
- low-grade fever (38°C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well-localized pain over McBurney's point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
- signs
  - inferior appendix: McBurney's sign (see sidebar), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness). McBurney's sign is present whenever the opening of the appendix at the cecum is directly under McBurney's point; therefore McBurney's sign is present even when the appendix is in different locations
  - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
  - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)

Complications
- perforation (especially if >24 h duration)
- abscess, phlegmon
- sepsis

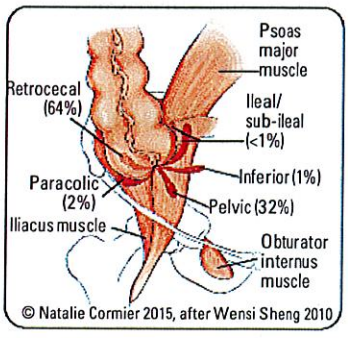


Figure 12. Appendix anatomy

McBurney's Sign
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side

Investigations
- laboratory
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - β-hCG to rule out ectopic pregnancy
  - urinalysis
- imaging
  - U/S: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/NPV/PPV 98%)
  - CT scan: thick wall, enlarged (>6 mm), wall enhancement, appendicolith, and inflammatory changes – overall accuracy 94-100%, optimal investigation

Treatment
- hydrate, correct electrolyte abnormalities
- appendectomy (gold standard)
  - laparoscopic is standard
  - complications: intra-abdominal abscess, appendiceal stump leak
  - perioperative antibiotics: cefazolin + metronidazole; if uncomplicated, perioperative dose is adequate
- consider treatment with postoperative antibiotics for perforated appendicitis
- for patients who present with an abscess (palpable mass or phlegmon on imaging and often delayed diagnosis with symptoms for >4-5 d), consider radiologic drainage + antibiotics x14 d ± interval appendectomy once inflammation has resolved = (controversial)
- medical management with antibiotic therapy should be reserved for those who are unfit for or refuse surgery
- colonoscopy in those >50 yr to rule out concurrent etiology (neoplasm)

Antibiotics versus Appendectomy for Acute Appendicitis - Longer-Term Outcomes
N Engl J Med 2021;385(25):2395. Epub 2021 Oct 25.
Purpose: Compare the efficacy of antibiotics vs. an appendectomy for acute appendicitis with respect to long-term outcomes.
Method: Randomized trial comparing antibiotic treatment with appendectomy in patients with appendicitis.
Results: The 30-day general health status of patients treated with antibiotics was comparable to the appendectomy group. However, 29 percent of medically-treated patients required appendectomy by 90 d. Longer-term data from this trial now confirm high rates of subsequent appendectomy after initial medical therapy: 40 percent at one year, 46 percent at two years, and 49 percent at three and four years.
Conclusions: Surgery should continue to be recommended for uncomplicated appendicitis and antibiotic therapy should be reserved for those who are medically unfit for or decline surgery.

Prognosis
- mortality rate: 0.09-0.24%

Inflammatory Bowel Disease

- see Gastroenterology, G22

Principles of Surgical Management
- medical management remains first line, but surgery can alleviate symptoms, address complications, and improve quality of life
- conserve bowel: resect as little as possible to avoid short gut syndrome
- perioperative management
  - optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - hold immunosuppressive therapy preoperative, provide preoperative stress dose of corticosteroid; if patient had recent steroid therapy, taper steroids postoperative
  - VTE prophylaxis: LMWH or heparin (IBD patients at increased risk of thromboembolic events)

Crohn's Disease

- see Gastroenterology, G23

Crohn's 3 Major Patterns
- Ileocecal 40% (RLQ pain, fever, weight loss)
- Small intestine 30% (especially terminal ileum)
- Colon 25% (diarrhea)

Treatment
- surgery is for symptom management; it is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), and perianal disease
- surgical procedures
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, or fistula
  - surgery should be attempted in the elective setting ideally off steroids
- resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

Findings in Crohn's
- "Cobblestoning" on mucosal surface due to edema and linear ulcerations
- "Skip lesions": normal mucosa in between
- "Creeping fat": mesentery infiltrated by fat
- Granulomas: 25-30%

Complications of Treatment
- anastomotic leak
- dehydration
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

Ulcerative Colitis

- see Gastroenterology, G25

Treatment
- indications for surgical management
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per yr after 10 yr of disease)
- surgical procedures
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment
- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis
- mortality: 5% over 10 yr
- total proctocolectomy will eliminate risk of cancer
- perforation of the colon is the leading cause of death from UC

LARGE INTESTINE

Large Bowel Obstruction

Mechanical Large Bowel Obstruction

Etiology

Table 18. Common Causes of LBO

Intraluminal	Intramural	Extramural
Constipation	Adenocarcinoma	Volvulus
Foreign bodies	Diverticulitis (edema, stricture)	Adhesions
	IBD stricture	Hernias (sigmoid colon in a large groin hernia)
	Radiation stricture	

Top 3 Causes of LBO (in order)
- Cancer (>60%)
- Volvulus (10-15%)
- Diverticulitis (10%)

In a patient with a clinical LBO consider impending perforation when:
- Cecum ≥12 cm in diameter
- Tenderness present over cecum

Clinical Features (unique to LBO)
- open loop (10-20%)
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical features similar to SBO
- closed loop (80-90%) (dangerous)
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

Investigations
- CBC with differential, BUN, electrolyte panel, creatinine, CEA if patient is suspected to have malignancy, and lactate for level of ischemia
- imaging: AXR and CT scan

Treatment
- supportive management: IV fluids, gastrointestinal decompression
- surgical intervention (75% of cases)
  - volvulus: initial decompression with flexible sigmoidoscopy, operative reduction or sigmoid resection dependent on severity
  - colorectal obstruction: ostomy alone (fecal diversion), colectomy with primary anastomosis, or Hartmann procedure
- may pursue stenting as a bridge to surgery or palliation

Prognosis
- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

Table 19. Bowel Obstruction vs. Paralytic Ileus

	SBO	LBO	Paralytic Ileus
N/V	Early, may be bilious	Late, may be feculent	Present
Abdominal Pain	Colicky	Colicky	Minimal or absent
Abdominal Distention	+ (prox SBO), ++ (distal SBO)	++	+
Constipation	+	+	+
Bowel Sounds	Normal, increased Absent if secondary ileus (delayed presentation)	Normal, increased (borborygmi) Absent if secondary ileus (delayed presentation)	Decreased, absent
AXR Findings	Air-fluid levels "Ladder" pattern (plicae circulares) Proximal distention (>3 cm) + no colonic gas	Air-fluid levels "Picture frame" appearance Proximal distention + distal decompression No small bowel air if competent ileocecal valve Coffee bean sign (sigmoid volvulus)	Air throughout small bowel and colon

Functional Large Bowel Obstruction: Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

Definition
- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- exact mechanism unknown, likely autonomic motor dysregulation

Associations
- most common: trauma, infection, and cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease, bed-bound nursing home patients, and paraplegia), drugs (narcotic use, laxative abuse, and polypharmacy), and other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, and diffuse carcinomatosis)

Clinical Features
- classically presents with abdominal distention (acute or gradual over 3-7 d)
- abdominal pain, N/V, constipation or diarrhea
- watch out for fever, leukocytosis, and presence of peritoneal signs (suggestive of colonic ischemia or perforation)

Investigations
- AXR: cecal dilatation (if diameter ≥12 cm, increased risk of perforation)

Treatment
- treat underlying cause
- NPO, NG tube
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), or surgical (ostomy/resection)
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

Prognosis
- most resolve with conservative management

Diverticular Disease

Definitions
- diverticulum: abnormal outpouching from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

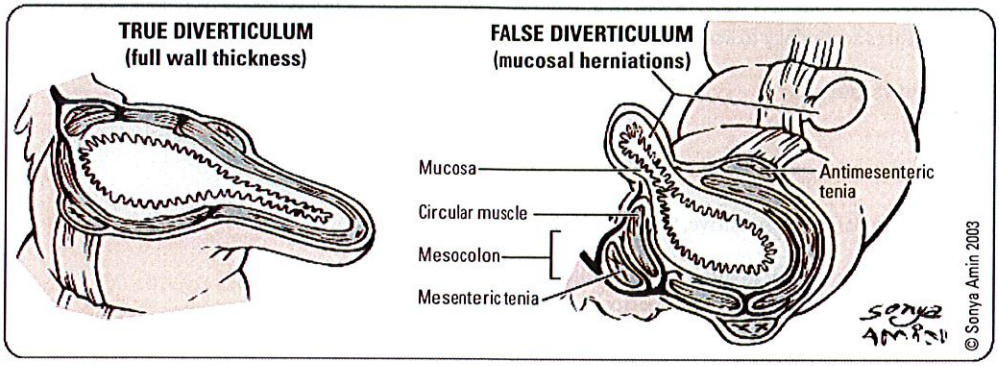


Figure 13. Diverticular disease – cross-sections of true and false diverticula

Diverticulosis

Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

Diverticulosis vs. Diverticulitis
Diverticulosis represents the presence of diverticuli (bulging pouches) within the colonic wall, whereas diverticulitis is the inflammation of one or more diverticuli

Pathogenesis
- risk factors
  - lifestyle: diet (low-fibre, high fat, red meat), inactivity, and obesity
  - muscle wall weakness from aging and illness (e.g. Ehlers-Danlos, Marfan's)
- high intraluminal pressures cause outpouching to occur at points of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer leading to an increased risk of hemorrhage

Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications:
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, and abdominal pain

Treatment
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

Diverticulitis

Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or obstruction can ensue
- poor containment results in free perforation and peritonitis

Clinical Features
- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, and urinary symptoms (with adjacent inflammation)
- low-grade fever, mild leukocytosis, and occult or gross blood in stool rarely coexist with acute diverticulitis
- complications (25% of cases)
  - abscess: palpable, tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, and colocutaneous
  - colonic obstruction: related to colonic strictures secondary to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
- recurrent attacks rarely lead to peritonitis

Investigations
- CT scan (test of choice)
  - very useful for assessment of severity and prognosis (97% sensitive, 99% specific)
  - usually done with rectal contrast
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), and fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- AXR, upright CXR
  - localized diverticulitis (ileus, thickened wall, SBO, and partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- colonoscopy or barium enema and flexible sigmoidoscopy (elective evaluation)
  - establish extent of disease and rule out other diagnoses (polyps and malignancy) AFTER resolution of acute episode

Treatment
- uncomplicated: conservative management
- outpatient: clear fluids only until improvement. Avoid treatment with antibiotics for those with uncomplicated acute diverticulitis
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, or fail to improve with outpatient management
  - treat with NPO, IV fluids, and IV antibiotics (e.g. IV ceftriaxone + metronidazole)
- image-guided (CT) percutaneous drainage of abscesses reduces the urgency of surgical resection in most patients
- surgery:
  - indications:
    - unstable patient with peritonitis
    - Hinchey stage 3-4 (see *Table 20*)
    - after 1 attack if immunosuppressed
    - consider if recurrent episodes of diverticulitis (≥3); recent trend is toward conservative management of recurrent mild/moderate attacks
  - procedures:
    - Hartmann resection (for unstable or complex cases)
    - colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo
  - for more stable patients with Hinchey stage 3 and 4 acute diverticulitis: colonic resection, primary anastomosis + diverting loop ileostomy is becoming more common, with benefits for mortality and morbidity
  - for Hinchey stage 3: laparoscopic peritoneal lavage with drain placement near the affected colon, in addition to 4 antibiotics (NO resection), has been proposed
  - complications: perforation, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management

Prognosis
- mortality rates: 6% for purulent peritonitis, 35% for feculent peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

Table 20. Hinchey Staging and Treatment for Diverticulitis

Hinchey Stage	Description	Acute Treatment
1	Phlegmon/small pericolic abscess	Medical
2	Large abscess/fistula	Medical, abscess drainage ± resection with primary anastomosis
3	Purulent peritonitis (ruptured abscess)	Resection or Hartmann procedure
4	Feculent peritonitis	Hartmann procedure

Efficacy and Safety of Nonantibiotic Outpatient Treatment in Mild Acute Diverticulitis (DINAMO-study): A Multicentre, Randomised, Open-label, Noninferiority Trial
Ann Surg 2021;274(5):e435
Background: In recent years, it has shown no benefit of antibiotics (ATB) in the treatment of uncomplicated Acute Diverticulitis in hospitalized patients.
Methods: Prospective, multicentre, open-label, noninferiority, randomized controlled trial.
Results: Differences in hospitalization rates, revisits, and poor pain control at 2 d follow-up were within the non-inferiority margin.
Conclusions: Nonantibiotic outpatient treatment of mild AD is safe and effective and is not inferior to current standard treatment.

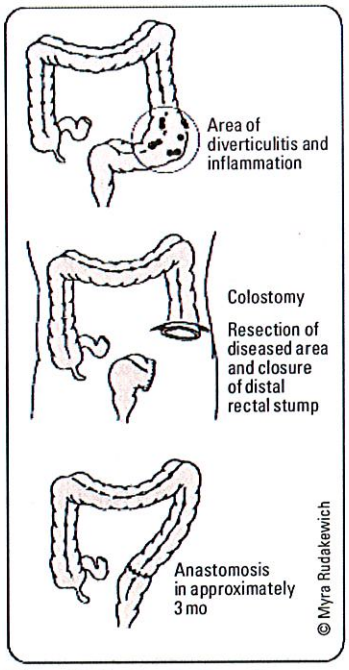


Figure 14. Hartmann procedure

Colorectal Neoplasms

Colorectal Polyps

Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
  - sessile (flat) or pedunculated (on a stalk)

Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70; M>F

Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, and mucus
- usually detected during routine endoscopy or familial/high-risk screening

Pathology
- non-neoplastic/non-adenomatous
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - malignant risk due to associated adenomas (large bowel)
    - low malignant potential → most spontaneously regress or autoamputate
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, and carcinoids
- neoplastic/adenomatous
  - adenomas: premalignant, considered carcinoma *in situ* if high-grade dysplasia
    - may contain invasive carcinoma ("malignant polyp" – 3-9%): invasion into submucosa
    - malignant potential related to histological type: villous > tubulovillous > tubular

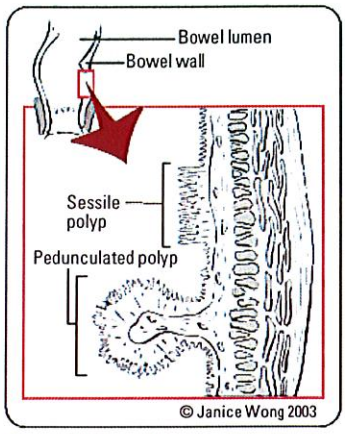


Figure 15. Sessile and pedunculated polyps

Table 21. Characteristics of Tubular vs. Villous Polyps

	Tubular	Villous
Incidence	Common (60-80%)	Less common (10%)
Size	Small (<2 cm)	Large (usually >2 cm)
Attachment	Pedunculated	Sessile
Malignant Potential	Lower	Higher
Distribution	Even	Left-sided predominance

Investigations
- colonoscopy with biopsy/resection (gold standard)
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy (if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy)

Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- indications for segmental resection for malignant polyps: 1) lymphovascular invasion; 2) tumour budding; 3) positive resection margin; 4) poorly differentiated cells; 5) evidence of regional or distant metastases on staging
  - most of these cases are usually discussed at multidisciplinary tumour boards
- follow-up endoscopy:
  - every 5 yr: if low-risk polyp (<10 mm tubular adenoma or <10 mm sessile serrated without dysplasia)
  - every 3 yr: if high-risk polyp (3-10 tubular adenomas, >10 mm tubular or serrated polyp, adenoma with villous features or high grade dysplasia, or sessile serrated with dysplasia)

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS

Epidemiology
- accounts for <1% of colorectal cancers, affects males and females equally

Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene

Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40's in attenuated FAP)
- virtually 100% lifetime risk of colon cancer (due to number of polyps)
- extracolonic manifestations
  - bile duct, pancreas, stomach, thyroid (large benign multinodular goitre), adrenal glands, and small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
- variants
  - Gardner's syndrome: FAP + extra-intestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + central nervous system tumours (childhood cerebellar medulloblastoma)

Investigations
- genetic testing (80-95% sensitive, 99-100% specific)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy, consider surgery, and consider upper endoscopy to evaluate for periampullary tumours

Treatment
- surgery indicated by ages 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

Referral Criteria for Genetic Screening for APC
- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 yr)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER – LYNCH SYNDROME

Epidemiology
- most common inherited colorectal cancer susceptibility syndrome and accounts for 3% of colorectal cancer diagnoses

Pathogenesis
- autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1, PMS2) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all CRCs

Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80%; M>F
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome → high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel, adrenal)

Diagnosis
- Amsterdam Criteria ("3-2-1 rule")
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr
  - FAP is excluded
- genetic testing (80% sensitive)
  - refer individuals for genetic screening if they fulfill either the Amsterdam Criteria or the revised Bethesda Criteria
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

Revised Bethesda Criteria for HNPCC and Microsatellite Instability (MSI)
Tumours from individuals should be tested for MSI in the following situations:
- Colorectal cancer diagnosed in a patient who is <50 yr
- Presence of synchronous, metachronous, colorectal, or other HNPCC-associated tumours, regardless of age
- Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 yr
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed <50 yr
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer

APR removes distal sigmoid colon, rectum, and anus; permanent end colostomy required
LAR removes distal sigmoid and rectum with anastomosis of distal colon to distal rectum/anus

Colorectal Carcinoma

Epidemiology
- 3rd most common cancer (lung > breast > colon), 2nd most common cause of cancer death

Risk Factors
- most patients have no specific risk factors
- ages >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, or family history of CRC
- colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal, gonadal, or breast cancer
- diet (increased fat, red meat, decreased fibre) and smoking
- DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Pathogenesis
- adenoma-carcinoma sequence; rarely arise de novo

Clinical Features
- often asymptomatic
- hematochezia/melena, abdominal pain, and change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, and obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread
  - direct extension, lymphatic, and hematogenous (liver most common, lung, bone, and brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: ovary and Blumer's shelf (pelvic cul-de-sac)

Table 22. Clinical Features of CRC

	Right Colon	Left Colon	Rectum
Frequency	25%	35%	30%
Pathology	Exophytic lesions with occult bleeding	Annular, invasive lesions	Ulcerating
Symptoms	Weight loss, weakness, rarely obstruction	Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool calibre, rectal bleeding	Obstruction, tenesmus, rectal bleeding
Signs	Fe-deficiency anemia, RLQ mass (10%)	BRBPR, LBO	Palpable mass on DRE, BRBPR

Investigations
- colonoscopy (gold standard): look for synchronous lesions (3-5% of patients)
  - if a patient is FOBT positive, has microcytic anemia, or has a change in bowel habits → colonoscopy
  - alternative: air contrast barium enema ("apple core" lesion) + sigmoidoscopy
- laboratory: CBC, U/A, LFTs, CEA (preoperative for baseline, >5 ng/mL have worse prognosis)
- staging: CT chest/abdomen/pelvis; bone scan and CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal U/S to determine T and N stage

Table 23. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/UICC 8th edition)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
Tx	Primary tumour cannot be assessed	Nx	Regional nodes cannot be assessed	M0	No distant metastasis
T0	No primary tumour found	N0	No regional node metastasis and no tumour deposits	M1a	Distant metastasis to 1 organ or site and no peritoneal metastasis
Tis	Carcinoma *in situ*, limited to intraepithelial or invasive lamina propria	N1a	Metastasis in 1 regional node	M1b	Distant metastasis to >1 (2 or more organs sites) and no peritoneal metastasis
T1	Invasion into submucosa	N1b	Metastasis in 2-3 regional nodes	M1c	Metastasis to peritoneal surface
T2	Invasion into muscularis propria	N1c	No regional node metastasis; tumour deposits were submucosal, mesangial or peritoneum-covered para-colorectal tissue		
T3	Invasion through muscularis propria and into pericolorectal tissues	N2a	Metastasis in 4-6 regional nodes		
T4a	Invasion through visceral peritoneum	N2b	Metastasis in ≥7 regional nodes		
T4b	Invasion or adherent to other organs or structures				

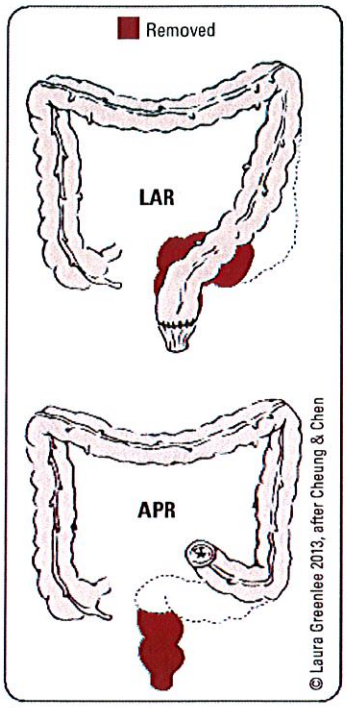


Figure 16. APR vs. LAR

5 Year Survival Rates for CRC

Stage	20-64 yr	≥65 yr
I	95.2%	89.1%
IIA	89.6%	84.4%
IIB	67.6%	55%
IIIA	91.3%	85.1%
IIIB	76.9%	64.6%
IIIC	61.8%	45.5%
IV	14.2%	7.4%

Preoperative vs. Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a Median Follow-Up of 11 Yr

J Clin Oncol 2012;30:1926-1933

Background: The CAO/ARO/AIO-94 trial (published 2004) recommended preoperative chemoradiotherapy (CRT) as standard treatment for locally advanced rectal cancer. However, no survival benefit was shown after median follow-up of 46 mo, and this study reports long-term effects.

Methods: Patients with stage II to III rectal cancer (n=799) were randomly assigned to preoperative (n=404) or postoperative CRT (n=395) with fluorouracil (FU), radiation, and adjuvant FU chemotherapy, in addition to total mesorectal excision surgery. Follow-up was designed to assess long-term overall survival as the primary endpoint and cumulative incidence of local and distant relapses as well as disease-free survival as secondary endpoints.

Results: 10 yr incidence of local relapse was significantly lower in the preoperative CRT group than in the postoperative group (7.1% vs. 10.1%, P=0.048). Overall survival at 10 yr was similar at ~60% for patients treated with preoperative or postoperative CRT (P=0.85). Disease-free survival rates at 10 yr was similar at ~68% for patients treated with preoperative or postoperative CRT (P=0.54). No significant difference was detected for 10 yr incidence of distant metastases (preoperative CRT 29.8% vs. postoperative CRT 29.6%, P=0.9).

Conclusion: There is long-term reduction in local recurrence of stage II to III rectal cancer with preoperative chemotherapy, but no improvement in overall survival or distant recurrence of disease.

Treatment
- colon cancer
  - wide surgical resection of lesion according to vascular distribution and regional lymphatic drainage; usually colectomy with primary anastomosis
  - curative: wide resection of lesion (5 cm margins) with nodes (>12) and mesentery
  - care is taken to not spread tumour by unnecessary palpation
  - adjuvant chemotherapy (oxaliplatin-based) for stage III and is considered in select stage II patients
  - palliative: if distant spread, local control for hemorrhage or obstruction
- metastatic lesions confined to the liver can be resected with curative intent
- rectal cancer
  - choice of operation depends on individual case
    - LAR: curative procedure of choice if adequate distal margins (~2 cm); uses technique of total mesorectal excision
      - APR: if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus permanent end colostomy required
    - transanal minimally invasive surgery (TAMIS): local excision for select T1 lesions only
  - palliative procedures involve proximal diversion with an ostomy for obstruction and radiation for bleeding or pain
  - combined neoadjuvant chemoradiation therapy followed by postoperative adjuvant chemotherapy for stages II and III

Follow-Up
- stage I: mixed recommendations; either routine colonoscopy or screening like stage II & III
- stage II & III: regular follow-up q3-6 mo for 3 yr, then q6 mo until 5 yr, with regular measurement of serum CEA for at least 3 yr; annual CT chest/abdo/pelvis for at least 3 yr; colonoscopy at 1, 3, and 5 yr
- stage IV: no data on surveillance strategy

Other Conditions of the Large Intestine

Angiodysplasia

Definition
- vascular malformation: focal submucosal venous dilatation and tortuosity

Clinical Features
- most frequently in right colon of patients >60 yr
- predisposition in end-stage renal disease, and Von Willebrand disease, and aortic stenosis
- bleeding typically intermittent, rarely massive, and not usually hypotensive (melena, anemia, and occult blood positive stools)
- >90% of cases cease bleeding spontaneously

Investigations
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, and delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

Treatment
- none if asymptomatic
- cautery, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

Volvulus

Definition
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), and splenic flexure (2%)
  - elderly >70 yr (sigmoid), adult 40-60yr (cecal), and neonates and infants (midgut)
- 5-10% of large bowel obstructions; 25% of intestinal obstructions during pregnancy

Risk Factors
- age (50% of patients >70 yr: stretching/elongation of bowel with age)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, and institutionalization (less frequent evacuation of bowels)
- megacolon
- intestinal bands/adhesions



Cecal Volvulus
AXR: Central cleft of "coffee bean" sign points to RLQ



Sigmoid Volvulus
AXR: Central cleft of "coffee bean" sign points to LLQ
Barium enema: "ace of spades" or "bird's beak" sign

Clinical Features
- symptoms due to bowel obstruction (see *Large Bowel Obstruction, GS37*) or intestinal ischemia (see *Intestinal Ischemia, GS31*)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, and vomiting

Investigations
- AXR (classic findings): "omega," "bent inner-tube," "coffee-bean" signs, multiple air-fluid levels
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT: "whirl pattern" of mesenteric vessels twisting about the volvulus axis
  - barium contrast and colonoscopy are contraindicated due to risk of perforation

Treatment
- initial supportive management same as initial management for bowel obstruction (see *Large Bowel Obstruction, GS37*)
- cecum
  - colonoscopic detorsion and decompression; successful 15-20% of cases
  - surgical
    - right colectomy + ileotransverse colonic anastomosis
- sigmoid
  - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
  - subsequent elective surgery recommended (50-70% recurrence)
  - surgical
    - surgical resection with or without primary anastomosis
    - indications for urgent surgical management: strangulation, perforation, or unsuccessful endoscopic decompression

Toxic Megacolon

Pathogenesis
- extension of inflammation into smooth muscle layer causing paralysis and leading to nonobstructive colonic dilatation
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

Etiology
- IBD (UC > Crohn's disease)
- infectious colitis: bacterial (*C. difficile, Salmonella, Shigella*, and *Campylobacter*), viral (cytomegalovirus), and parasitic (E. histolytica)

Clinical Features
- infectious colitis usually presents for >1 wk before colonic dilatation
- diarrhea ± blood (sudden improvement of diarrhea may signify onset of megacolon)
- abdominal distention, tenderness, ± local/general peritoneal signs (suggests perforation)
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, and anticholinergics), barium enema, and colonoscopy

Diagnostic Criteria
- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon >6 cm, and
- three of: fever, HR >120, WBC >10.5, anemia and
- one of: dehydration, electrolyte disturbances, hypotension, or altered LOC

Investigations
- CBC (leukocytosis with left shift and anemia from bloody diarrhea), electrolytes, elevated c-reactive protein, and ESR
  - metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease severity and possible complications (i.e. abscess, perforation, ascending pylephlebitis)

Treatment
- NPO, NG tube, stop constipating agents, correct fluid and electrolyte abnormalities, and transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis and anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD and metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management)
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC, especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (possible re-anastomosis later)

Use caution when giving antidiarrheal agents, especially with bloody diarrhea

Prognosis
- 25-30% mortality

Fistula

Definition
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, and entero-enteric)

Etiology
- foreign object erosion (e.g. drainage tube, gallstone, graft)
- inflammatory states (e.g. infection, IBD (Crohn's > UC), and diverticular disease)
- iatrogenic/surgery (e.g. postoperative anastomotic leak and radiation)
- congenital, trauma
- neoplastic

Why Fistulae Stay Open

FRIENDO
Foreign body
Radiation
Infection
Epithelialization
Neoplasm
Distal obstruction (most common)
Others: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

Investigations
- U/S, CT scan, fistulogram
- measure amount of drainage from fistula

Treatment
- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas)

Stomas

Definition
- an opening of the GI tract onto the surface of the abdomen wall
  - end stomas: the proximal end of the GI tract forms the stoma and the distal end of the GI tract is not part of the stoma
  - loop stomas: a loop of the GI tract is brought up to the skin and the antimesenteric surface of the bowel is matured as a stoma

Colostomy/Ileostomy
- Connection of proximal limb of colon or ileum to abdominal wall skin
- Mucous fistula
- Connection of distal limb of resection margin to abdominal wall skin
- Ileal Conduit
- Connection of bowel to ureter proximally and abdominal wall distally to drain urine

Ileostomy
- usually positioned in RLQ; ileum is brought through rectus abdominis muscles
- indications: after proctocolectomy for UC, some cases of Crohn's disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum (ileal pouch anal anastomosis)

Colostomy
- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy (expels stool/digital removal of feces)
- chronic paracolostomy hernia is a common complication

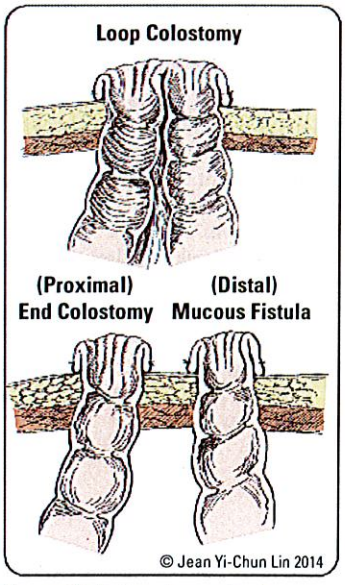


Figure 17. End vs. loop colostomy

Complications (10%)
- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output), which may lead to fluid, electrolyte, and nutritional imbalances

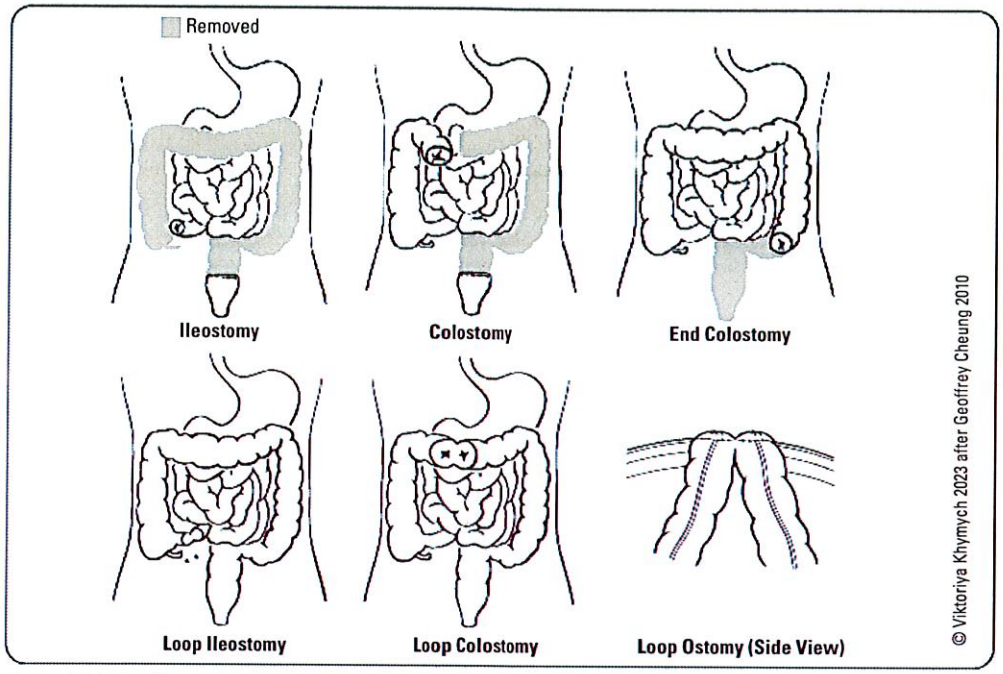


Figure 18. Ostomies

Anorectum

Hemorrhoids

Etiology
- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
- internal: superior hemorrhoidal veins, above dentate line, portal circulation
- external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors
- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting

Clinical Features and Treatment
- internal hemorrhoids
  - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - painless rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, and rectal fullness
    - **1st degree**: bleed but do not prolapse through the anus
      - treatment: high fibre/bulk diet, sitz baths, steroid cream (short course), pramoxine (Anusol®), phlebotonics, rubber band ligation, sclerotherapy, and photocoagulation
    - **2nd degree**: bleed, prolapse with straining, and spontaneous reduction
      - treatment: rubber band ligation, and photocoagulation
    - **3rd degree**: bleed, prolapse, and require manual reduction
      - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - **4th degree**: bleed, permanently prolapsed, and cannot be manually reduced
      - treatment: closed hemorrhoidectomy
- external hemorrhoids
  - dilated venules usually mildly symptomatic
    - pain after bowel movement, associated with poor hygiene
    - medical treatment: dietary fibre, stool softeners, steroid cream (short course), pramoxine (Anusol®), phlebotonics, and avoid prolonged straining
  - thrombosed hemorrhoids are very painful
    - resolve within 2 wk, may leave excess skin = perianal skin tag
    - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment
- indications for referral for endoscopic evaluation: history of melena, postural vital sign abnormalities, constitutional symptoms suggestive of malignancy, and family history of inherited colorectal syndromes

Prevention
- high fibre diets, prevent constipation, stool softeners

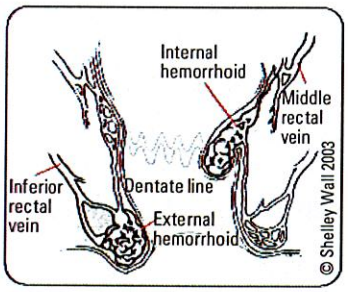


Figure 19. Hemorrhoids

Always rule out more serious causes (e.g. colon cancer or anal canal cancer) in a person with hemorrhoids and rectal bleeding

Band ligation can be done as outpatient

External hemorrhoids will often recur

Table 24. Signs and Symptoms of Internal vs. External Hemorrhoids

Internal Hemorrhoids	External Hemorrhoids
Painless BRBPR	Sudden severe perianal pain
Rectal fullness or discomfort	Perianal mass
Mucus discharge	

Anal Fissures

Definition
- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline because posteromedial area is poorly perfused, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STIs, TB, leukemia, or anal carcinoma
- repetitive injury cycle after first tear
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

Etiology
- local trauma: constipation, irritation, diarrhea, vaginal delivery, anal intercourse
- secondary to: Crohn's disease, granulomatous diseases, malignancy, communicable diseases
- further tearing by internal anal sphincter spasm and hypertonicity

Clinical Features
- acute fissure
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agents, and sitz baths (heals 90%)
- chronic fissure (anal ulcer)
  - triad: fissure, sentinel skin tags, and hypertrophied papillae
  - treatment
    - stool softeners, increased fibre intake, and sitz baths
    - topical nitroglycerin or calcium channel blocker (nifedipine or diltiazem): increases local blood flow, promotes healing, and relieves sphincter spasm
    - lateral internal anal sphincterotomy (most effective): relieves sphincter spasm to increase blood flow and promote healing; reserved for medically-refractory cases due to 5% chance of fecal incontinence
    - alternative treatment: botulinum toxin A; inhibits release of acetylcholine (ACh), reducing sphincter spasm

Prevention
- avoid diarrhea or constipation, avoid straining during defecation, high fibre diet, adequate fluids

Anorectal Abscess

Definition
- infection typically originating within an obstructed anal crypt which forms an abscess
- common bacterial: *E. coli, Proteus, Streptococci, Staphylococci, Bacteroides*, and anaerobes

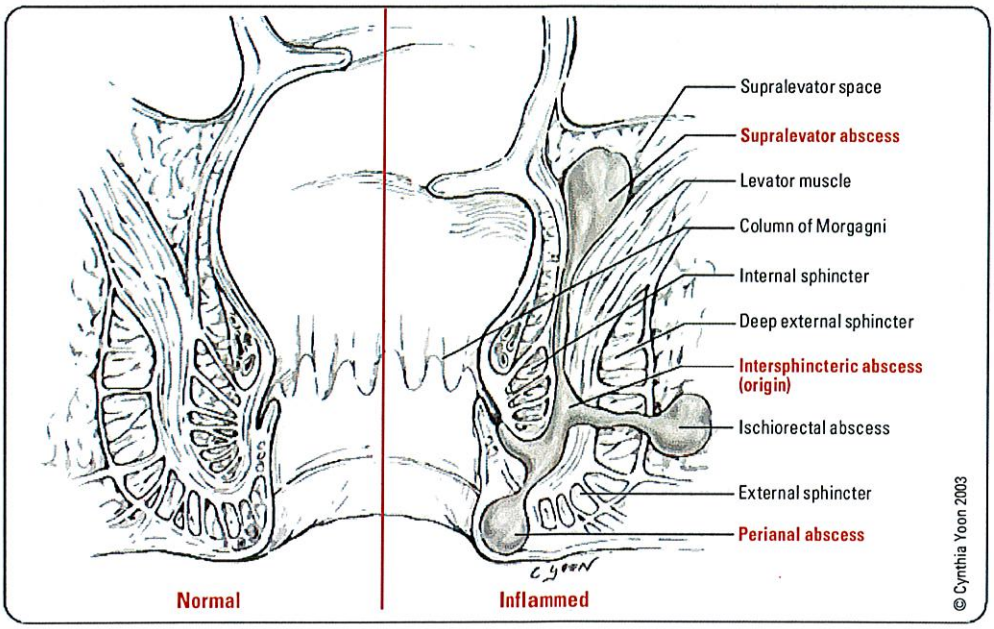


Figure 20. Different types of perianal abscesses

Clinical Features
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

Treatment
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
- may require antibiotics if patient has DM, a heart murmur, or cellulitis

Recurrent perianal abscesses is associated with Crohn's disease

Antibiotics are not typically helpful in the treatment of perianal abscesses

Fistula-In-Ano

Definition
- fistula from anal canal to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

Etiology
- see *Fistula, GS46*
- same processes that lead to the formation of an anal abscess
- other causes: postoperative, trauma, anal fissure, malignancy, and radiation proctitis

Clinical Features
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract
- inflamed or excoriated perianal skin
- MRI best imaging but can use CT or U/S depending on location

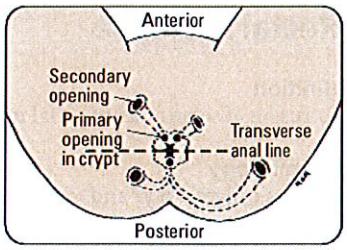


Figure 21. Goodsall's rule

Treatment
- identification
  - internal opening
    - Goodsall's rule: fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia
- surgery
  - primary fistulotomy: unroof tract from external to internal opening, allows drainage, heals by secondary intention
    - best treatment for low lying fistula (does not involve external sphincter)
  - staged fistulotomy with Seton (rubber band or suture) placed through tract
    - used for high lying fistula (involves external sphincter)
    - promotes drainage, fibrosis, and decreases incidence of incontinence
    - delineates anatomy and usually done to spare muscle
  - ligation of intersphincteric fistula tract (LIFT) procedure
    - access fistula between sphincter muscles, sparing them
  - endoanal advancement flaps

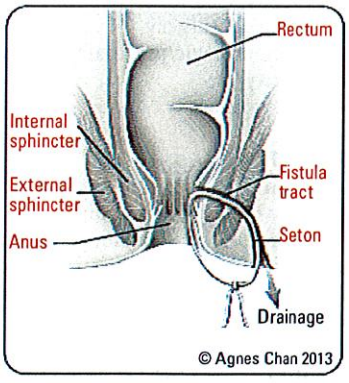


Figure 22. Fistulotomy with Seton suture

Postoperative
- sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

Complications
- recurrence
- rarely fecal incontinence

Pilonidal Disease

Definition
- pilo = hair, nidal = nest; cyst or abscess near or on the intergluteal cleft of the sacrococcygeal area containing hair and skin debris

Epidemiology
- occurs most frequently in young men ages 15-35; rare in >50 yr

Etiology
- obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses
- associated with occupations that require prolonged sitting, obesity, and high amounts of body hair

Clinical Features
- asymptomatic or chronically itchy until acutely infected, then pain/tenderness, purulent discharge, and increased moisture near the tailbone

Treatment
- acute abscess
  - I&D (often performed by primary care physicians)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery
  - indication: failure of healing after I&D, recurrent disease, or complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention (vac dressing), primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

Rectal Prolapse

Definition
- protrusion of some or all of rectal mucosa through external anal sphincter

Epidemiology
- extremes of ages: <5 yr and >50 yr
- 85% women

Etiology
- lengthened attachment of rectum secondary to constant straining
- 2 types
  1. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  2. true/complete (most common): full-thickness extrusion of rectal wall, concentric folds in:
     - 1st degree: prolapse includes mucocutaneous junction
     - 2nd degree: without involvement of mucocutaneous junction
     - 3rd degree (internal intussusception): prolapse is internal, concealed, or occult

Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility e.g. chronic constipation
- multiparity
- weak pelvic floor

Clinical Features
- extrusion of mass with increased intra-abdominal pressure
- difficulty in bowel regulation
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration, and constant soiling
- may be associated with urinary incontinence or uterine prolapse
- pain is not common

Treatment
- type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, and trans-sacral approaches

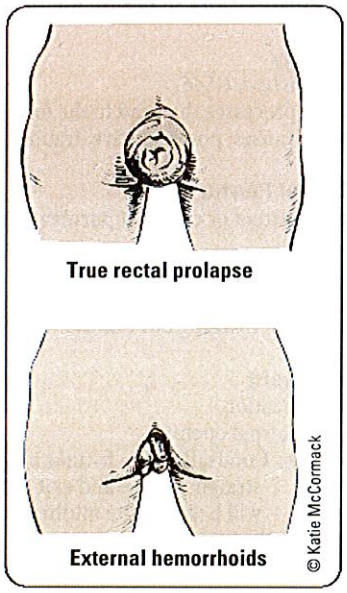


Figure 23. Rectal prolapse (true vs. false)

Anal Neoplasms

ANAL CANAL

Squamous Cell Carcinoma of Anal Canal (Distal to Dentate Line)
- most common tumour of anal canal (75%)
- anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intraepithelial lesions (ASIL)
  - high-grade squamous intraepithelial lesion (HSIL) and low-grade squamous intraepithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, and pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5 yr survival

Malignant Melanoma of Anal Canal

- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- occasionally an incidental finding in pathological evaluation of an anal specimen
- clinical features: bleeding, mass anorectal pain, change in bowel habits, pigmented in one third cases, regional lymph node involvement
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5 yr survival

ANAL MARGIN

- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC in situ), and Paget's disease

Liver

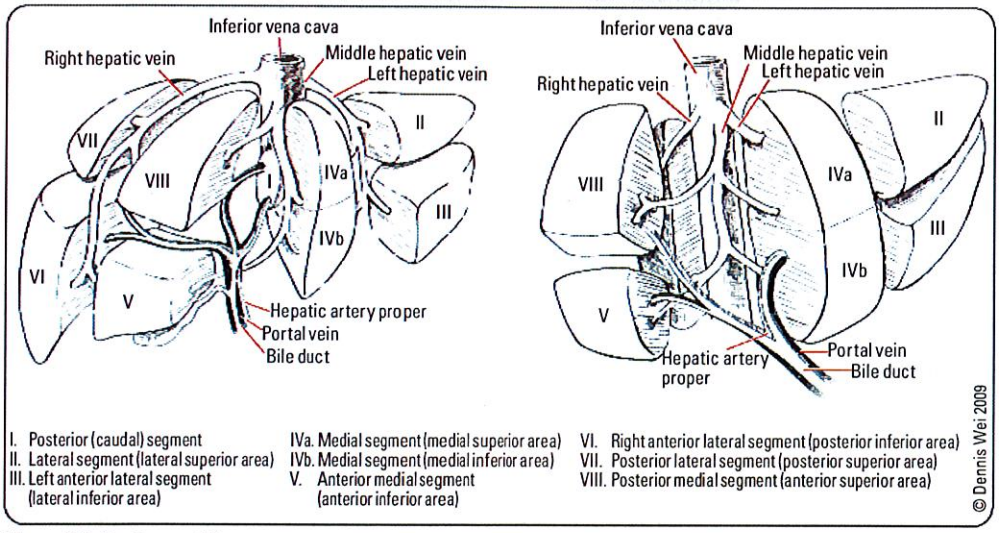


Figure 24. Anatomy of liver

Liver Cysts

Table 25. Characteristics of Liver Cysts

	Simple Cysts	Polycystic Liver Disease	Choledochal Cysts	Hydatid (Cystic Echinococcosis)	Cystadenoma (Premalignant)/ Cystadenocarcinoma
Description	Form from biliary ducts that do not communicate with the intrahepatic biliary tree and contain clear fluid Most common May have multiple cysts Always benign Examples include congenital cysts, Caroli disease, biliary hamartomas, and polycystic liver disease (PCLD)	Several (>20) cysts that replace much of the liver parenchyma Autosomal-dominant condition More common in females	Congenital malformations of the bile ducts High-risk of malignancy Majority present before age 10 Todani classification based on anatomical characteristics within biliary tree	Infection with parasite *Echinococcus granulosus* Associated with exposure to dogs, sheep, horses, pigs, goats, camels, and cattle in Southern Europe, Middle East, Australasia, South America Ingested parasitic eggs hatch in the small intestine, where larvae enter blood and lymph	Cystadenomas are rare cystic neoplasms arising from the bile ducts Cystadenoma is the most common premalignant liver lesion Cystadenocarcinoma is an invasive carcinoma
Clinical Features	Usually asymptomatic Mass effect can cause: dull RUQ pain, N/V, bloating, and/or early satiety	Minority present with acute complications due to cyst rupture, hemorrhage, infection, and compression of adjacent structures Progressive 50% associated with polycystic kidney disease (if over age 60)	Recurrent abdominal pain Intermittent jaundice RUQ mass Cholangitis Symptomatic gallstones Pancreatitis Portal HTN	Usually asymptomatic May have palpable RUQ mass or hepatomegaly Chronic RUQ pain when symptomatic Nausea, fever, and dyspepsia are non-specific symptoms	Upper abdominal mass Abdominal pain Anorexia
Investigations	Labs: some have elevated GGT, CEA, CA 19-9 U/S: Used for diagnosis and follow-up CT: well demarcated lesion that does not enhance with contrast	U/S: cysts are well circumscribed and nonenhancing MRI: more sensitive and specific, used for preoperative planning	Labs: LFT abnormalities U/S CT Transhepatic cholangiography ERCP MRCP	Labs: anti-Echinococcus ab U/S CT: calcified cystic walls Needle biopsy	Labs: cystadenocarcinoma may have elevated LFTs, CEA, or CA 19-9 U/S: anechoic mass with internal septations that are highly echogenic CT MRI MRCP ERCP Need histology for definite diagnosis

Table 25. Characteristics of Liver Cysts

	Simple Cysts	Polycystic Liver Disease	Choledochal Cysts	Hydatid (Cystic Echinococcosis)	Cystadenoma (Premalignant)/ Cystadenocarcinoma
Treatment	Not required unless very large and/or symptomatic Monitor if >4 cm. Laparoscopic or open cyst wall removal (unroofing) is established treatment and is usually curative Percutaneous aspiration and ethanol sclerotherapy also an option, but not curative	Symptomatic patients: cyst aspiration with sclerosis, cyst fenestration, hepatic resection, transarterial embolization, and transplantation	Complete excision of cysts Liver resection or transplantation if cystic dilatation involves intrahepatic bile ducts (Caroli's disease)	Systemic chemotherapy: Albendazole (anti-helminthic drug) cure up to 30% Surgical: radical (total pericystectomy, partial hepatectomy, or lobectomy) vs. conservative (drainage or open/ closed cystectomy) Percutaneous: PAIR (puncture, aspiration, injection, re-aspiration)	All complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk
Complications	Hemorrhage, rupture, infection, and biliary obstruction more likely in larger cysts Intracystic hemorrhage is rare and presents with severe abdominal pain		Biliary cirrhosis, portal HTN, cyst rupture, or cholangiocarcinoma Increased risk of biliary malignancy	IVC compression Cyst rupture which can cause fever, pruritus, eosinophilia, biliary colic, jaundice, cholangitis, pancreatitis, or anaphylaxis	Cystadenocarcinoma can invade adjacent tissues and metastasize

Liver Abscesses

Etiology

- types
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *Klebsiella, E. coli, Proteus, Streptococcus, Staphylococcus*, and anaerobes
  - parasitic (amoebic): *Entamoeba histolytica*, Echinococcal cyst
  - fungal: *Candida*
  - sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features

- fever, malaise, chills, anorexia, weight loss, abdominal pain, and nausea
- RUQ tenderness, hepatomegaly, and jaundice

Investigations

- CBC (leukocytosis, anemia), LFTs (elevated ALP and hypoalbuminemia common; elevated transaminases and bilirubin variable), blood cultures, INR/PTT, stool cultures, and serology (*E. histolytica* and *Echinococcus*)
- CT or U/S are the imaging modalities used for diagnosis with abscess drainage for C&S to confirm diagnosis; MRI can also be used.



Differential Diagnosis of Metastatic Liver Mass

Some **GU C**ancers **P**roduce **B**umpy **L**umps

Stomach
GUrinary cancers (kidney, ovary, uterus)
Colon
Pancreas
Breast
Lung

Treatment

- treat underlying cause
- pyogenic abscesses generally treated with antibiotic therapy (e.g. ceftriaxone and metronidazole or piperacillin-tazobactam) and U/S- or CT-guided percutaneous drainage or surgical drainage
- consider potential source of sepsis (e.g. biliary source, infected tumour)

Prognosis

- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition, elderly, ICU admissions, shock, cancer, cirrhosis, chronic kidney disease (CKD), acute respiratory failure, and biliary origin of abscess

Neoplasms

BENIGN LIVER NEOPLASMS

Hemangioma (cavernous)

- pathogenesis: most common benign hepatic tumour; results from malformation and proliferation of vascular endothelial cells
- risk factors: M:F=3:1
- clinical features
  - usually small and asymptomatic, those greater than 10 cm are considered giant and may cause abdominal pain or discomfort
  - consumptive coagulopathy if giant (in children)
- investigations
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement on arterial phase with centripetal filling on delayed phases), U/S (homogeneous hyperechoic mass), MRI
  - avoid biopsy: may result in hemorrhage

- treatment
  - none if asymptomatic
  - in symptomatic patients or those with hemangiomas large enough causing mass effect, surgical resection should be considered after other causes of pain are excluded
  - surgical resection options: liver resection, hepatic artery ligation, enucleation, and in severe cases liver transplantation.
  - non-surgical treatment: hepatic artery embolization and radiotherapy

Focal Nodular Hyperplasia

- pathogenesis: unclear, hyperplastic response to vascular anomaly leading to disorganized growth of hepatocytes and bile ducts
- risk factors: female, reproductive age
- clinical features: usually asymptomatic, rarely grows or bleeds, and no malignant potential
- investigations: central stellate scar surrounded by homogenous lesion on CT scan; MRI, biopsy may be required
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential)
  - if confirmed to be FNH → no treatment required

Adenoma

- pathogenesis: benign abnormal growth of glandular epithelium
- risk factors: female, ages 20-50, estrogen (OCP, pregnancy), obesity, anabolic androgen use, and type 1 glycogen storage disease
- clinical features: asymptomatic, 25% present with RUQ pain or mass, may present with bleeding
- investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy can be considered, with bleeding risk taken into account
- treatment
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to HCC and spontaneous rupture/hemorrhage

MALIGNANT LIVER NEOPLASMS

Primary

- most commonly HCC and cholangiocarcinoma
- others include angiosarcoma, hepatoblastoma, and hemangioendothelioma
- risk factors
  - chronic liver inflammation: cirrhosis from any cause, chronic hepatitis B (inherently oncogenic) and hepatitis C, hemochromatosis, α1-antitrypsin deficiency, and non-alcoholic steatohepatitis
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, betel nuts chewing
  - chemical carcinogens: aflatoxin, microcystin, and vinyl chloride (associated with angiosarcoma)
- clinical features
  - RUQ discomfort and right shoulder pain
  - jaundice, weakness, weight loss, and ± fever (if central tumour necrosis)
  - hepatomegaly, bruit, and hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes: hypoglycemia, hypercalcemia, erythrocytosis, and watery diarrhea
  - metastasis: lung, intra-abdominal lymph nodes, bone, adrenal gland, brain, and peritoneal seeding
- investigations
  - INR and LFTs: AST, ALT, ALP, bilirubin, and albumin
  - elevated ALP, bilirubin, and α-fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echoes), triphasic CT (enhancement on arterial phase and washout on portal venous phase), and MRI
- treatment
  - cirrhosis is a relative contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant; may use bridging therapy while awaiting transplant
    - absolute contraindications: extrahepatic disease and vascular invasion
    - relative contraindications: dependent on liver transplant protocol based on staging criteria followed by transplant centre
  - non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (consider sorafenib for HCC; preoperative chemotherapy for hepatoblastoma is standard of care), and radiotherapy
- prognosis
  - 5 yr survival: 18% of all patients; 40-70% of patients undergoing complete resection



Liver Transplantation Criteria for Hepatocellular Carcinoma

Milan Criteria*	1 tumour ≤5 cm Up to 3 tumours each ≤3 cm
UCSF Criteria*	1 tumour ≤6.5 cm Up to 3 tumours each ≤4.5 cm, total diameter ≤8 cm
Toronto Criteria*	No tumour size or number restrictions No systemic symptoms Not poorly differentiated

*Each criteria assumes no extrahepatic and no macrovascular invasion



Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, including Postoperatively)

	1 Point	2 Points	3 Points
Albumin (g/L)	>35	28-35	<28
Ascites	Absent	Easily controlled	Poorly controlled
Bilirubin (μmol/L)	<34	34-51	>51
(mg/dL)	<2.0	2.0-3.0	>3.0
Coagulation (INR)	<1.7	1.7-2.3	>2.3
Hepatic Encephalopathy	None	Minimal	
(Grade I-II)	Advanced		
(Grade III-IV)			

Points	Class	One Yr Survival	Two Yr Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Secondary

- metastases to the liver are the most common malignant tumours found in the liver
- etiology
  - GI (colorectal most common), lung, breast, pancreas, GI NET, stomach, melanoma, ovary, uterus, kidney, gallbladder, and prostate
- treatment
  - depends on the primary cancer site and prognosis
    - often liver metastases are a manifestation of Stage IV disease and chemotherapy is indicated
  - metastasectomy may be appropriate for cancers either through surgical resection or local treatment (i.e. embolization)
    - hepatic resection of metastatic colorectal liver metastases is standard of care as part of multi-modality treatment that includes chemotherapy if complete resection of the primary cancer and metastases is possible
    - transplant also a new and emerging alternative for metastatic disease in the liver
- prognosis
  - following liver resection for colorectal metastases is an overall survival of 30-60% at 5 yr



Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from colorectal, lung, and breast cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure

Liver Transplantation

Table 26. Conditions Leading to Transplantation

Parenchymal Disease	Cholestatic Disease	Inborn Errors	Tumours
Chronic hepatitis B or C*	Biliary atresia**	α1-antitrypsin deficiency	Hepatocellular carcinoma
Alcoholic cirrhosis	Primary biliary cirrhosis	Wilson's disease	Hepatoblastoma
Acute liver failure	Sclerosing cholangitis	Hemochromatosis	Metastatic NETs
Budd-Chiari syndrome			Colorectal cancer
Congenital hepatic fibrosis			
CF			
Autoimmune hepatitis			
Cryptogenic cirrhosis			
Drug induced hepatotoxicity			
Non-alcoholic steatohepatitis			

*leading cause in adults; **leading cause in children



Living Liver Donors vs. Deceased Liver Donors
The right lobe of a living donor liver is transplanted into the recipient. This is due to the larger right lobe providing a greater graft volume to sustain the metabolic demand of recipients. Donor safety and graft suitability for recipients should be considered in living donor liver transplants. Whole livers from deceased donors are transplanted orthotopically into the recipient

Clinical Indications

- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - unresectable primary liver cancers
  - unresectable but localized liver metastasis of colorectal cancer - new emerging indication
  - acute liver failure
  - liver-based metabolic conditions including α-1-antitrypsin deficiency
- end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate
  - suitable HCC not amenable to liver resection

Criteria for Transplantation

- Model for End-Stage Liver Disease (MELD): prognostic model to estimate 3 mo survival following transjugular intrahepatic portosystemic shunt (TIPS) procedure and to prioritize patients awaiting liver transplant; based on creatinine, bilirubin, INR, sodium (MELD-Na), female sex, and serum albumin; MELD scores used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and the abdominal surgery perioperative mortality of chronic liver disease and cirrhosis; patient must have ≥7 points (Class B) for transplant evaluation

Contraindications

- active alcohol/substance use
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease
- active uncontrolled infection

Postoperative Complications

- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis

- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

Biliary Tract

Cholelithiasis

Definition
- the presence of stones in the gallbladder

Pathogenesis
- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excess hepatic cholesterol secretion relative to bile salts and lecithin → supersaturated cholesterol which precipitates as gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
- cholesterol stones
  - obesity
  - increasing age
  - prevalence higher in females (especially females <50 yr)
  - estrogens: female, multiparity, OCPs
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate)
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
  - terminal ileal resection or disease (e.g. Crohn's disease)
- protective factors
  - statins, physical activity, vitamin C, poly- and monounsaturated fats and nuts, coffee

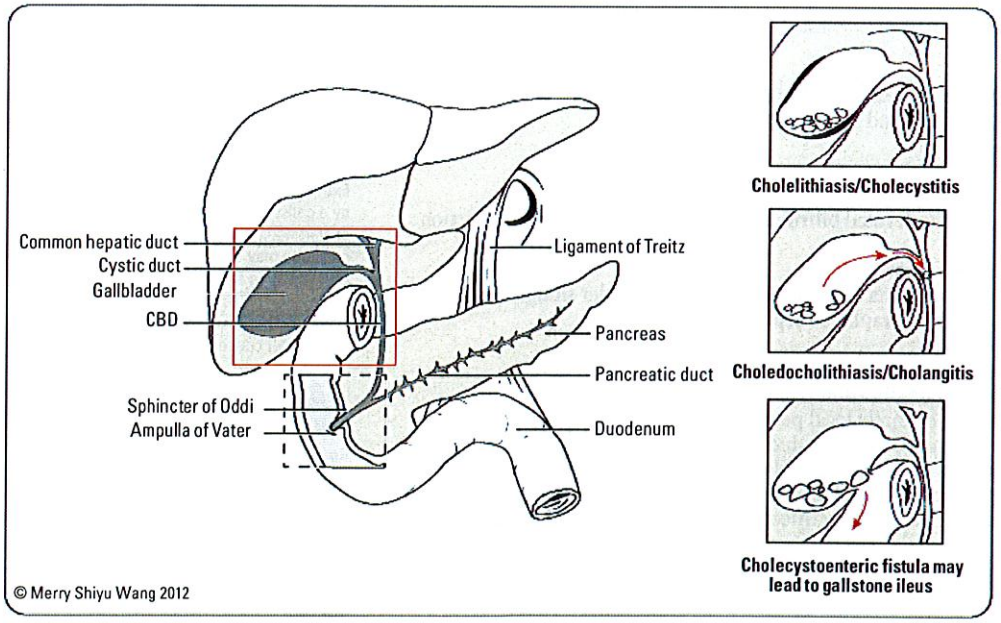


Figure 25. Gallstone disease

Clinical Features
- asymptomatic (80%): found incidentally
  - 18% risk of progression to symptomatic gallstone disease within 20 yr
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli's disease, porcelain or calcified gallbladder), sickle cell disease, paediatric patient, bariatric surgery, or immunosuppression
- biliary colic (10-25%)

Investigations
- normal bloodwork: CBC, electrolytes, Cr, LFTs, bilirubin, lipase
- U/S: diagnostic procedure of choice
  - image for signs of inflammation, obstruction, and localization of stones
  - 95% specific for detecting stones

Risk Factors for Cholesterol Stones

4Fs
Fat
Female
Fertile
Forties

Summary of Biliary Tract Conditions

Gallbladder	Asymptomatic	Pain Only	Infection + Pain
Cholelithiasis	✓ (majority)		
Biliary Colic		✓	
Cholecystitis			✓
Common Bile Duct	**Asymptomatic**	**Pain Only**	**Infection + Pain**
Choledocholithiasis	✓ (majority)	✓	
Cholangitis			✓ (majority)

Biliary Colic

Pathogenesis
- gallstone transiently impacted in cystic duct, no infection

Clinical Features
- an episode of steady, severe dull pain in the epigastrium or RUQ lasting minutes to hours (<6 h), crescendo-decrescendo pattern
- can present with chest pain, right shoulder tip pain, scapular pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- no peritoneal findings, no systemic signs

Investigations
- normal blood work: CBC, electrolytes, Cr, LFTs, bilirubin, lipase
- U/S shows cholelithiasis, may show stone in cystic duct (neck of gallbladder)

Treatment
- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success)
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, and vessel injury leading to liver damage
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery

Acute Cholecystitis

Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see *Acalculous Cholecystitis, GS57*)

Clinical Features
- often have history of biliary colic
- severe constant (>6 h) epigastric or RUQ pain, anorexia, N/V, and low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable and tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

Investigations
- blood work: elevated WBC and left shift, mildly elevated bilirubin concerning for bile duct obstruction (either stones or Mirizzi syndrome)
- U/S: 98% sensitive, consider HIDA scan if U/S negative
  - signs: gallbladder wall thickening >4 mm, edema (double-wall sign), gallbladder sludge, cholelithiasis, pericholecystic fluid, and sonographic Murphy's sign

Complications
- gangrenous gallbladder (20%) most common complication
- perforation (10%): result in abscess formation or rarely local peritonitis
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct
- empyema of gallbladder: suppurative cholecystitis (pus in gallbladder) and sick patient
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient); organisms involved in secondary infection: *C. welchii, E. coli, Klebsiella,* anaerobic streptococci, Enterococcus
- cholecystoenteric fistula (from repeated attacks of cholecystitis) can lead to gallstone ileus

Treatment
- admit, hydrate, NPO, NG tube (if persistent vomiting from associated ileus), analgesics
- antibiotics
  - cefazolin if uncomplicated cholecystitis
- ERCP prior to surgery if CBD stones are present on U/S
  - MRCP ± ERCP if CBD is markedly dilated or CBD stones suspected
- cholecystectomy
  - early (within 72 h) vs. delayed (after 6 wk, not standard)
  - equal morbidity and mortality
  - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
  - emergent OR indicated if high-risk, e.g. sepsis
  - laparoscopic is standard of care (convert to open for complications or difficult case)
    - reduced risk of wound infections, shorter hospital stay, reduced postoperative pain, and increased risk of bile duct injury
- intraoperative cholangiography (IOC)
  - indications: clarify bile duct anatomy, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), and jaundice
  - has been mostly replaced by preoperative MRCP



Biliary colic is a pain that comes and goes, but cholecystitis is a pain which is constant and usually increasing



2 Most Important Lab Tests for Biliary Pain

Lipase: to determine if element of pancreatitis

Bilirubin: to determine if bile duct obstruction



Biliary colic is treated with analgesia and elective cholecystectomy
Acute cholecystitis is treated with antibiotics and early cholecystectomy if surgical risk appropriate



Toronto Video Atlas of Surgery: Standard Laparoscopic Cholecystectomy
TVAsurg is an open access library of animation enhanced surgical videos created by surgeons in Toronto. For a video simulation of a standard laparoscopic cholecystectomy, see http://pie.med.utoronto.ca/TVASurg/project/standardlapchole/



Mirizzi Syndrome
Extrinsic compression of the CHD by a gallstone in the cystic duct or Hartmann's pouch. Impacted gallstone may erode into the CHD or CBD, creating a cholecystohepatic or cholecystocholedochal fistula; Mirizzi syndrome has an association with gallbladder cancer



Rouviere's Sulcus
Fissure between right lobe and caudate process (segment I) of liver; keeping dissection anterior to this landmark can minimize bile duct injury



Critical View of Safety (CVS)
Decreases risk of injury to CBD during laparoscopic cholecystectomy, 3 criteria are required to achieve the CVS:
1. The hepatocystic triangle (formed by the cystic duct, CHD, and inferior edge of the liver) is cleared of fat and fibrous tissue
2. The lower one third of the gallbladder is separated from the liver to expose the cystic plate
3. Two and only two structures should be seen entering the gallbladder (cystic duct and artery)

- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated
- some centres can perform percutaneous stone extraction to avoid cholecystectomy or create fistulas from stomach to gallbladder to decompress and create an internal cholecystostomy tube without the morbidity of percutaneous tube



Early vs. Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: A Meta-Analysis of Randomized Clinical Trials
Am J Surg 2008;196(1):40-47
Purpose: Evaluate effects of early versus late laparoscopic cholecystectomy in treatment of acute cholecystitis.
Methods: Systematic review and meta-analysis of randomized studies in Medline, Embase, Cochrane, and Google Scholar between 1987-2006. Endpoints included rates of conversion to open surgery, postoperative complications, length of stay, and duration of surgery.
Results: 4 RCTs included with a total of 375 patients. No differences were found between early and late groups in rates of conversion to open surgery (P=0.718) or postoperative complications (P=0.813). Length of stay was shorter for the early group (P=0.0005) while duration of surgery was shorter for the late group (P=0.002).
Conclusions: Early laparoscopic cholecystectomy for acute cholecystitis reduces length of hospital stay with comparable rates of conversion to open surgery and postoperative complications compared with late surgery.

Acalculous Cholecystitis

Definition
- acute or chronic cholecystitis in the absence of stones

Pathogenesis
- typically due to gallbladder ischemia and stasis

Risk Factors
- ICU admission (most common), DM, immunosuppression, trauma patient, TPN, and sepsis

Clinical Features
- see *Acute Cholecystitis, GS56*
- occurs in 10% of cases of acute cholecystitis

Investigations
- bloodwork: CBC, electrolytes, Cr, LFTs, liver enzymes, bilirubin, and lipase
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis, GS56*)
- CT or HIDA scan

Treatment
- NPO, IV fluids, and pain management
- IV broad-spectrum antibiotics, cholecystectomy
- if patient unstable → percutaneous cholecystostomy

Choledocholithiasis

Definition
- stones in CBD

Clinical Features
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, and fluctuating jaundice
- primary vs. secondary stones
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, and CF)
  - secondary: formed in gallbladder (85% of cases in the U.S.)



American Society of Gastrointestinal Endoscopy 2019 Guideline on Role of Endoscopy in Evaluating Choledocolithiasis

Proceed directly to ERCP
- CBD stone on U/S
- Clinical ascending cholangitis
- Bilirubin >4 mg/dL (>347 umol/L) & dilated CBD on U/S

Perform U/S, MRCP, Laparoscopic IOC or Intraoperative US
- Abnormal liver tests
- Age >55 yr
- Dilated CBD on U/S

Investigations
- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
- lipase: to rule out gallstone pancreatitis
- U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- MRCP (90% sensitive)
  - visualization of ampullary region, biliary, and pancreatic anatomy
  - non-invasive diagnostic test of choice
- ERCP
  - CBD stones in periampullary region
  - diagnostic and therapeutic; removal of stones and sphincterotomy possible
  - complications: retained stones, ERCP pancreatitis (1-2%), pancreatic or biliary sepsis
- Percutaneous Transhepatic Cholangiography
  - percutaneous approach to the proximal biliary tree (i.e. intrahepatic biliary system) via the hepatic parenchyma
  - useful for proximal bile duct obstruction or when ERCP fails or not available
  - contraindications: ascites, peri/intrahepatic sepsis, and disease of right lower lung or pleura
  - complications: bile peritonitis, chylothorax, pneumothorax, biliary sepsis, and hemobilia
- Intraoperative Cholangiography (IOC)
  - intraoperative injection of radiographic contrast into the cystic duct to evaluate CBD during laparoscopic cholecystectomy
  - useful for identifying CBD stones, clarifying biliary anatomy, and preventing CBD injury during cholecystectomy

Complications
- cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

Treatment
- treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients
- biliary tree flushing with laparoscopic cholecystectomy:
  - during a laparoscopic cholecystectomy ± cholangiogram, the cystic duct can be flushed to the CBD with the use of glucagon to relax the sphincter between the CBD and duodenum. Can also use cholangiogram to confirm stones flushed into duodenum

Acute Cholangitis

Pathogenesis
- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration, and biliary sepsis – may be life-threatening, especially in elderly

Etiology
- choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), and biliary stent
- organisms: *E. coli, Klebsiella, Enterobacter, Pseudomonas, Enterococcus, B. fragilis*, and *Proteus*



Charcot's Triad
Fever, RUQ pain, jaundice



Reynolds' Pentad
Fever, RUQ pain, jaundice, shock, and altered mental status



Common Bacteria in Biliary Tract

KEEPS
Klebsiella
Enterococcus
E. coli, Enterobacter
Proteus, Pseudomonas
Serratia

Clinical Features
- Charcot's triad: fever, RUQ pain, and jaundice
- Reynold's pentad: Charcot's triad, hypotension, and altered mental status
- may have N/V, abdominal distention, ileus, acholic stools, and tea-coloured urine (elevated direct bilirubin)

Investigations
- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, possible mild increase in AST, ALT)
- lipase: rule out pancreatitis
- U/S: intra-/extra-hepatic duct dilatation
- CT: bile duct dilatation and can identify biliary stenosis
- MRCP when diagnosis is unclear

Treatment
- initial: NPO, fluid and electrolyte resuscitation, ± NG tube, IV antibiotics (treats 80%)
- biliary decompression
  - ERCP + sphincterotomy: diagnostic and therapeutic
  - PTC with catheter drainage: if ERCP not available or unsuccessful
  - open or laparoscopic CBD exploration and T-tube placement if above fails
- in addition to biliary decompression, the underlying cause should be addressed. In the case of patients with choledocholithiasis, elective cholecystectomy is recommended after resolution of acute cholangitis to prevent re-occurrence

Prognosis
- suppurative cholangitis mortality rate: 20-30%

Gallstone Ileus



Rigler's Triad of Gallstone Ileus
Pneumobilia
Small bowel obstruction
Gallstone

Pathogenesis
- repeated inflammation causes a cholecystoenteric fistula (usually duodenal) → large gallstone enters the GI tract (impacting near the ileocecal valve) causing a mechanical bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features
- crampy abdominal pain, N/V, constipation/obstipation (see *Large Bowel Obstruction, GS37*)



Bouveret's Syndrome
Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula

Investigations
- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, and air in biliary tree (pneumobilia) (40%)
- CT: biliary tract air, obstruction, and gallstone in intestine
- Rigler's triad: pneumobilia, SBO (partial or complete), and gallstone (usually in right iliac fossa)

Treatment
- fluid resuscitation, NG tube decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy is generally not performed

Carcinoma of the Gallbladder

Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (Salmonella, Helicobacter), primary sclerosing cholangitis, and abnormal pancreaticobiliary duct junction

Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of open cholecystectomies OR 0.1% in laparoscopic cholecystectomies)
- many patients are asymptomatic until late
- local: non-specific RUQ pain ± palpable RUQ mass
- Courvoisier's gallbladder sign: enlarged gallbladder and painless jaundice due to obstruction of CBD, suggestive of gallbladder or pancreatic malignancy
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, anorexia, N/V, weight loss, and malaise
- early local extension to liver, peritoneum, may extend to stomach, duodenum
- early metastasis common to lung, pleura, liver, bone

Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, and fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as, polyps, staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, and distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

Treatment
- if carcinoma of the gallbladder is suspected preoperatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, and dissection of hepatoduodenal lymph nodes

Prognosis
- poor 5 yr survival (20%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

Cholangiocarcinoma

Definition
- malignancy of the epithelial cells of extra- or intrahepatic bile ducts

Risk Factors
- ages 50-70, gallstones, UC, primary sclerosing cholangitis, choledochal cyst, Clonorchis sinensis infection (liver fluke), chronic intrahepatic stones (hepatolithiasis), genetic disorders (Lynch syndrome, CF, multiple biliary papillomatosis, BAP1 tumour predisposition syndrome)

Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, and pale stools
- anorexia, weight loss, RUQ pain, Courvoisier's sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery, peritoneum, lungs, pleura, liver
- Klatskin tumour: cholangiocarcinoma located at bifurcation of CHD



Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma

Investigations
- LFTs show obstructive picture, carbohydrate antigen 19-9 (CA 19-9), CEA may be elevated
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Treatment
- if resectable: biliary drainage and wide excision margin
- intrahepatic lesions: liver resection after clear discussion at multidisciplinary tumour boards and prognosis understood
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure

- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in select patients with Klatskin tumours or NET with no evidence of extrahepatic disease and relative stability

Prognosis
- overall 5 yr survival: localized 30%, regional 24%, distant 2%

Pancreas

Acute Pancreatitis

- see Gastroenterology, G48

GALLSTONE PANCREATITIS (45% of Acute Pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (Pancreatitis of Any Etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, and fever
- Inglefinger's sign: pain worse when supine, and better when sitting forward
- may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)
  - APACHE II score for determining prognosis of severe acute pancreatitis
- physical exam may show tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen's sign, and Grey Turner's sign

Ranson's Criteria
A. At admission
1. Ages >55 yr
2. WBC >16 x 10^9/L
3. Glucose >11 mmol/L
4. LDH ≥350 IU/L
5. AST >250 IU/L

B. During initial 48 h
1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial PO_2 <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >6 L

C. Interpretation
<3 = severe pancreatitis unlikely (2% mortality)
≥3 = high mortality (≥15%)

Investigations
- lipase (most sensitive and specific), elevated amylase (higher than alcoholic pancreatitis), and leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), and edematous pancreas
- CXR, AXR, and CT (if severe to evaluate for complications)

Treatment
- supportive: e.g. NPO, hydration, analgesia, and early enteral nutrition
- antibiotics are not indicated for initial diagnosis. This is reserved for clear signs of infection on imaging
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if CBD stone impacted or cholangitis
- surgical indications in acute pancreatitis (rare):
  - drain placement and debridement for necrotizing pancreatitis if refractory to medical management, if septic, or in ICU without other sources of sepsis

Complications
- local complications
  - acute fluid collections
  - walled-off pancreatic fluid collection/pseudocyst (>4 wk)
  - abscess/infection, necrosis
- systemic complications
  - splenic/mesenteric/portal vessel thrombosis
  - pancreatic ascites/pancreatic pleural effusion
  - DM (due to pancreatic & insulin insufficiency)
  - ARDS/sepsis/multiorgan failure
  - coagulopathy/DIC
  - severe hypocalcemia

Chronic Pancreatitis

- see Gastroenterology, G50

Surgical Treatment

- treatment is generally medical
- indications for surgery
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, and rupture
  - CBD obstruction (e.g. strictures) and duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- preoperative CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery
- surgical options
  - drainage procedures: only effective if ductal system is dilated
  - Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - pancreatectomy: best option in absence of dilated duct
  - Whipple procedure (pancreaticoduodenectomy): proximal disease
  - distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy: distal disease
  - total pancreatectomy: refractory disease
- islet cells autotransplantation can be used to control insulin-related morbidity
  - denervation of celiac ganglion and splanchnic nerves

The hallmark of chronic pancreatitis is epigastric pain radiating to the back

Total Pancreatectomy and Islet Autotransplantation: A Decade Nationwide Analysis
World J Transplant 2016;6(1):233-238
Purpose: To investigate outcomes and predictors of in-hospital morbidity and mortality after total pancreatectomy (TP) and islet autotransplantation.
Results: A total of 923 patients underwent IAT after pancreatectomy during 2002-2012. The most common indication of surgery was chronic pancreatitis (86%) followed by acute pancreatitis (12%). Overall mortality and morbidity of patients were 0% and 57.8 %, respectively. Postoperative hypoinsulinemia was reported in 42.3% of patients, indicating that 57.7% of patients were insulin independent during hospitalization. Predictors of in-hospital morbidity were obesity, fluid and electrolyte disorders, alcohol use, and weight loss.
Conclusion: Total pancreatectomy + islet autotransplantation is a safe procedure with no mortality, acceptable morbidity, and achieved high rate of early insulin independence. Obesity is the most significant predictor of in-hospital morbidity.

WALLED-OFF PANCREATIC FLUID COLLECTIONS (PSEUDOCYSTS)

- localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
- complication of chronic and/or acute pancreatitis
- up to 40% resolve spontaneously
- cyst wall must be mature prior to drainage (4-6 wk)
- pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

Pseudocyst Management

- if asymptomatic: expectant management
- if symptomatic: choice of drainage procedure depends on location of fluid collection
  - endoscopic drainage: transmural vs. transpapillary (pseudoaneurysm an absolute contraindication, must embolize first)
  - surgical drainage: cystogastrostomy vs. cystoduodenostomy vs. cystojejunostomy
  - percutaneous catheter drainage
  - resection
  - if draining, attempt to biopsy cyst wall to rule out cystadenocarcinoma

Pancreatic Cancer

Epidemiology

- 4th most common cause of cancer-related mortality in both men and women in Canada
- M:F=1.3:1, average ages: 50-70

Risk Factors

- increased age
- smoking: 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets
- heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy
- cholecystectomy
- chemicals: β-naphthylamine, benzidine
- African descent

Clinical Features
- the most common presenting symptoms are abdominal pain, jaundice, and weight loss
- head of the pancreas (70%)
  - pancreatic head tumours typically present with jaundice, steatorrhea, and weight loss
  - other features include anorexia, dark urine, hepatomegaly, cachexia, Courvoisier's sign, recent onset DM
- body or tail of pancreas (30%)
  - tends to present later and usually inoperable (80% are unresectable at diagnosis)
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced

Investigations
- serum chemistry is non-specific, LFTs may show obstructive jaundice (elevated ALP and bilirubin)
- CA 19-9 most useful serum marker of pancreatic cancer
- U/S, CT (also evaluates metastasis and resectability) ± ERCP, MRI, EUS

Pathology
- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: pancreatic NETs (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar cell carcinoma
- see *Surgical Endocrinology, GS72* for functional pancreatic NETs

Treatment
- resectable (10-20% of pancreatic cancer)
  - no involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure <5% mortality
  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
  - adjuvant chemotherapy recommended (gemcitabine ± capecitabine, 5-FU/leucovorin)
- locally advanced, borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- locally advanced, non-resectable (palliative → relieve pain, obstruction)
  - encasement of major vascular structures including arteries
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - palliative chemotherapy (gemcitabine + nab-paclitaxel, FOLFIRINOX) ± radiotherapy

Prognosis
- most important poor prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

Table 27. TNM Classification System for Exocrine Tumours of the Pancreas (AJCC 8th edition)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma *in situ*	N1	Metastasis in one to three regional lymph nodes		
T1	Tumour ≤2 cm in greatest dimension				
N2	Metastasis in four or more regional lymph nodes				
T2	Tumour >2 cm and ≤4 cm in greatest dimension				
T3	Tumour >4 cm in greatest dimension				
T4	Tumour involves celiac axis, SMA, or common hepatic artery				



Trousseau's Sign
Spontaneous peripheral venous thrombosis, often associated with pancreatic and other cancers



Vague abdominal pain with weight loss ± jaundice in a patient over 50 yr is pancreatic cancer until proven otherwise



Courvoisier's Sign
Palpable, nontender, distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger



Steps of a Whipple Resection (Pancreaticoduodenectomy)
1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the hepatic flexure of the colon
3. Mobilization of the duodenum (Kocher maneuver) and head of the pancreas
4. Identification of the superior mesenteric vein and mobilization of the pancreatic neck
5. Mobilization of the stomach; dissection of the hepatoduodenal ligament and cholecystectomy
6. Division of the stomach, proximal jejunum, and CBD
7. Transection of the pancreatic neck and dissection of the uncinate process from the retroperitoneum
8. Restoration of gastrointestinal continuity: construction of a pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy using a neoduodenum

Remove
- CBD
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)



Oncological Benefits of Neoadjuvant Chemoradiation with Gemcitabine vs. Upfront Surgery in Patients with Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial
Ann Surg 2018;268:215-222
Purpose: To determine whether neoadjuvant treatment increases survival in patients with borderline resectable pancreatic cancer (BRPC).
Methods: A total of 50 patients were randomized to neoadjuvant gemcitabine-based chemoradiotherapy or upfront surgery.
Results: The 2-yr survival rate (2YSR) and median survival of patients treated with neoadjuvant chemoradiation was significantly improved (40.7% 2YSR, 21 mo median survival) compared to upfront surgery (26.1% 2YSR, 12 mo median survival). The R0 resection rate was also significantly increased in the neoadjuvant chemoradiation group.
Conclusion: Neoadjuvant chemoradiation provides survival and surgical benefits in patients with BRPC.

Table 28. Staging and Treatment of Pancreatic Cancer

Stage	Classification	5 Yr Survival	Treatment
0	Tis, N0, M0		Surgical resection ± chemotherapy
IA	T1, N0, M0	14%	Same as above
IB	T2, N0, M0	12%	Same as above
IIA	T3, N0, M0	7%	Same as above
IIB	T1-3, N1, M0	5%	Same as above
III	T1-3, N2, M0 T4, any N, M0	3%	Borderline resectable, trial of chemotherapy and radiation
IV	any T, any N, M1	1%	Non-resectable, palliative treatments

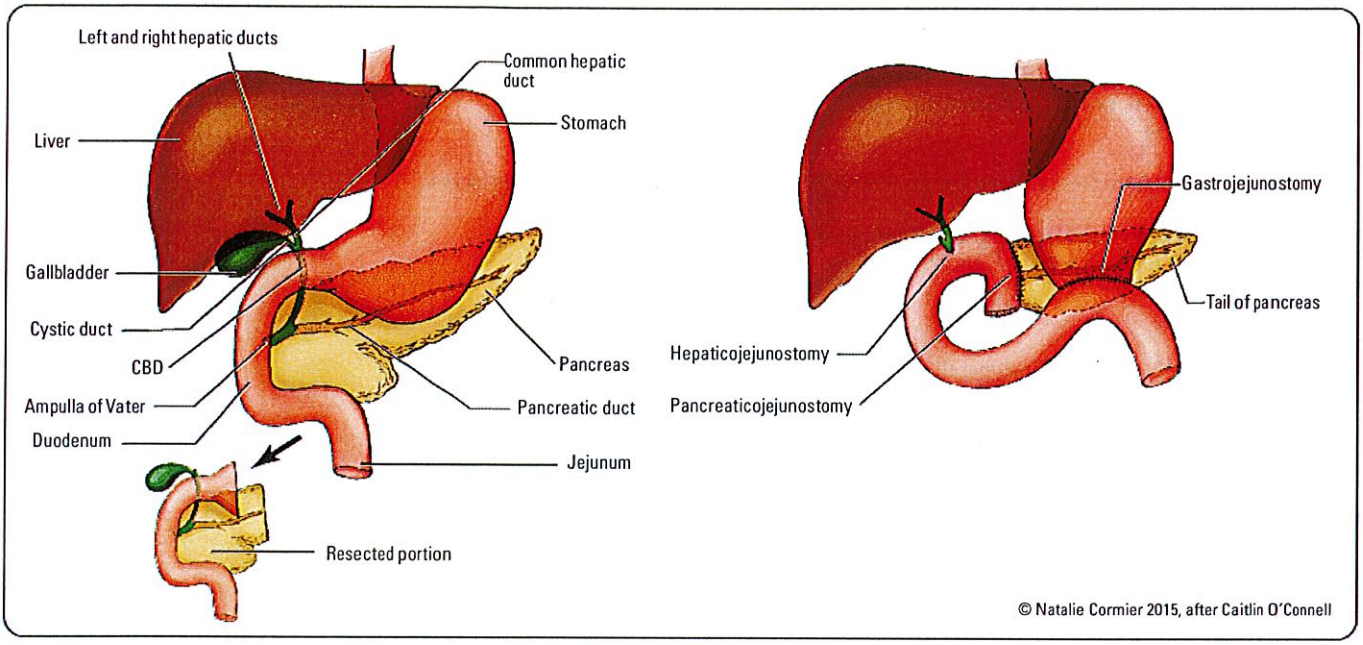


Figure 26. Schematic of Whipple resection showing the resected components

Spleen

Splenic Trauma

Clinical Features

- most common intra-abdominal organ injury in blunt trauma (especially can occur in people with splenomegaly)
- may have Kehr's sign
- patients may be hemodynamically unstable with altered mental status
- initial presentation may be masked by other injuries and contained ruptures may have few symptoms



Kehr's Sign
Left shoulder pain due to diaphragmatic irritation from splenic rupture, worsens with inspiration

Investigations

- FAST (used in trauma with hemodynamically unstable patients)
- CT with oral or IV contrast (once stable or when FAST negative)

Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative
  - hemodynamically unstable patients with positive FAST will undergo emergent operative surgical exploration
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh (if patient is hemodynamically stable)
  - splenectomy if patient unstable or high-grade injury or ongoing bleeding with hemodynamic instability
  - packing the spleen with temporary abdominal closure and relook laparotomy in 48 h

Splenectomy

Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), and sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIG



Indication of Splenectomy

SHIRTS
Splenic abscess/splenomegaly
Hereditary spherocytosis
Immune thrombocytopenic purpura
Rupture of spleen
Thrombotic thrombocytopenic purpura
Splenic vein thrombosis

Complications

- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas) and their vascular supply
  - postoperative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk <16 yr)
  - splenosis: intra-abdominal "seeding" of splenic tissue during removal
  - increased risk of malignancy, DVT, and PE
- 50% mortality

Prophylaxis

- vaccinations, ideally 2 wk pre- or postoperative (pneumococcal, *H. influenzae*, and meningococcus)
- liberal use of penicillin especially in children <6 yr

Splenic Infarct

Pathophysiology

- splenic artery occlusion or oxygen-delivery insufficiency leading to parenchymal ischemia and necrosis
- can occur in sickle cell disease, thromboembolism, myelofibrosis, CML, and hypercoagulable states

Clinical Features

- patient can be asymptomatic or can have LUQ pain (70%), N/V, fever, chills, and Kehr's sign

Investigations

- CT with contrast; MRI
- peripheral blood smear abnormalities

Treatment

- non-operative: close follow-up, analgesia
- indications for splenectomy: complications such as rupture, abscess, persistent pseudocyst, bleeding, or sepsis

Breast

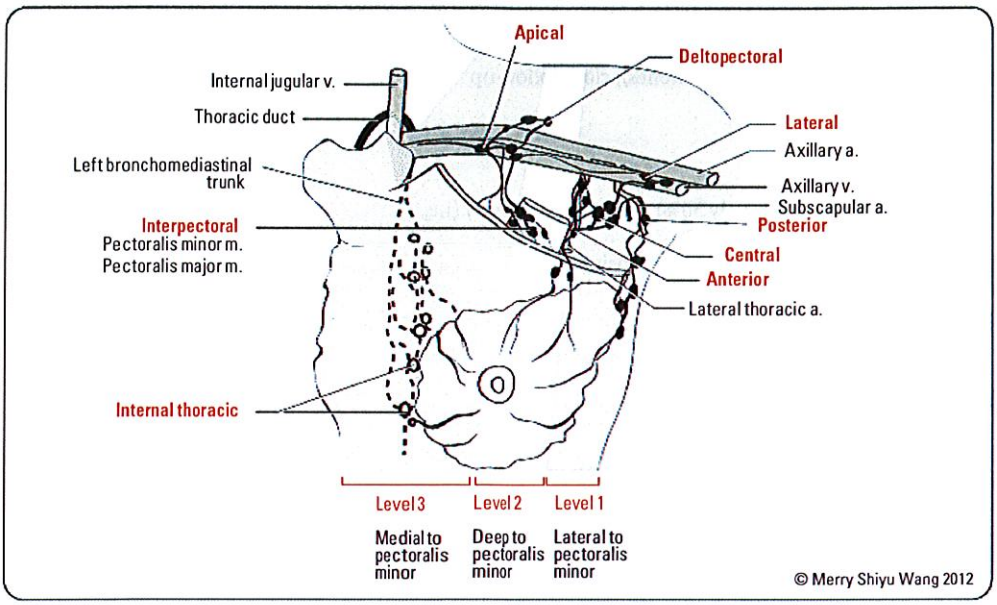


Figure 27. Anatomy of the breast

Levels of Axillary Lymph Nodes
Level I: lateral to pectoralis minor
Level II: deep to pectoralis minor
Level III: medial to pectoralis minor
(higher level of nodal involvement = worse prognosis)

DDx for Breast Mass
Benign
- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes)
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

Malignant
- Breast cancer (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)

Benign Breast Lesions

Three Categories
1. non-proliferative
2. proliferative without atypia
3. atypical hyperplasia

NON-PROLIFERATIVE LESIONS
- benign breast condition characterized by fibrous and cystic changes in the breast (fibrocystic changes/disease)
- most common: breast cysts
- other lesions include papillary apocrine change, epithelial-related calcifications, and mild hyperplasia of the usual type
- no increased risk of breast cancer
- age 30 to menopause (and after if hormone replacement therapy (HRT) used)
- clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, and nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass (U/S, mammography as indicated) and reassurance
  - analgesia (e.g. ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

PROLIFERATIVE LESIONS – WITHOUT ATYPIA

Table 29. Proliferative Lesions - Without Atypia

		Clinical Features	Diagnosis	Treatment	Risk of Breast Cancer
Fibroadenoma	Most common breast tumour in women <30 yr	Nodules: firm, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone-dependent (unlike cysts), needle aspiration yields no fluid	Core or excisional biopsy sometimes required if concerned about malignancy U/S and FNA alone cannot differentiate fibroadenoma from phyllodes tumour	Generally conservative serial observation Consider excision if size 2-3 cm and growing on serial U/S (q6 mo x 2 yr is usual follow-up), if symptomatic, formed after age 35, patient preference or features on core biopsy suggestive of a phyllodes tumour	Increased if complex, adjacent atypia or strong family history of breast cancer
Intraductal Papilloma	Solitary intraductal benign polyp	Can present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge = pathologic nipple discharge), breast mass, nodule on U/S		Surgical excision of involved duct to ensure no atypia	Can harbour areas of atypia or DCIS
Usual Ductal Hyperplasia	Increased number of cells within the ductal space	Incidental finding on biopsy of mammographic abnormalities or breast masses		None required	Generally low-risk, slightly increased if moderate or florid hyperplasia
Sclerosing Adenosis	Lobular lesion with increased fibrous tissue and glandular cells	Mass or mammographic abnormality		None required	Low-risk

ATYPICAL HYPERPLASIA
- can involve ducts (atypical ductal hyperplasia) or lobules (atypical lobular hyperplasia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

OTHER LESIONS

Fat Necrosis
- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness, ± ecchymosis
- regress spontaneously, but complete imaging ± biopsy to rule out carcinoma
- oil cysts on mammography are pathognomonic for fat necrosis

Mammary Duct Ectasia
- obstruction of a subareolar duct (see Obstetrics, *Mastitis, OB48*)

Abscess
- lactational vs. non-lactational (periductal/subareolar) (see Obstetrics, *Mastitis, OB48*)

Breast Cancer

Epidemiology
- leading cancer diagnosis in women in North America, 2nd leading cause of cancer mortality in women
- 1 in 8 (12.9% lifetime risk) women in Canada will be diagnosed with breast cancer in their lifetime
- 1 in 31 women in Canada will die from breast cancer
- all age relative survival is 87%



Female sex, followed by age, are the two greatest risk factors for breast cancer

Risk Factors
- sex (99% female)
- age (83% >50 yr)
- personal history of breast cancer and/or prior breast biopsy (regardless of pathology)
- family history of breast cancer (greater risk if relative was first degree and premenopausal)
- estrogen exposure
  - nulliparity, first pregnancy >30 yr, menarche <12 yr, or menopause >55 yr
  - decreased risk with lactation, early menopause, and early childbirth
  - >5 yr HRT use, >10 yr OCP use
- high breast density
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- BRCA1 and BRCA2 gene mutations
- alcohol use, obesity, and sedentary lifestyle



Any palpable dominant breast mass requires further investigation

Male Breast Cancer (<1%)
- most commonly invasive ductal carcinoma
- often diagnosed at later stages
- stage-for-stage similar prognosis to breast cancer in females
- consider genetic testing: most often hormone receptor positive



Breast Lymphatic Drainage:
Axillary lymph nodes
Internal mammary lymph nodes
Infra-/supra-clavicular lymph nodes

Investigations
- see margin for physical exam findings
- mammography
  - indications: screening guidelines (see Family Medicine, FM4)
  - findings indicative of higher risk of malignancy
    - mass that is poorly defined, spiculated border
    - microcalcifications
    - architectural distortion
    - interval mammographic changes
  - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity. Use annual MRI and mammography for patients with 25% lifetime risk of breast cancer
  - Digital Breast Tomosynthesis (DBT): improved lesion localization and characterization in noncalcified lesions
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup indicated in Stage II-IV disease: bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (if specific neurological symptoms)



Physical Exam Findings in Breast Cancer:
Lump/mass: Often firm, irregular, non-mobile, unilateral
Pain: Usually thought of as painless, however pain may be present with rapidly expanding tumours or inflammatory cancer
Inflammation (and peau d'orange): There are many benign causes of inflammation, however inflammatory cancer can present similarly
Nipple or skin retractions/changes: Nipple or skin retractions/changes: Attachment of the tumour to skin/nipple may cause retraction/distortion
Nipple discharge: Majority due to benign causes, bloody spontaneous discharge should be investigated for malignancy

Diagnostic Procedures

- "triple test" for diagnosis of breast cancer:
  - clinical breast exam
  - imaging
    - ≥30 yr: mammography and U/S
    - <30 yr or lactating or pregnant: U/S (high breast density)
  - pathology (biopsy)
    - U/S or mammography guided core needle biopsy: most common
    - needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
    - excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Genetic Screening

- consider testing for BRCA1/2 if:
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer



Phyllodes tumours are rare fibroepithelial breast tumours that can be benign or malignant that mostly affect women from 35-55 yr

Staging

- patients are assigned a clinical stage preoperatively (cTNM); following surgery the pathologic stage is determined (pTNM)
- clinical
  - tumour size by palpation, mammogram, U/S, and/or MRI
  - nodal involvement by palpation, imaging
  - metastasis by physical exam, CXR, abdominal U/S (or CT chest/abdomen/pelvis), and bone scan (usually done postoperative if node-positive disease)
- pathological
  - tumour size and type
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade
  - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, and sentinel lymph node biopsy (SLNB) positive/negative
  - tumour biology: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu oncogene status
  - margins: for invasive breast cancer, negative margin is sufficient; for DCIS prefer 2 mm margin
  - lymphovascular invasion (LVI)
  - extensive *in situ* component (EIC): DCIS in surrounding tissue
  - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

Table 30. TNM Classification System for Staging of Breast Cancer (AJCC 2017)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Ductal carcinoma *in situ*	N1	Involvement of 1-3 axillary lymph nodes and/or clinically negative internal mammary nodes on sentinel node biopsy		
T1	Tumour ≤2 cm in greatest dimension				
N2	Involvement of 4-9 axillary lymph nodes or clinically positive ipsilateral internal mammary lymph node				
T2	Tumour >2 cm but ≤5 cm in greatest dimension				
T3	Tumour >5 cm in greatest dimension				
T4	Tumour of any size with direct extension to chest wall and/or skin				



Favourable Features	Unfavourable Features
<2 cm	>5 cm
Grade I (low grade)	Grade III (high grade)
Node negative	Node positive
ER positive	ER negative
Mucinous pattern	Inflammatory cancer
	Her2/Neu positive
	Positive margins
	Lymphovascularinvasion
	Epidermal inclusion cyst
	Dermal lymphatics involved

Pathology

NON-INVASIVE

Ductal Carcinoma *in situ* (DCIS)

- proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
- 80% non-palpable; detected by screening mammogram as microcalcifications
- risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
- treatment
  - lumpectomy with wide excision margins + radiation (5-10% risk of invasive cancer)
  - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
  - possibly tamoxifen as an adjuvant treatment
  - 99% 5 yr survival



Analysis of Circulating Tumour DNA to Monitor Metastatic Breast Cancer
NEJM 2013;368:1199-1209
Study: The quantification of circulating tumour DNA, cancer antigen 15-3 (CA 15-3), and circulating tumour cells in 30 women with metastatic breast cancer receiving systemic therapy. The results were compared with radiographic imaging of tumours.
Results/Conclusions: Circulating tumour DNA was detected in 97% of women and showed greater correlation with changes in tumour burden than did CA 15-3 or circulating tumour cells, providing the earliest measure of treatment response in 53% of women. CA 15-3 and circulating tumour cells were detected in 78% and 87% of women, respectively. Circulating tumour DNA may therefore be an informative biomarker for metastatic breast cancer.

Lobular Carcinoma *in situ* (LCIS)

- neoplastic cells completely contained within breast lobule
- no palpable mass and no mammographic findings; usually incidental finding on breast biopsy for another indication
- LCIS is a risk factor for invasive carcinoma (approximately 1%/yr)
- treatment
  - if diagnosed on core biopsy, excisional biopsy necessary to rule out malignancy
  - if diagnosed on excisional biopsy, wide excision not needed since LCIS is often multicentric and not managed as precursor lesion
  - clinical follow-up and surveillance; consider chemoprevention (e.g. tamoxifen)



10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study
Lancet Oncol 2016;17(8):1158.
See Landmark General and Thoracic Surgery Trials table for more information on the 10 yr survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer.

INVASIVE

Invasive Ductal Carcinoma (most common 80%)

- originates from ductal epithelium and infiltrates supporting stroma
- four types: tubular, mucinous, medullary, and inflammatory
- characteristics: hard, scirrhous, infiltrating tentacles, and gritty on cross-section
  - divided into three grades based on cytologic and architectural features: well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3)

Invasive Lobular Carcinoma (8-10%)

- originates from lobular epithelium, 20% bilateral
- subtle thickening originating from lobes/lobules; usually positive for estrogen and progesterone receptors
- harder to detect on mammography due to lack of microcalcifications (may benefit from MRI)

Paget's Disease of the Breast (1-3%)

- ductal carcinoma that invades nipple with scaling, ulceration, erythema, and eczematous lesion

Inflammatory Carcinoma (1-3%)

- most aggressive form of breast cancer
- ductal carcinoma that grows in nests (vs. solid tumour); invades and blocks dermal lymphatics
- clinical features: erythema, skin edema, warm, swollen, and tender breast ± lump, nipple changes
- peau d'orange indicates advanced disease (IIIb-IV)

Sarcomas: rare

- most commonly phyllodes tumour, a variant of fibroadenoma with potential for malignancy
- can also be angiosarcomas – after previous radiation

Lymphoma: rare

Other

- papillary, medullary, mucinous, and tubular cancers
- generally better prognosis

Treatment

Table 31. Breast Cancer Treatment by Stage

Stage	Primary Treatment Options	Adjuvant Systemic Therapy
0 (*in situ*) Tis, N0, M0	BCS + radiotherapy BCS alone if margins >1 cm and low nuclear grade Mastectomy* ± SLNB	Consider postoperative tamoxifen for ER+, trastuzumab for HER2+
I IA: T1, N0, M0 IB: T1, N1mi, M0	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	May not be needed; discuss risks/benefits of chemotherapy and tamoxifen
II A: T0, N1, M0 T1, N1, M0 T2, N0, M0 B: T2, N1, M0 T3, N0, M0	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	Chemotherapy for premenopausal women or postmenopausal and ER negative, followed by tamoxifen if ER+
III A: T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0 B: T4, N0, M0 T4, N1, M0 T4, N2, M0	Likely mastectomy + axillary node dissection + radiotherapy after chemotherapy (neoadjuvant)	Neoadjuvant therapy should be considered (i.e. preoperative) especially if not resectable chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. postoperative)
Inflammatory	Mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy
IV any T, any N, M1	Surgery as appropriate for local control	Primary treatment is systemic therapy (i.e. chemotherapy) and/or hormone therapy

BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy
*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient's preference since choice of local treatment does not significantly affect survival if local control is achieved

PRIMARY SURGICAL TREATMENT

Breast Conservation Surgery (BCS)

- lumpectomy must be combined with radiation for survival equivalent to mastectomy
- contraindications include
  - high-risk of local recurrence (e.g. extensive malignant-type calcifications on mammogram), and multifocal primary tumours
  - failure to obtain tumour-free margins after re-excision
  - not suitable for radiation therapy (pregnancy, previous radiation, and collagen vascular disease)
  - large tumour size relative to breast

Mastectomy

- radical mastectomy (rare): removes all breast tissue, skin, pectoralis muscle, and axillary nodes
- modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
- simple mastectomy: removes all breast tissue and skin
- see Plastic Surgery, PL38 for breast reconstruction

Sentinel Lymph Node Biopsy (SLNB)

- performed in women with clinically node-negative invasive breast cancer and those with extensive DCIS who are undergoing mastectomy
- patients with clinically suspicious nodes should get U/S + FNA prior to decision to proceed with SLNB
- technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
- intraoperative frozen section evaluated can be considered
- proceed with ALND if >3 positive nodes, with 1-3 nodes whole breast radiation therapy may be an alternative
- 5% false negative rate

Axillary Lymph Node Dissection (ALND)

- perform in patients with:
  - locally advanced (T4a, b, c) or inflammatory breast cancer
  - clinically node-positive axilla, confirmed by FNA or core biopsy, in a patient for whom neoadjuvant chemotherapy is not planned
  - several other specific cases (sentinel or axillary nodes, which remain positive after neoadjuvant chemotherapy, axillary recurrence following previous breast cancer treatment, among others)
- side effects: risk of arm lymphedema (10-15%), especially if getting radiation therapy, decreased arm sensation, and shoulder pain



BCS can be offered to most women with stage I/II disease



There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease



Effect of Radiotherapy after Mastectomy and Axillary Surgery on 10 Year Recurrence and 20 Year Breast Cancer Mortality: Meta-Analysis of Individual Patient Data for 8135 Women in 22 Randomised Trials
EBCTCG (Early Breast Cancer Trialists' Collaborative Group)
Lancet 2014;383(9935):2127-2135
Study: Assessed the effect of radiotherapy in women with one to three positive lymph node(s) after mastectomy and axillary dissection in a meta-analysis of 8135 women in 22 trials.
Results: For 700 women with axillary dissection and no positive nodes, radiotherapy had no significant effect on local regional recurrence, overall recurrence, or breast cancer mortality. For 1314 women with axillary dissection and one to three positive nodes, radiotherapy reduced local regional, overall recurrence, and breast cancer mortality. 1133 of these 1314 women were in trials in which systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was given in both trial groups and radiotherapy again reduced local regional recurrence, overall recurrence, and breast cancer mortality. For 1772 women with axillary dissection and four or more positive nodes, radiotherapy reduced local regional recurrence, overall recurrence, and breast cancer mortality.
Conclusion: Post mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given.

ADJUVANT/NEOADJUVANT

Radiation
- indications
  - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy
  - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement

Hormonal
- indications
  - ER positive plus node-positive or high-risk node-negative
  - selective estrogen receptor modulators (SERM) if premenopausal (e.g. tamoxifen) or aromatase inhibitors if postmenopausal (e.g. anastrozole); optimal duration 5-10 yr
  - other options include ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), and androgens (e.g. fluoxymesterone)
  - palliation for metastatic disease

Chemotherapy
- indications
  - ER negative plus node-positive or high-risk node-negative
  - triple-negative disease (ER/PR and HER2-negative) - more common in younger and African-American women
  - ER positive and young age
  - stage I disease at high-risk of recurrence (high grade, lymphovascular invasion)
  - palliation for metastatic disease
  - for HER2 positive breast cancer, add trastuzumab ± pertuzumab to the chemotherapy regimen

Effect of Axillary Dissection vs. No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial
JAMA 2017;318(10):918-926
Purpose: Assessed whether the 10 yr overall survival of patients with sentinel lymph node metastases treated with breast-conserving therapy and sentinel lymph node dissection (SLND) alone without axillary lymph node dissection (ALND) is noninferior to that of women treated with axillary dissection.
Results: The 10 yr overall survival was 86.3% in the SLND alone group and 83.6% in the ALND group. The 10 yr disease-free survival was 80.2% in the SLND alone group and 78.2% in the ALND group. 10 yr regional recurrence did not differ significantly between the 2 groups.
Conclusion: Among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases, 10-yr overall survival for patients treated with SLND alone was noninferior to overall survival for those treated with ALND.

FOLLOW-UP

Post-Treatment Follow-Up
- assessment and physical exam q3-6 mo x 3 yr, q6-12 mo x 2 yr, and annually thereafter
- following BCS mammography q6-12 mo; can reduce to annual once stable, no other routine imaging unless clinically indicated
- women who receive tamoxifen should have regular gynecologic follow-up (increased risk of endometrial cancer)

Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per yr up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis
- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation
- overall survival of metastatic breast cancer is 36-60 mo

Surgical Endocrinology

Thyroid and Parathyroid

- see Endocrinology, E24

Thyroidectomy

- indications: some thyroid cancers or suspicious thyroid nodules, metastases to thyroid, large (substernal) or symptomatic thyroid goitre, toxic nodules, or some patients with definitive management of Graves' disease (not candidates for RAI). There are minimally invasive approaches to thyroid nodules including Scarless (Transoral)Thyroidectomy and RFA (Radiofrequency Ablation) of large symptomatic or hot thyroid nodules.
- preoperative workup: thyroid U/S for thyroid nodules, FNA for nodules ≥1 cm with suspicious U/S features or for most nodules ≥1.5 cm with lower suspicion U/S features, and CT neck for preoperative staging when advanced disease is suspected
- complications
  - lobectomy: recurrent laryngeal nerve palsy (hoarseness or swallowing issues), neck hematoma
  - total thyroidectomy: same as above plus hypoparathyroidism/hypocalcemia, bilateral RLN palsy (potentially requiring tracheostomy)
  - 20-75% of patients need thyroxine after lobectomy and 100% need thyroxine after total thyroidectomy

Parathyroidectomy

- elevated calcium found for any reason as an outpatient (but also incidental finding as inpatient) is likely primary hyperparathyroidism and should be investigated further
- indications: symptomatic primary hyperparathyroidism (osteoporosis/stones), asymptomatic primary hyperparathyroidism with specific laboratory criteria (profoundly elevated serum Ca^{2+}, hypercalciuria/asymptomatic kidney stones, Cr clearance <30% normal, <50 yr)
- contraindications: familial hypocalciuric hypercalcemia
- preoperative localization to find parathyroid adenoma. Localizing studies include: 99mTc sestamibi scanning with ± SPECT (single-photon emission computed tomography), U/S, contrast CT
- complications: recurrent/superior laryngeal nerve injury, postoperative hypocalcemia, infection, and bleeding

Adrenal Gland

- see Endocrinology, E33 and E40
- functional anatomy
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), and reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types of adrenal tumours: functional (e.g. Cushing's syndrome, Conn's syndrome, pheochromocytoma) or non-functional

INCIDENTALOMA

- adrenal mass discovered by investigation of unrelated symptoms/issues

Epidemiology

- benign adenoma (70-80%) > metastases to adrenal (22%) >> cyst carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, and kidney
- peak incidence of carcinoma: females ages 50-60, risk decreases with increasing age and male gender

Investigations

- CT: size >4-6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm), MRI is not as good as CT and does NOT need to be done after CT
- functional studies
  - pheochromocytoma: plasma metanephrines (highly specific and sensitive). If not available, 24 h urine catecholamines
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, AM aldosterone, AM plasma renin activity level, ARR (Aldosterone-Renin-Ratio). If inconclusive, saline suppression test if appropriate
  - not routinely - only if clinical suspicion: adrenal androgens (17-OH progesterone and DHEAS)
- FNA biopsy: NOT APPROPRIATE in most cases. Diagnostic adrenalectomy by high volume endocrine surgeon ideal if diagnostic uncertainty

Treatment
- functional tumour: resect
- non-functional tumour
  - >4 cm: consider resection
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement
  - genetic testing important for ALL Pheochromocytoma/paragangliomas as >30% are related to genetic syndrome

Pancreas

INSULINOMA
- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

Clinical Features
- Whipple's triad
- palpitations, trembling, diaphoresis, confusion, seizure, and personality changes

Investigations
- blood work: decreased serum glucose and increased serum insulin and C-peptide, pro-insulin
- CT, EUS, MRI: insulinomas evenly distributed throughout head, body, tail of pancreas

Treatment
- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
- tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

GASTRINOMA
- tumour secreting gastrin; cause of Zollinger-Ellison syndrome, associated with MEN1

Clinical Features
- abdominal pain, PUD, severe esophagitis
- multiple ulcers in atypical locations refractory to antacid therapy

Investigations
- blood work: serum gastrin levels (usually >1000 pg/mL), secretin stimulation test
- endoscopy: 90% of patients develop peptic ulcers
- CT, EUS, MRI: 70-90% found in Passaro's triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
- somatostatin receptor scintigraphy scan

Treatment
- 50% are malignant
- surgical resection of tumour dependent on location
- non-surgical treatment: high dose PPI, octreotide (somatostatin analogs)
- radiation therapy may be considered for nonsurgical candidates

VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
- tumour secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

Clinical Features
- severe watery diarrhea causing dehydration, anorexia, weakness, and electrolyte imbalance (hypokalemia)

Investigations
- blood work: serum VIP levels
- CT, MRI, EUS

Treatment
- repletion of fluid and electrolytes
- somatostatin analogues
- surgical resection/palliative debulking



Whipple's Triad
- Symptomatic fasting hypoglycemia
- Serum glucose <2.8 mmol/L
- Relief of symptoms when glucose is administered



Zollinger-Ellison Syndrome
Characterized by gastric acid hypersecretion caused by secretion of gastrin from gastrinomas; patient experiences diarrhea and abdominal pain, as well as peptic disease and reflux disease



Hypertrophic Pyloric Stenosis
Non-bilious emesis in infants is the classic presentation



Rule of 2s for Meckel's Diverticulum
- **2**% of the population
- **2**:1 male-to-female ratio
- Symptomatic in **2**% of cases
- Found within **2** feet (10-90 cm) of the ileocecal (IC) valve
- **2** inches in length
- **2** inches in diameter
- **2** types of tissue (ileal or ectopic gastric, pancreatic)
- Often present by **2** y/o

Pediatric Surgery

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Hydrocele (see Urology, U32)	1-2% of live births Majority resolve spontaneous by 1 yr M:F=6:1 Prematurity	Communicating hydroceles: processus vaginalis connects peritoneum with tunica vaginalis, so peritoneal fluid flows freely between the two with potential for abdominal contents to enter groin (i.e. inguinal hernia) Noncommunicating hydroceles: processus vaginalis is closed and more fluid produced than absorbed in tunica vaginalis; in older children, may be secondary to testicular pathology (e.g. reactive hydrocele)	Painless scrotal mass Communicating hydroceles increase in size with standing or valsalva, may be absent in the morning and large in the evening	Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk	U/S if suspect pathology	Most resolve spontaneously by 1 yr Surgical repair if: Persistence >2 yr Pain Fluctuating in size which suggests communication Cosmetic reasons Infection	<2% recurrence
Hypertrophic Pyloric Stenosis	0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F=4:1 Early erythromycin exposure (<13 d)	Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction Hypovolemia caused by emesis of gastric contents causes hypochloremic, hypokalemic metabolic alkalosis Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria	Projectile non-bilious vomiting Vomiting 30-60 min after feeds Hungry after vomiting Dehydration (variable severity)	Smooth oblong 1-2 cm "olive" mass palpable above umbilicus in the RUQ Visible left-to-right gastric contraction "waves" after feeding	Electrolytes (assess hypochloremia, dehydration) U/S shows pyloric length 17 mm, muscle thickness >4 mm Upper GI series (necessary only when U/S is unavailable or non-diagnostic) will show "string sign"	Fluid resuscitate with NS, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate NG tube decompression unnecessary Pyloromyotomy, open (Ramstedt vs. transumbilical or laparoscopic approach) is the definitive treatment Alternative therapies such as TPN/wait or atropine impractical due to long time course of effect	Pyloromyotomy curative
Congenital Diaphragmatic Hernias 3 types: Posterolateral (Bochdalek) Left-sided (85%) Right-sided (13%) Bilateral, rare, often fatal Anterior (Morgagni) Hiatus	1 in 2000 to 5000 live births Presents within hours of life although some cases of delayed presentation M=F >10% are associated with other congenital anomalies Prenatal diagnosis common	Combinations of small bowel, large bowel, stomach, and solid viscera (spleen, liver) may herniate into thorax Varying degrees of pulmonary hypoplasia and pulmonary hypertension possible	Early respiratory distress Cyanosis Scaphoid abdomen Prenatal diagnosis	Decreased air entry ± bowel sounds in the chest Displaced heart sounds	Prenatal US/MRI ABG CXR (bowel loops in hemithorax, shifted heart) Echocardiography Genetic consultation if warranted	Intubate/ventilate Orogastric suction Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation) Surgical repair after stable by hernia reduction and closure of diaphragmatic defect open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect	Better outcomes in later presentations Neurodevelopmental impairment Hearing deficit (40%) Associated GERD MSK defects chest wall and scoliotic defects as potential complications of thoracotomy Long-term surveillance for potential recurrence Failure to thrive Chronic lung disease if severe hypoplasia
Meckel's Diverticulum Most common remnant of vitelline duct that connects yolk sac with primitive midgut	1-3% of population M:F=3:1 Present most frequently during first 5 yr of life Symptomatic in 2% of cases	Failure of vitelline duct to regress 5-7 wk *in utero*; 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, and fibrous band	BRBPR (heterotopic gastric mucosa in Meckel's causing mucosal ulceration and bleeding in adjacent small bowel mucosa) Abdominal sepsis (Meckel's diverticulitis ± perforation) Small bowel volvulus around fibrous band Intestinal obstruction symptoms	Tenderness and distension (lower abdomen) near umbilicus	AXR Meckel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%)	Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy	Resection curative
Malrotation	1 in 500 live births 1/3 present by 1 wk of age, 3/4 by 1 mo of age, 90% by 1 yr of age M:F=1:1 Higher incidence among patients with cardiac anomalies or heterotaxy syndromes	Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high-risk for volvulus)	Cardinal sign: bilious emesis (especially if abdomen nondistended) If bilious emesis with distended abdomen, consider surgical exploration to rule out volvulus Rectal bleed (late/ominous signs) Intermittent symptoms	Bilious drainage from NG tube Tachycardic, pale Diaphoretic Flat abdomen Tenderness	AXR: proximal SBO, double-bubble sign, intestinal wall thickened Immediate UGI: dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, "corkscrew" sign indicating volvulus U/S: "whirlpool" sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies	IV antibiotics Fluid resuscitation EMERGENT LAPAROTOMY Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd's bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy Positioning the bowel into non-rotation (SBO in right abdomen, LBO in left abdomen)	Mortality related to length of bowel loss: 10% necrosis 100% survival rate, 75% necrosis 35% survival rate Recurrence 2-6%

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Gastroschisis	1 in 2000 live births Antenatal diagnosis common Increased risk with younger maternal age and associated with IUGR Rate slightly higher in male infants Smoking	Defect of abdominal wall near umbilicus, with free extrusion of intestine into amniotic cavity No specific environmental factor identified Defect in embryogenesis unclear	Not associated with genetic syndromes 10% with intestinal atresia Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel	Hollow viscera (stomach, small and large bowels) Defect lateral to cord (usually right) Bowel may be inflamed, thickened, matted, foreshortened Defect size variable	Prenatal U/S Elevated MS-AFP	NG tube decompression IV fluids IV antibiotics Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo May have bowel dysmotility requiring motility medications	>90% survival rate
Omphalocele	1 in 5000 live births Antenatal diagnosis common Lower gestational age Increased maternal age M:F=1.5:1	Defect of abdominal wall and umbilical ring, with extrusion of sac-covered viscera (amnion, Wharton's jelly, peritoneum) through the umbilical ring Duhamel's theory failure of body wall morphogenesis Commonly associated with rotational abnormalities of the intestine	30-70% associated with genetic syndromes (e.g. Pentalogy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome, Trisomy 18) Associated pulmonary hypoplasia	Hollow viscera (stomach, small and large bowels, often liver) Sac present with cord attached	Prenatal U/S Elevated MS-AFP	NG tube decompression IV fluids, IV antibiotics Small defect (<2 cm): Primary closure Medium (2-4 cm) and large (>4 cm) defects: silver sulfadiazine coupled with compression dressing (to allow epithelialization and gradual reduction) or Silon Silo Pouch, followed by future repair ± mesh	40-70% survival rate Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles
Umbilical Hernias	Incidence 2-14% Increases with prematurity Decreases with increasing age	Incomplete closure of peritoneal and fascial layers within umbilicus by 4 yr Hernia is peritoneum-lined and skin-covered Size of fascial defect determines chances of spontaneous closure	Majority asymptomatic Majority (95%) spontaneously resolve by age 4 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood	Protrusion from umbilicus Different from less common abdominal wall hernias that do not spontaneously resolve (e.g. epigastric hernias) Most defects >1.5 cm in infancy will not close spontaneously	None if uncomplicated	Repair if not spontaneously closed by age 5 Earlier repair of large "proboscoid" hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect	Rarely become incarcerated Low risk of recurrence
Intestinal Atresia	Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or "double-bubble" sign on x-ray for duodenal atresia Decreased with increasing age	Duodenal failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10) Jejunal/ileal acquired as a result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends Colonic mechanism unknown, thought to be similar to small bowel atresia	Gastric distension and vomiting (usually bilious) Duodenal may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal within 2 d of birth, may be associated with CF Colonic within 3 d of birth	Complete physical Special attention to abdominal exam, perineum, and anus Include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice	Contrast enema ± UGI with small bowel follow through (SBFT) Group and screen INR and PTT if for surgery	NPO NG tube decompression Fluid resuscitation TPN Broad spectrum antibiotics Duodenal duodenoduodenostomy or duodenojejunostomy Jejunal/ileal primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic primary anastomosis	Long-term survival: Duodenal 86% Jejunal/ileal 84% Colonic 100%
Congenital Aganglionic Meirschsprung's Disease	1 in 5000 births M:F=3:1 to 4:1, approaches 1:1 when whole colon involved Can have aganglionosis of small bowel as well Familial Hirschsprung's in <5% of cases	Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristalse and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively Starts in the rectum and variable involvement proximally; RET mutation	Failure to pass meconium spontaneously within 48 h of life (95% pass meconium within 24 h, 5% within 48 h) Symptoms of bowel obstruction: abdominal distension, constipation, bilious emesis Enterocolitis/sepsis Failure to thrive	± Abdominal distension Squirt/blast sign	Rectal biopsy (gold standard) look for aganglionosis and neural hypertrophy AXR Contrast enema to find narrow rectum and transition zone Anal manometry unreliable in infants classic finding is absence of rectoanal inhibitory reflex	Duhamel pull-through procedure: surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis	Most have normal/ near-normal anorectal function Complications: fecal incontinence and constipation, postoperative enterocolitis (medical emergency if progresses to sepsis)
Cryptorchidism	Most common congenital abnormality of the GU tract 2-5% of term males most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend Suspect in prematurity	Idiopathic Descent is mediated by INSL3 and testosterone Descent usually begins at 28 wk	Palpable testicle within inguinal canal or testicle which can be milked down into the scrotum (called retractile testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities	Scrotal asymmetry Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile testis (which is "high" testis due to hyperactive cremasteric muscles)	Depends on age of presentation Older child: LH, FSH, Müllerian inhibiting substance, hCG stimulation test for gonadotropin production Infant: U/S, FSH, LH, karyotype, MIS, 17-hydroxy-progesterone If non-palpable: exam under anesthesia, exploratory laparoscopy	hCG to stimulate testosterone production and descent Orchidopexy especially if undescended by age 6 mo-2 yr	Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testicle Descent can preserve spermatogenesis if performed by 1 yr

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Intussusception	Most common cause of bowel obstruction between 6-36 mo 26 in 100,000 newborns M:F=3:2 Pathologic lead points: enlarged Peyer's patches due to viral infections of the GI tract, polyps, Meckel's diverticulum CF, lymphoma and IBD may increase risk	Usually idiopathic Usually starts at ileocecal junction Telescoping of bowel into itself causing an obstruction and vascular compromise	Acute onset abdominal pain Episodic "colicky" pain Vomiting ± bilious Abdominal mass Currant-jelly stool suggests mucosal necrosis and sloughing	Abdominal exam Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness Signs of bowel obstruction: distended abdomen Look for localized peritonitis which suggests transmural ischemia	AXR for signs of bowel obstruction or perforation U/S if suspect pathology	If peritonitis, consider operative management Non-operative management involves reduction via air contrast enema Operative reduction (open or laparoscopically) Resection of involved colon if failure to reduce or bowel appears compromised	10% recurrence rate If recurrent = more likely non-idiopathic If successfully reduced by enema in older children, allow 2 wk resolution of edema before performing SBFT to rule out pathologic lead points
Tracheoesophageal Fistula (TEF)	1 in 3000 to 1 in 4500 live births Typically occurs with esophageal atresia	Defect in the lateral septation of the foregut into the esophagus and trachea causing connection between the esophagus and trachea Associated anomalies in 50%: VACTERL association	Varies with type of fistula May have history of maternal polyhydramnios May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth, and nose that return after suctioning	Abdominal distention	X-ray: anatomic abnormalities, NG tube curled in pouch	Investigate for other congenital anomalies Early repair by surgical ligation to prevent lung damage and maintain nutrition and growth	Complications: pneumonia, sepsis, reactive airways disease Following repair: esophageal stenosis and strictures at repair site, GERD, and poor swallowing (i.e. dysphagia, regurgitation)
Inguinal Hernias	5% of all term newborns 2x risk and more likely bilateral if pre-term M:F=4:1 Low birth weight increases risk 1/5 inguinal hernias will become incarcerated if patient is <1 yr Incarceration is more common in females Associated with other conditions: androgen insensitivity, connective tissue diseases	All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis Inguinal hernia can be reducible, incarcerated (unreducible), or strangulated	Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele) If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted	Palpate for "bag of worms" - suggests possible testicular varicocele Biannual testicular exam + palpation along inguinal canal to evaluate for any masses "Silk sign" palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen Must always try reduction to confirm that hernia is not incarcerated	Physical exam is gold standard U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult)	Manual reduction in the ER to relieve acute symptoms For reducible hernia: repair within a few wk (if <1 yr) vs. elective repair (if >1 yr) For incarcerated hernia: repair immediately (emergency) Herniorrhaphy (laparoscopic or open) definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias	Risk of recurrence after surgical reduction <3%, higher if repair done in premature infants or if hernia was incarcerated/ strangulated

Skin Lesions

- see Dermatology, D8; Emergency Medicine, ER43; Plastic Surgery, PL5

All inguinal hernias of infancy and childhood require repair at the earliest convenience; emergent repair if incarcerated/strangulated

Common Medications

Types	Drugs and Dosing
Antiemetics	dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6 h prn
	prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM BID-TID prn
	metoclopramide (Maxeran®) 10 mg IV/IM q2-3 h prn, 10-15 mg PO QID (30 min before meals and QHS)
	ondansetron (Zofran®) 4-8 mg PO q8 h prn
	granisetron (Kytril®) 1 mg PO BID (for nausea from chemotherapy/radiation)
Analgesics	acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6 h PO/PR prn
	hydromorphone 1-2 tabs PO q4 h prn, 0.5-2 mg IV q3-4 h prn
	ibuprofen 200-400 mg PO q4-6 h prn
	morphine 2.5-10 mg IM/SC q4-6 h prn + 1-2 mg IV q1 h prn for breakthrough
	ketorolac (Toradol®) 30-60 mg IM/IV q6 h prn
	acetaminophen/oxycodone (Percocet®) 325/5 mg, 1-2 tabs PO q4-6 h prn
DVT Prophylaxis	heparin 5000 units SC BID; if cancer patient, then heparin 5000 units SC TID/BID
	dalteparin (Fragmin®) 5000 units SC daily
	enoxaparin (Lovenox®) 40 mg SC daily
Antidiarrheals	loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d
	diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO QID
Laxatives	sennosides (Senokot®) 1-2 tabs QHS
	docusate sodium (Colace®) 100 mg PO BID
	glycerine suppository 1 tab PR prn
	lactulose 15-30 mL PO QID prn
	milk of magnesia (MOM) 30-60 mL PO QID prn
	bisacodyl (Dulcolax®) 10-15 mg PO prn
Sedatives	zopiclone (Imovane®) 5-7.5 mg PO QHS prn
	lorazepam (Ativan®) 0.5-2 mg PO/SL QHS prn
Antibiotics	cefazolin (Ancef®) 1 g IV/IM on call to OR or q8 h – GP except *Enterococcus*, GN only *E. coli, Klebsiella*, and *Proteus*
	cefalexin (Keflex®) 250-500 mg PO QID – Listeria, GP except *Enterococcus*, GN only *E. coli, Klebsiella*, and *Proteus*
	ceftriaxone 1-2 g IM/IV q24 h broad coverage including Pseudomonas
	ampicillin 1-2 g IV q4-6 h – *Listeria*, GP (*Enterococcus*) except *Streptococcus* and *E. coli*, oral anaerobes
Bacteroides	gentamicin 3-5 mg/kg/d IM/IV divided q8 h; monitor creatinine, gentamicin levels GN including *Pseudomonas*
	ciprofloxacin 400 mg IV q12 h, 500 mg PO BID – GN including *Pseudomonas*
	metronidazole (Flagyl®) 500 mg PO/IV BID (500 mg PO TID for *C. difficile*) – anaerobes
	clindamycin 600-900 mg IV q8 h, 150-400 mg PO QID – GP except *Enterococcus*, anaerobes
	piperacillin/tazobactam 3.375 g IV q6 h – GP, GN, and anaerobes
	vancomycin 1g IV q12 h – GP and MRSA
	sulfamethoxazole/trimethoprim DS (Septra®) PO BID – GP, GN including *Nocardia*
Over-the-Counter Medications	bismuth subsalicylate (Pepto-Bismol®) 2 tabs or 30 mL PO q30 min-1 h up to 8 doses/d
	side effects: black stools, risk of Reye's syndrome in children
	ASA + citrate + bicarbonate (Alka-Seltzer®) 2 tabs in 4 oz water PO q4 h prn, max 8 tabs
	aluminum hydroxide + magnesium hydroxide (Maalox®) 10-20 mL or 1-4 tabs PO prn
	calcium carbonate (Tums®) 1-3 g PO q2 h prn
	calcium carbonate and magnesium hydroxide (Rolaids®) 2-4 tabs PO q1 h prn, max 12 tabs/d

Landmark General and Thoracic Surgery Trials

Trial Name	Reference	Clinical Trial Details
GROIN HERNIAS		
Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias	JAMA Surg 2013;148:1043-1048	**Title:** Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias **Purpose:** To compare outcomes of patients undergoing laparoscopic ventral hernia repair (LVHR) vs. open ventral hernia repair (OVHR). **Methods:** Single centre, retrospective study of 532 consecutive patients who underwent an elective primary ventral hernia (PVH) repair. The outcomes of the LVHR and OVHR were compared in terms of the primary outcomes of interest SSI, hernia recurrence, and bulging. **Results:** 79 patients with LVHR matched to 79 patients with OVHR with mesh with a median follow-up of 56 mo. LVHR was associated with fewer SSIs (7.6% vs. 34.1%) but more cases of bulging (21.5% vs. 1.3%) and port-site hernia (2.5% vs. 0.0%). No differences in recurrence were observed. **Conclusions:** LVHR is associated with fewer SSIs but more clinical cases of bulging and risk of developing a port-site hernia, compared to OVHR.
ACUTE CHOLECYSTITIS		
Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial	BMJ 2018;363:k3965	**Title:** Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial **Purpose:** To assess whether laparoscopic cholecystectomy is superior to percutaneous catheter drainage in high risk patients with acute calculous cholecystitis. **Methods:** 142 patients were randomized to either the laparoscopic cholecystectomy group or to the percutaneous catheter drainage group. **Results:** Although rate of death did not differ significantly between the laparoscopic cholecystectomy and percutaneous catheter drainage group, the complication rate in the laparoscopic cholecystectomy was significantly lower than that of the percutaneous catheter drainage (12% vs. 65%). The drainage group compared to the cholecystectomy group required reintervention at a higher rate, had recurrent biliary disease more frequently, and had longer lengths of stay. **Conclusions:** Laparoscopic cholecystectomy compared with percutaneous catheter drainage reduced the rate of major complications in high risk patients with acute cholecystitis.
BREAST CANCER		
10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study	Lancet Oncol 2016;17(8):1158	**Title:** 10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study **Purpose:** To evaluate 10 yr overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy compared with mastectomy in Dutch women with early breast cancer. **Methods:** Population study of women from the Netherlands Cancer Registry diagnosed with primary, invasive, stage T1-2, N0-1, M0 breast cancer, undergoing either breast-conserving surgery plus radiotherapy or undergoing mastectomy. **Results:** Breast-conserving surgery plus radiotherapy showed improved 10 yr overall and relative survival compared with mastectomy in early breast cancer, but 10 yr distant metastasis-free survival was improved with breast-conserving surgery plus radiotherapy compared with mastectomy in the T1N0 subgroup only, indicating a possible role of confounding by severity. **Conclusions:** Breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to survival and may influence treatment decisions for patients.

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GM Geriatric Medicine

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Acronyms

ACEI	angiotensin converting enzyme inhibitor	ESAS	Edmonton Symptom Assessment Scale	MAR	medication administration record	POA	power of attorney
ADL	activities of daily living	ESR	erythrocyte sedimentation rate	MMSE	Mini Mental Status Examination	PPS	Palliative Performance Scale
ADR	adverse drug reaction	GABA	gamma-aminobutyric acid	MS	multiple sclerosis	PR	per rectal
BADL	basic activities of daily living	GCA	giant cell arteritis	MSK	musculoskeletal	PTH	parathyroid hormone
BPH	benign prostatic hypertrophy	GERD	gastroesophageal reflux disease	NE	norepinephrine	PSW	personal support worker
BUN	blood urea nitrogen	GFR	glomerular filtration rate	NP	nurse practitioner	PUD	peptic ulcer disease
CBT	cognitive behavioural therapy	IADL	instrumental activities of daily living	NPIAP	National Pressure Injury Advisory Panel	PVD	peripheral vascular disease
CGA	comprehensive geriatric assessment	IBD	inflammatory bowel disease	NSTEMI	non-ST elevation myocardial infarction	RA	rheumatoid arthritis
CKD	chronic kidney disease	IBS	irritable bowel syndrome	NYD	not yet diagnosed	SNRI	serotonin-norepinephrine reuptake inhibitor
CNS	central nervous system	INR	international normalized ratio	OTC	over the counter	SSRI	selective serotonin reuptake inhibitor
CO	cardiac output	LOC	level of consciousness	PCI	percutaneous coronary intervention	TIA	transient ischemic attack
CrCl	creatinine clearance	LV	left ventricle			TCA	tricyclic antidepressant
						UI	urinary incontinence

Physiology and Pathology of Aging

Holistic Considerations for Aging

- aging results from the impact of the accumulation of a wide variety of molecular and cellular damage over time
- some of these changes are specific to the tissues of certain organs, whereas others occur over a number of organ systems
- normal age-related changes represent biologic processes common to everyone as they age; however, the rate and extent is extremely heterogeneous; thus, for the same chronological age, individuals may present with a different biological or phenotypic age or frailty level
- common geriatric syndromes are associated with advanced age. Often, there are many factors contributing to certain geriatric syndromes, such as falls and frailty, as opposed to a single cause

The table below outlines the physiological changes that occur with aging and their organ specific impacts. In addition, it outlines pathological conditions occurring in greater frequency in older adults. Physiological changes may predispose older adults to pathological conditions; however, unlike normal changes of aging, not all older adults will develop pathological changes associated with aging.

Table 1. A Systems-Based Analysis of Potential Changes That Can Occur with Aging

System	Physiological Changes	Impact of Physiologic Changes (Normal Aging)	Pathological Changes Occurring Frequently with Older Adults
Neurologic	Decreased brain mass and cerebral blood flow Increased white matter changes Reduced number of neurons Reduced action potential speed	Mild impact on working memory and processing speed Reduced sleep time Reduced fine-motor control Reduced reflex response	Insomnia, neurocognitive disorders (e.g. Vascular dementia, Alzheimer's disease), stroke
Senses	Eyes: thickened lenses, reduced pupil diameter, increased lipid infiltrates, decreased lacrimal gland secretion ENT: reduced saliva, atrophied hair cells, reduced cochlear and inner ear neurons, reduced ossicular articulation	Eyes: reduced visual acuity, dark adaptation ENT: reduced sense of smell and taste, reduced detection of higher frequency sounds (presbycusis – sensorineural hearing loss), reduced vestibular function	Increased glaucoma, cataracts, macular degeneration, tinnitus, vertigo, oral dryness
Cardiovascular	Increased left ventricular thickness and stiffness Increased vascular resistance Reduced pacemaker cells Decreased baroreflex and autonomic reflexes Decreased vessel elasticity, cardiac myocyte size and number, β-adrenergic responsiveness	Increased sBP, decreased dBP, HR, CO, wide pulse pressure Heart and blood vessels less responsive to physiological stress	Increased atherosclerosis, CAD, MI, CHF, HTN, arrhythmias, orthostatic hypotension
Respiratory	Increased tracheal cartilage calcification, mucous gland hypertrophy Decreased elastic recoil, increased residual volume, reduced vital capacity, forced expiratory volume Reduced chest wall compliance	Decreased arterial partial pressure of oxygen, decreased exercise tolerance, decreased pulmonary reserve	Increased COPD, pneumonia, pulmonary embolism
Gastrointestinal	Increased intestinal villous atrophy Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium, and iron absorption	Reduced B_{12}, calcium and iron absorption	Increased dysphagia, cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction, malnutrition, weight loss
Renal and Urologic	Decreased renal mass and number of renal tubules and glomeruli, reduced renal blood flow Reduced nerve density and diminished detrusor function in bladder Reduced diurnal antidiuretic hormone	Decreased eGFR and concentration ability of kidney Increased urine pH Reduced hydroxylation of vitamin D Proteinuria Urinary frequency and urgency Nocturia	Increased urinary incontinence and urgency, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI, testicular atrophy, urinary retention

Functional Assessment (ADLs and IADLs)

ADLs: ABCDE-TT	IADLs: SHAFT-TT
Ambulating	Shopping
Bathing	Housework
Continence	Accounting/Managing finances
Dressing	Food preparation
Eating	Transportation
Transferring	Telephone
Toileting	Taking medications

Comprehensive Geriatric Assessment for Older Adults Admitted to Hospital
Cochrane DB Syst Rev 2017;CD006211
Purpose: To determine whether CGA can improve care provided to older adults admitted to hospital.
Results/Conclusions: Inpatient CGA increases likelihood that patients will be alive in their own homes at 3-12 mo follow-up (risk ratio (RR) 1.06, 95% CI 1.01-1.10), decreases the likelihood that patients will be admitted to a nursing home at 3-12 mo (RR 0.80, 95% CI 0.72-0.89), and results in little or no difference in dependence (RR 0.97, 95% CI 0.89-1.04). Evidence for cost-effectiveness of performing a CGA in older adults admitted to hospital is inconclusive due to imprecision and inconsistency among studies.

Comprehensive Geriatric Assessment for Community-Dwelling, High-Risk, And Frail Older People
Cochrane DB Syst Rev 2022;CD0012705
Purpose: Appraisal of the effectiveness of using the CGA for community-dwelling, high-risk, and frail older adults.
Results/Conclusions: CGA resulted in no difference in mortality during median follow-up at 12 mo (RR 0.88 95% CI 0.76-1.02), and concurrently no difference in nursing home admission (RR 0.93, 95% CI 0.76 to 1.14). CGA may decrease the risk of unplanned hospital admission over 14 mo of follow-up (RR 0.83 95% CI 0.70 to 0.99).

Table 1. A Systems-Based Analysis of Potential Changes That Can Occur with Aging

System	Physiological Changes	Impact of Physiologic Changes (Normal Aging)	Pathological Changes Occurring Frequently with Older Adults
Reproductive	Decreased androgen, estrogen, sperm count, vaginal secretion Decreased ovary, uterus, vagina, and breast size		Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis
Endocrine	Increased NE, PTH, insulin, vasopressin Decreased thyroid and adrenal corticosteroid secretion	Impaired stress response	Increased DM, hypothyroidism
MSK	Increased calcium loss from bone Decreased muscle mass/sarcopenia, cartilage, synovial fluid lubrication	Decreased strength (note: reduced motor strength on neurological examination is not expected) Joint stiffness and reduced joint capsule flexibility	Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica
Integumentary	Atrophy of sebaceous and sweat glands Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis, elastin synthesis	Increased skin laxity, wrinkles, and skin stiffness, and easy bruising	Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis, pressure injuries, skin cancer, onychomycosis, senile purpura, xerosis cutis
Immunologic	Decreased antigen-antibody affinity, decreased efficacy of neutrophils and macrophages, decreased numbers of B and T cells (excluding memory B and memory T cells)	Reduced response to new pathogens, reduced response to immunizations and increased need for boosters Blunted fever response and atypical presentation of infections which may lead to delayed care	Increased susceptibility to malignancies, infections, and autoimmune conditions
Psychiatric	Decreased processing speed, cognitive flexibility, visuospatial perception, working memory, and divided attention Loss of synaptic plasticity		Increased depression, dementia, delirium, suicidality, anxiety, sleep disruption

Framework for the Approach to the Older Adult

History: A Brief Geriatric Screen Using "The 5 M's Framework"

- Mind: consider mentation, dementia, delirium, and depression
  - consider more validated screening when concerns are raised from patients and/or family members/caregivers
  - consider asking if patients suffer from chronic pain
- Mobility: observe for impaired gait and balance and consider fall injury prevention strategies
  - consider evidenced-based ways to reduce injuries: exercise, vision evaluation and treatment, home safety assessment, occupational therapy support, calcium and vitamin D supplementation
- Medications: monitor for polypharmacy, practice optimal prescribing, consider de-prescribing where possible, check adherence, check medication understanding from patient perspective, be cautious of adverse medication effects
- Multimorbidity: use a bio-psycho-social approach to assess a patient's comorbidities
- Matters most: explore values and priorities (maintaining independence, preventing adverse events, optimizing comfort, prioritizing prolonged life)

Focused Geriatric Physical Exam

- general and vital signs: weight (signs of cachexia, unintentional weight loss), height (reduction may indicate vertebral compression fractures or osteoporosis), orthostatic vitals (blood pressure and heart rate)
- head and neck: test visual acuity, in-office hearing screen (whisper test), dentition, denture fit, lymphadenopathy, and neck masses
- cardiac: auscultate for arrhythmias, murmurs, extra heart sounds
- respiratory: auscultate, observe for SOB
- peripheral vascular exam: assess for arterial or venous insufficiency, inspect for edema and ulcers, palpate for diminished peripheral pulses
- dermatologic: look for premalignant/malignant lesions especially on sun-exposed areas, examine for pressure injuries in who are immobile, foot wounds in those with diabetes, neuropathy and peripheral vascular disease, examine for unexplained bruises or signs of elder abuse
- MSK: determine range of motion focused joint exam based on history
- gait: check footwear and fit of gait aids, assess gait systematically, Romberg for balance, and sit-to-stand test. Consider additional balance tests such as pull-back test, forward reach, tandem stance and gait
- neurologic: examine cranial nerves, tone, reflexes, sensation. Assess for signs of parkinsonism, tremor, and perform cerebellar testing

Presentations in Older Adults

Constipation

• see Gastroenterology, G28

Definition
• Rome IV Diagnostic Criteria (≥2 must be present in ≥1/4 of bowel movements for ≥3 mo with symptom onset ≥6 mo prior):
  - straining
  - hard stools
  - sensation of incomplete evacuation
  - use of manual maneuvers to facilitate defecation
  - sensation of anorectal obstruction/blockage
  - <3 bowel movements per wk
  - patients must meet both of the following criteria:
    - loose stool rarely present without the use of laxatives
    - does not meet Rome IV criteria for IBS

Epidemiology
• chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation and 1/2 of patients >80 yr)
• in the elderly, chronic constipation may present as fecal impaction and overflow diarrhea

Etiology
• neurological: dementia, parkinsonism, autonomic dysfunction, spinal cord injuries
• metabolic: hypercalcemia, hypothyroidism, hypokalemia, hypomagnesemia
• nutritional: low dietary fibre, dehydration
• cancer/cancer related: colorectal cancer, post-radiation, tumour compression or bowel obstruction
• bowel related: IBS, IBD, strictures
• systemic diseases: systemic sclerosis, amyloidosis
• drugs associated with constipation:
  - opioids
  - psychotropics (e.g. antipsychotics, TCAs)
  - anticholinergics (e.g. dimenhydrinate, diphenhydramine, TCAs, antimuscarinics for urinary incontinence)
  - calcium channel blockers
  - diuretics
  - supplements (e.g. iron, calcium)
  - immobility and non-optimal positioning)

Pathophysiology
• impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
• colorectal dysmotility

Alarm Symptoms
• fever
• hematochezia, blood in stool, positive fecal occult blood test / fecal immunochemistry test
• severe nausea/vomiting, severe abdominal pain
• abdominal/rectal mass
• obstipation
• new changes in bowel habits when age >50 yr
• unexplained anemia or iron deficiency on blood work
• acute onset
• severe constipation that is unresponsive to treatment
• weight loss >5kg in previous 6 mo
• change in stool caliber
• family history of colon cancer

Treatment
• non-pharmacological
  - bowel training
  - increase fibre intake to 20-30g per day (note: bulking agents, e.g. psyllium, Metamucil®, may worsen constipation in some), especially if insufficient fluid intake)
  - ensure adequate fluid intake
  - increase physical activity and optimize positioning for defecation (seated position, with knees at or above the level of hips)
• pharmacological
  - see Figure 1
  - discourage chronic laxative use
  - review medication regime, reduce dosages or substitute
• see *Common Medications, GM18*



A Double-Blind, Placebo-Controlled Study of Prucalopride in Elderly Patients with Chronic Constipation
Neurogastroenterol Motil 2010;22(9):991-98
Purpose: To assess the efficacy, safety, and tolerability of prucalopride in chronically constipated elderly patients.
Results/Conclusions: The prucalopride dose range tested (1-4 mg daily) is effective at promoting bowel movements, minimizing constipation-associated symptoms, and improving quality of life. It is safe and well-tolerated in elderly patients with chronic constipation.



The Effect of Probiotics as a Treatment for Constipation in the Elderly: A Systematic Review
Arch Gerontol Geriatr 2017;71:142-49
Purpose: Evaluate the effectiveness of probiotics in treating elderly constipation, as an alternative to traditional drug-based treatments.
Results/Conclusions: Analysis of placebo-controlled RCTs suggested that administration of probiotics significantly improved constipation in the elderly by 10-40% compared to placebo. Further trials are required to elucidate optimal protocols of probiotic treatment regimens.



Treatment of Constipation in Older People
CMAJ 2013 May 14;185(8):663–67
Purpose: To summarize the treatments for constipation in older people and provide a guide to the assessment and management of constipation in older adults.
Results/Conclusions: The efficacy and safety of treatments for constipation in older people is presented and a step-wise approach to constipation in older adults is proposed.

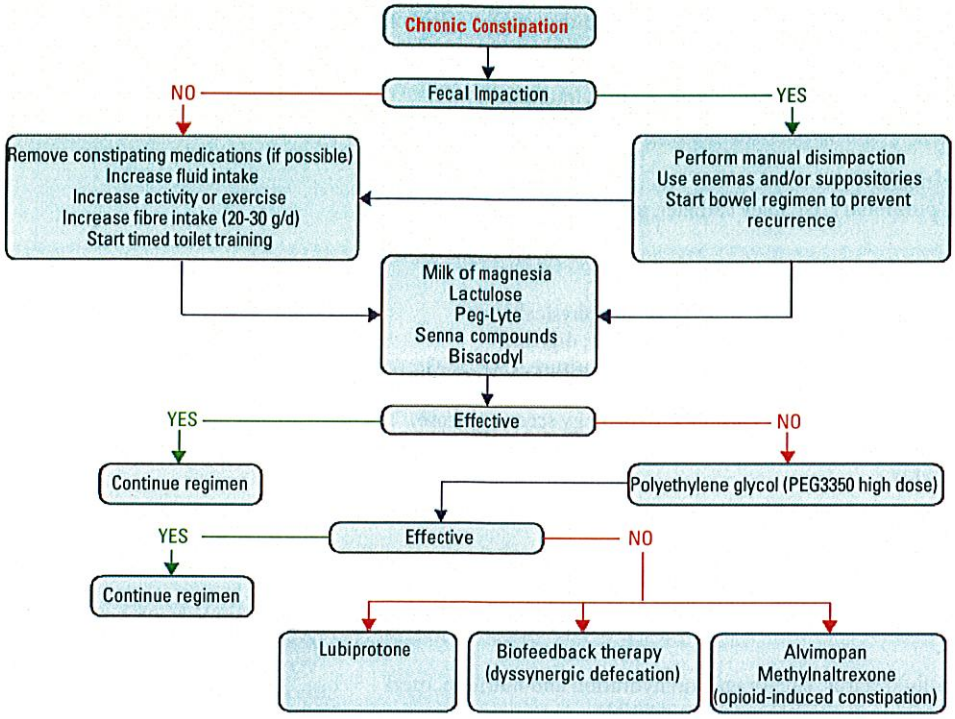


Figure 1. Treatment algorithm for the management of chronic constipation in older adults
Adapted from: Clin Interv Aging 2010;5:163-171

Delirium

• see Psychiatry, PS23 and Neurology, N21

Definition
• acute and potentially reversible disturbance in cognition, attention, or level of consciousness

Epidemiology
• delirium is especially common among patients in the ICU setting, postsurgical setting, and general medical setting
  ▪ up to 25% of patients after elective surgery
  ▪ 50% of patients after high-risk procedures (e.g. cardiac surgery, hip-fracture repair)
  ▪ up to 75% of mechanically ventilated patients in the ICU
• can affect all ages but is especially common in hospitalized older adults
  ▪ one-third of general medical patients >70 yr have delirium

Screening/Diagnostic Tools
• screened using the Confusion Assessment Method: delirium likely if 1 + 2 and either 3 or 4 are present
  1. acute onset and fluctuating course
  2. inattention
  3. disorganized thinking
  4. altered level of consciousness
• classified as: hyperactive, hypoactive, or mixed

Differential Diagnosis
• 3Ds (dementia, delirium, depression) can present with overlapping cognitive changes
• seizure
• stroke

Assessment
• history should ascertain patient's baseline cognitive function from informant
• ascertain course in hospital, obtain course of confusion with allied health
• review MARs for medications received in hospital, compare to home medications)
• substance use history, day of last use
• history and physical exams to assess for precipitating etiologies (DIMES)

Delirium in Older Persons: Advances in Diagnosis and Treatment
JAMA 2017;318(12):1161-74
Purpose: To provide overview of current state of diagnosis and treatment of delirium and identify promising areas for future research
Methods: Controlled vocabulary and keyword terms were searched in Ovid MEDLINE, Embase and the Cochrane Library with focus on studies conducted in elderly populations.
Results: 127 articles met inclusion criteria. High sensitivity and specificity brief screening tools and measures of delirium severity contribute to ability to diagnose, treat, risk stratify, and prognosticate patients. Nonpharmacologic approaches are effective for delirium prevention and recommended for delirium treatment. Pharmacologic treatment (antipsychotics, other sedatives) for agitation should only be used if the patient is at safety risk to themselves or others or is impeding medical treatment of the underlying cause.
Conclusion: Better screening and diagnosis of delirium leads to better risk stratification. Nonpharmacologic approaches of delirium prevention are effective, whereas pharmacological management of delirium is controversial.

Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review
Ann Intern Med 2019;171:485-95
Purpose: Evaluate with current literature the risks and benefits of antipsychotics in delirium management for hospitalized adults.
Study Selection: RCTs of antipsychotic vs. placebo or another antipsychotic, as well as prospective observational studies that report harms, are selected through searches on PubMed, Embase, CENTRAL, CINAHL, and PsycINFO from inception to July 2019. The review selected 16 RCTs and 10 observational studies of hospitalized adults.
Data Synthesis: No significant difference in sedation, delirium, hospital length-of-stay, or mortality between haloperidol and second-generation antipsychotics vs. placebo. No difference in mortality in direct comparisons between second-generation antipsychotics. While short term use of antipsychotics for delirium management does not appear to pose neurological harm, it poses a risk of QT prolongation.
Conclusion: The current evidence does not support the routine use of haloperidol or second-generation antipsychotics in delirium management for adult inpatients.

A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients
NEJM 1999;340:(9):669-676
Purpose: To evaluate the effectiveness of a multicomponent strategy for the prevention of delirium.
Conclusion: The multicomponent intervention lead to significant reductions in the number and duration of episodes of delirium in hospitalized older patients.

Assess for Precipitants "DIMES"

- **D**: drugs (consider prescribed, over the counter, overdose, intoxication, and withdrawal) (e.g. alcohol, benzodiazepine, nicotine, cannabis))
- **I**: infection (consider urinary tract, lungs, skin, bacteremia, CNS)
- **M**: metabolic disturbances (consider fluid imbalances, electrolyte abnormalities (hyponatremia, hypercalcemia), nutritional deficiencies (B12, B1), hepatic encephalopathy, hypothyroidism/ hyperthyroidism
- **E**: environmental (room changes, lighting, noise)
- **S**: structural insults (cardiovascular, CNS, pulmonary, GI, foley catheter, urinary retention, constipation)

Work-Up

- work-up is not universal and depends on possible causes based on history and physical exam:
  - drugs: toxicology screen, therapeutic drug-levels (Dilantin, carbamazepine, digoxin)
  - infection, infarction, inflammation: CBC, urinalysis, urine culture, blood culture, CXR, ECG, troponin, creatinine kinase
  - metabolic: basic and extended electrolytes, vitamin B12, TSH, LFT, toxicology screen, glucose, arterial blood gas/venous blood gas, creatinine
  - structural: neuroimaging, abdominal x-ray

Delirium Prevention in Older Adults

- orientation: orient to date/time, clocks and calendars visible in room
- cognitive stimulation: therapeutic activities, family visitation and education
- sleep enhancement: reduce interruptions at night, dim light., avoid sleep aids, stimulation during the day
- early and safe mobilization
- adequate nutrition and hydration: monitor fluid status, encourage oral hydration and nutrition, meal set-up and feeding assistance, use of dentures, up in chair to eat when possible
- optimal prescribing and avoid precipitating medications: multimodal pain control to limit opioid use, avoiding sedatives, anticholinergics. and antipsychotics, monitor for interactions and adverse events
- correction of sensory deficits: bring and use glasses & hearing aids, amplification devices
- reduce, monitor for and address acute insults: remove foleys as soon as possible, monitor for urinary retention and constipation, spirometry

Table 2. Differentiating the Three Ds of Cognitive Impairment

	Dementia	Delirium	Depression
Onset	Gradual or step-wise decline	Acute (hours to days)	Subacute (weeks to months)
Duration	Months to years	Days to weeks, may take months for deficits to fully resolve	Variable
Natural History	Progressive, usually irreversible, gradual loss of ADL/IADLs	Fluctuating, reversible High morbidity/mortality in very old Increased risk of subsequent development of dementia	Usually reversible May be recurrent
Level of Consciousness	Normal	Fluctuating Hyperactive/alert or depressed	Normal
Attention	Intact initially	Impaired	Possible reduced concentration
Orientation	Intact initially	Impaired, fluctuating	Intact
Behaviour	Disinhibition, personality change	Psychomotor agitation or retardation	Importuning, self-harm/suicide
Psychomotor	Normal	Fluctuates between extremes	Slowing
Sleep-Wake Cycle	Fragmented sleep at night	Reversed sleep-wake cycle	Early morning awakening
Mood and Affect	Can be unchanged Some may develop apathy, depression, anxiety, labile affect	Anxious, irritable, fluctuating	Depressed, flat affect, stable
Cognition	Gradually progressive decline in cognition Domains impacted depend on dementia subtype	Fluctuation Inattention predominant	Impaired concentration
Memory Loss	Short term memory impairment is predominant in Alzheimer's dementia	May have impaired short-term memory	Possible impairment in episodic memory

Evidence on Management of Delirium:

- see "Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review"
- see "Delirium in Older Persons: Advances in Diagnosis and Treatment"

Elder Abuse Prevalence in Community Settings: A Systematic Review and Meta-Analysis
Lancet Glob Health 2017;5:147-56
Purpose: Since quantitative syntheses of elder abuse prevalence are rare, the study aimed to quantify and understand prevalence variation at global and regional levels.
Methods: A comprehensive search strategy from 14 databases was employed to identify elder abuse prevalence studies in the community, published from inception to June 2015. Subgroup analysis and meta-regression were used to explore heterogeneity.
Results: 52 of the 38544 initially identified studies were eligible for inclusion, all of which were geographically diverse (28 countries). The pooled prevalence estimates were 11.6% for psychological abuse, 6.8% for financial abuse, 4.2% for neglect, 2.6% for physical abuse, and 0.9% for sexual abuse. Significant heterogeneity was found in associations with overall prevalence estimates, including sample size, income classification, and method of data collection, but not with gender.
Conclusion: Elder abuse is a neglected public health priority, especially compared with other types of violence. Elder abuse seems to affect 1 in 6 older adults worldwide, a figure totaling 141 million people.

Elder Abuse Screening Tools: A Systematic Review
J Adult Prot 2017;19:368-79
Context and Purpose: With high rates of morbidity and mortality, along with deleterious psychological harms, elder abuse is often difficult to detect. This study seeks to review currently available elder abuse screening tools.
Results: 11 of 34 full text studies met inclusion criteria and were included in the final analysis. Of these, three studies reported sensitivity and specificity while the remainder reported validity and reliability testing. Ultimately, the clinical environment will dictate the choice of screening tool.
Limitations: Variations in tool qualities and characteristics led to challenges in data synthesis. A further challenge was the lack of a gold standard screening tool for elder abuse, for evaluation of heterogeneity.
Conclusion: Research on screening tools remains hard-pressed in distinguishing those assessing suspected or actual elder abuse and those assessing risk factors for abuse. Although screening tools carry inherent limitations, they can be used to guide further assessments for an objective diagnosis.

Elder Abuse

Definition
- includes physical abuse, sexual abuse, emotional/psychological abuse, financial exploitation, and neglect
- elder abuse is a criminal offence under the Criminal Code of Canada and in most U.S. states

Epidemiology
- in Canada in 2019, almost 4518 seniors were victims of police-reported family violence
- the perpetrators of family violence against seniors were identified to be their grown child (34% of cases) and their spouses (26% of the cases)
- in older adults ≥60 yr, elder abuse is estimated to occur in 10% of patients
- insufficient evidence to include/exclude screening in the Periodic Health Exam

Risk Factors

Table 3. Risk Factors for Elder Abuse

Situational Factors	Social (e.g. isolation)
Victim Characteristics	Physical or emotional dependence on caregiver
	Lack of close family ties
	History of family violence
	Dementia or recent deterioration in health
Perpetrator Characteristics	Related to victim
	Dependency on older adult (e.g. financial dependency)

Screening Tools
- Elder Abuse Suspicion Index© (EASI©): a six-item questionnaire to raise a physician's level of suspicion for elder abuse and promote referral of possible victims for further assessment by social services

Management
- assess patient's decision-making capacity regarding any proposed intervention
- address imminent safety
- consider referral to local resources (home care, respite agencies, shelters, legal services, police services, government-supported elder abuse consultants)
- create emergency safety plan
- offer assistance with reporting abuse
- in Ontario, reporting elder abuse is mandatory when an older adult resides in a Long-term Care Home or a Retirement Home

EASI©
For each of the 6 items below, indicate "yes," "no," or "did not answer." A response of "yes" on 1+ of questions 2-6 is concerning for elder abuse
Q.1-Q.5 asked of patient; Q.6 answered by doctor (Within the last 12 mo)

1 Have you relied on people for any of the following: bathing, dressing, shopping, banking, or meals?
2 Has anyone prevented you from getting food, clothes, medication, glasses, hearing aids or medical care, or from being with people you wanted to be with?
3 Have you been upset because someone talked to you in a way that made you feel shamed or threatened?
4 Has anyone tried to force you to sign papers or to use your money against your will?
5 Has anyone made you afraid, touched you in ways that you did not want, or hurt you physically?
6 Doctor: Elder abuse may be associated with findings such as: poor eye contact, withdrawn nature, malnourishment, hygiene issues, cuts, bruises, inappropriate clothing, or medication compliance issues. Did you notice any of these today or in the last 12 mo?

Yaffe MJ, Wolfson C, Lithwick M, et al. Development and validation of a tool to assist physicians' identification of elder abuse: The Elder Abuse Suspicion Index (EASI ©). J Elder Abuse Negl 2008;20(3):276-300.
https://www.mcgill.ca/familymed/research/projects/elder

Additional Canadian Resources for Management of Suspected Elder Abuse
Older Adults Safety Line: 24/7 confidential phone line providing information and referrals for older adults experiencing abuse
Advocacy Centre for the Elderly
Canadian Network for Prevention of Elder Abuse

Falls

Definition
- an event resulting in a person coming to rest inadvertently on a lower level, other than as a consequence of sudden paralysis, epileptic seizure, or overwhelming external force

Epidemiology
- approximately 20-30% of older adults ≥65 yr fall each year in Canada, prevalence increases with age
  - falls resulting in injury (e.g. broken/fractured bones, sprain/strain, concussion) were more likely to occur in women than men
  - 25% associated with serious and 1/3 of hospitalizations were associated with hip fractures
  - more than 1/3 of older adults are admitted to long-term care after hospitalization

Etiology
- intrinsic factors
  - age-related changes and diseases associated with aging: MSK (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), and metabolic (glucose, electrolytes)
  - orthostatic/syncopal
  - acute illness, exacerbation of chronic illness
- extrinsic factors
  - environmental (e.g. home layout, slippery surfaces, overcrowding, new environments)
  - side effects of medications, polypharmacy (>4 medications), and substance misuse (e.g. alcohol misuse)
- situational factors
  - activities (e.g. rushing to the toilet, walking while distracted)

History and Physical Exam
- falls history: pre-fall symptoms (chest pain, syncope, presyncope, palpitations), infectious symptoms, mechanisms, loss of consciousness, head trauma, neck/cervical spine trauma, post-fall (how long were they on the ground, who helped them up, post-fall confusion or amnesia)
- extended history: previous falls and/or gait instability, intrinsic, extrinsic and situational factors, associated symptoms, medication and alcohol use, change in medications

Key Clinical History Findings in Falls Evaluation

SPLATT
Symptoms
Previous falls
Location of falls
Activity at the time of fall
Time of fall
Trauma

Impact of Medication Classes on Falls Risk in Geriatrics (Odds Ratios)

Antidepressants (1.68)
Neuroleptics/antipsychotics (1.59)
Benzodiazepines (1.57)
Sedatives/hypnotics (1.47)
Antihypertensive agents (1.24)
NSAIDs (1.21)
Diuretics (1.07)
β-blockers (1.01)

Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009:169(21):1952-1960

- have a witness present, if possible, for interview
- physical exam: orthostatic BP, injury screen, cardiac, visual acuity, examination of feet and footwear, gait assessment, Timed Up-and-Go Test, MSK, neurologic

Investigations
- CGA to identify potential causes
- investigations should be tailored based on history and physical examination. They might consist of:
  - CBC, electrolytes, BUN, creatinine, glucose, Ca^{2+}, TSH, vitamin B_{12}, urinalysis, cardiac enzymes, ECG, CT head (as directed by history and physical), coagulation profile
- bone densitometry (dual-energy x-ray absorptiometry) for osteoporosis screening in all women and men >65 yr

Interventions
- interventions depend on the identified intrinsic and extrinsic risk factors. First address any acute illness that precipitated the fall and treat any injuries or complications
- multidisciplinary, multifactorial, health and environmental risk factor assessment, and intervtion programs in the community
- muscle strengthening, balance retraining (e.g. Tai Chi) with appropriate assistive devices, and group exercise programs
- home hazard assessment and modification with potential for collaboration with occupational therapy (e.g. remove loose rugs and tripping hazards, add shower bars and stair railing, improve lighting)
- fitted gait aid
- taper or gradual discontinuation of psychotropic medication
- postural hypotension, heart rate, and rhythm abnormalities management
- eyesight (cataract surgery) and footwear optimization
- compression socks if venous stasis edema
- hip protectors
- prescription of vitamin D 1000 IU daily if vitamin D stores are low
- optimization of daily calcium intake via diet or calcium supplementation calcium in diet with 1200 mg of supplemental calcium advised if osteoporosis is a risk

Will My Patient Fall?
JAMA 2007;297:77-86
Purpose: To identify the prognostic value of risk factors for future falls among older patients.
Study Selection: Meta-analysis of prospective cohort studies of risk factors for falls.
Results: 18 studies were included. Clinically identifiable risk factors were identified across 6 domains: orthostatic hypotension, visual impairment, impairment of gait or balance, medication use, limitations in ADLs or IADLs, and cognitive impairment. The estimated pretest probability of falling at least once in any given yr for individuals ≥65 yr was 27% (95% CI 19-36%). Patients who have fallen in the past year are more likely to fall again (LR2.3-2.8). Best predictors of future falls were disturbances in gait or balance (LR 1.7-2.4), while visual impairment, impaired cognition, and medication were not reliable predictors.
Conclusions: Screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past yr. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problem are at higher risk of future falls.

Frailty

Definition
- frailty: clinically-recognizable state of decreased reserve in older adults with increased vulnerability to acute stressors resulting from functional decline across multiple physiologic systems
- functional decline: progressive limitation in the ability to carry out basic functional activities
- frailty is associated with higher risk of in-hospital death, adverse events, length of stay, hospital re-admission, and newly dependent at discharge following critical illness

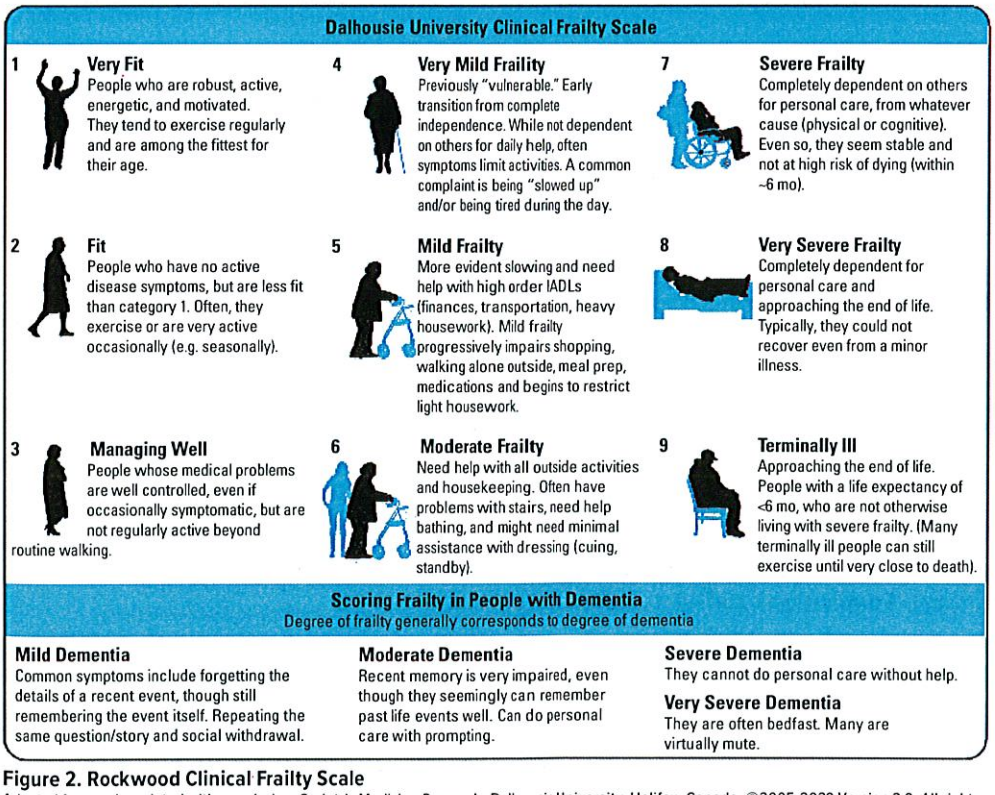


Figure 2. Rockwood Clinical Frailty Scale
Adapted from and reprinted with permission: Geriatric Medicine Research, Dalhousie University, Halifax, Canada. ©2005-2020 Version 2.0. All rights reserved

MODELS OF FRAILTY

Physical Frailty (PF) Phenotype (Fried et al.)

- Frail: ≥3 criteria; at-risk or pre-frail = 1 or 2 criteria
  1. shrinking: unintentional weight loss (baseline: >=10 lbs or 5% total body weight lost in prior yr)
  2. weakness: grip strength in lowest 20% (by gender, BMI)
  3. poor endurance: as indicated by self-report of exhaustion
  4. slowness: walking time/15 feet in slowest 20% (by gender, height)
  5. low activity: kcals/wk in lowest 20% (males: <383 kcals/wk, females: <270 kcals/wk)

Cumulative Deficit Approach (Rockwood et al.)

- balance between assets (e.g. health, attitudes, resources, caregiver) and deficits (e.g. illness, disability, dependence, caregiver burden) that determines whether a person can maintain independence in the community
- frailty index: number of deficits present/number of deficits possible

Etiology

- multifactorial: dysregulated immune, endocrine, stress, and energy response systems lead to development of clinical frailty

Table 4. Etiologies of Frailty

Etiology	Mechanism
Physiologic Changes with Aging	Sarcopenia (age-related loss of skeletal muscle and strength), decreased mass and increased stiffness of organs, decreased reserve capacity of systems
Immune System	Elevated levels of circulating interleukin-6, C-reactive protein, white blood cells, and monocytes associated with skeletal muscle decline Elevated clotting markers (factor VIII, fibrinogen, D-dimer) upregulates clotting cascade Chronic inflammation
Endocrine System	Sarcopenia via: Decreased growth hormone and IGF-1 Increased cortisol levels Decreased DHEA-S Decreased 25 (OH) vitamin D
Stress dysregulation of autonomic nervous system	
Age-related changes in renin-angiotensin system and mitochondria likely impact sarcopenia and inflammation	

Evidence-based Approach to the Frail Older Patient

- CGA
  - includes: past medical history, medications, allergies, social history, function, and geriatric review of systems (cognition, mood, sleep, pain, nutrition, falls, continence, vision/hearing, skin, and safety)
  - physical exam
  - investigations: CBC, electrolytes, TSH, vitamin B12, vitamin D, LFTs, extended electrolytes
- management
  - CGA to tailor management of geriatric syndromes (e.g. falls, cognitive impairment, incontinence)
  - physical activity programs, nutritional optimization, multicomponent interventions
  - interdisciplinary primary care
  - referral to Acute Care for Elders (ACE) unit for inpatients who are living with frailty
  - medication optimization
  - caregiver support

Immobility

Definition

- limitation in independent and voluntary physical movement of the body or one or more lower
- extremities associated with disability, increased frailty and risk of falls, decreased quality of life

Etiology and Risk Factors

- multifactorial; functional assessment in addition to comprehensive history-taking and interdisciplinary approach to care is crucial
- psychological
  - fear of falling, motivation, depression
- physical changes
  - MSK disorders: history of hip or leg fractures, osteoporosis, arthritis
  - neurologic disorders: stroke, Parkinson's disease, severe dementia, neuropathies
  - cardiovascular: CHF, angina secondary to CAD, claudication secondary to PVD
  - sensory: poor vision, decreased peripheral sensation/proprioception
- interpersonal/social factors

- environmental changes
  - iatrogenic (healthcare facilities)
  - deconditioning secondary to prolonged bed rest
  - inadequate mobility aids
  - poorly controlled chronic and acute pain

Complications
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- MSK: atrophy, contractures, bone loss
- skin: pressure injuries
- psychological: sensory deprivation, delirium, depression

Incontinence

Fecal Incontinence

Definition
- involuntary or inappropriate passing of feces that impacts social functioning or hygiene
- severity can range from unintentional flatus to the complete evacuation of bowel contents
- there are three subtypes:
  1. passive incontinence: involuntary discharge of stool or gas without awareness
  2. urge incontinence: discharge of fecal matter in spite of active attempts to retain bowel contents
  3. fecal seepage: leakage of stool following otherwise normal evacuation

Epidemiology
- the incidence of fecal incontinence differs by setting: community (17-36%), hospital (16%), and nursing home (33-65%)
- risk factors: constipation, age >80 yr, female sex, UI, impaired mobility, dementia, neurologic disease

Etiology
- physiological changes with age >80 yr (e.g. decreased external sphincter strength, decreased resting tone of internal sphincter, weakened anal squeeze, increased rectal compliance, and impaired anal sensation)
- trauma (e.g. vaginal delivery, pudendal nerve damage, cauda equina)
- iatrogenic
  - surgical (e.g. anorectal surgery, lateral internal sphincterotomy, hemorrhoidectomy, colorectal resection)
  - radiation (e.g. pelvic radiation)
- neurogenic (e.g. neuropathy, stroke, MS, diabetic neuropathy)
- anorectal/colorectal diseases (e.g. rectal prolapse, hemorrhoids, IBD, rectocele, cancer)
- medication (e.g. laxative, anticholinergics, antidepressants, caffeine, muscle relaxants)
- cognitive (e.g. dementia, willful soiling with psychosis)
- constipation/fecal impaction

Investigations (if cause not apparent from history and physical)
- differentiate true incontinence from frequency and urgency
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

Management
- physiological changes with age: medication management (antimotility agents (e.g. loperamide), diet/bulking agents for loose stool), increase fluid intake, biofeedback, retraining of pelvic floor muscles, surgery
- trauma: direct surgical repair or augmentation of the sphincters
- iatrogenic: surgical repair, artificial sphincters
- neurogenic: medication management, abdominal massage, digital stimulation for dysfunction, biofeedback and behavioural training, prevent autonomic dysreflexia in spinal injury
- anorectal/colorectal diseases: treat underlying cause (optimize IBD medications), surgical (e.g. mass removal, prolapse repair, hemorrhoid removal, colostomy)
- medication-related causes: stop laxatives, lower dose, or discontinue any other offending agents
- cognitive: regular defecation program in patients with dementia, psychiatric consult (optimize medications and cognitive function)
- constipation/fecal impaction: disimpaction, prevent impaction, enema, or rectal irrigation
- safety assessment: assess bathroom distance, fall prevention strategies, need for a bedside commode, liaise with occupational therapy if necessary

Urinary Incontinence

- see Urology, U6

Definition

- complaint of any involuntary loss of urine
- there are 4 subtypes:
  1. stress incontinence: leakage associated with physical strain
  2. urge incontinence: leakage associated with strong urge to urinate
  3. overflow incontinence: leakage associated with poor bladder emptying
  4. functional incontinence: leakage due to illness or disability not related to the urinary tract



Transient Causes of Incontinence

DIAPERS
Delirium
Infection
Atrophic urethritis/vaginitis
Pharmaceuticals
Excessive urine output
Restricted mobility
Stool impaction

Epidemiology

- 15-30% prevalence dwelling in community and at least 50% of institutionalized older adults
- morbidity: cellulitis, pressure injuries, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality
- risk factors: impaired mobility, falls, medications, depression, TIA/stroke, dementia, CHF, obesity

Etiology

- physiologic changes with age: (e.g. decreased bladder capacity)
- genitourinary diseases (e.g. cystitis, urethritis, BPH)
- neurogenic (e.g. cauda equina syndrome, stroke, MS)
- iatrogenic: (e.g. prostate surgery)
- trauma: (e.g. pelvic trauma, traumatic spinal cord injury)
- drugs (e.g. alcohol, loop diuretics, sedative hypnotics, GABAergic agents)
- cognitive (e.g. dementia, depression)
- functional impairment (e.g. arthritis, poor vision)

Investigations

- laboratory tests: urinalysis and urine culture, serum creatinine, BUN
- imaging: post-void residual, renal ultrasound
- other: voiding diary, pad test

Management

- lifestyle modification: avoid excessive fluid intake and alcohol
- pharmacologic: β-adrenergic agonists to reduce involuntary bladder contractions
- physiologic changes with age: pelvic muscle exercises, bladder training, biofeedback
- genitourinary diseases: treat underlying cause (empiric antimicrobial treatment for cystitis, α blockers/5-α reductase inhibitors for BPH)
- functional impairment: incontinence pads, environmental modification, personal assistance
- cognitive: referral to incontinence program if needed
- safety assessment: assess bathroom distance, fall prevention strategies, need for a bedside commode, liaise with occupational therapy if necessary

Malnutrition

Definition

- no uniformly accepted definition of malnutrition in older adults. One definition provided by the 2018 Global Leadership Initiative on Malnutrition requires a combination of one phenotypic and one etiologic finding:
  - phenotype
    - weight loss: >5% within past 6 mo or 10% beyond 6 mo
    - low BMI
    - reduced muscle mass measured by DXA, BIA, CT or MRI
  - etiology
    - reduced food intake
    - inflammation: from acute disease/injury or chronic disease-related
- other definitions include: hypocholesterolemia (<4.1 mmol/L), hypoalbuminemia (community: ≤38 g/L; hospital: ≤35 g/L), insufficient energy intake, fluid accumulation (e.g. edema), loss of subcutaneous fat, decreased hand-grip function



Etiology of Malnutrition in Older Adults

MEALS ON WHEELS
Medications
Emotional problems
Anorexia
Late-life paranoia
Swallowing disorders
Oral problems
Nosocomial infections
Wandering/dementia related activity
Hyperthyroid/hypercalcemia/hypoadrenalism
Enteric disorders
Eating problems
Low-salt/low-fat diet
Stones

Etiology

- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals, or feeding oneself due to functional impairment), substance use
- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia

- age-related changes: decreased thirst, decreased smell and taste, delayed gastric emptying causing early satiety, decreased ghrelin production
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

Clinical Features
- history
  - weight loss in 6 mo prior to examination
  - recent or chronic illness
  - constitutional symptoms (e.g. recent weight loss)
  - dietary intake in relation to usual pattern
  - depression, GI symptoms (e.g. anorexia, nausea, vomiting, diarrhea)
  - functional disability: impaired ADLs and IADLs, cognitive decline ("forgetting meals")
  - social factors: economic barriers, dental problems, and living situation (e.g. living alone)
  - substance use (e.g. alcohol, smoking, IV or recreational drug use)
- physical exam
  - BMI <23.5 in males and <22.0 in females should raise concern
  - muscle wasting, temporal wasting, presence of triceps skin fold
  - loss of subcutaneous fat
  - ankle or sacral edema, ascites
  - assess cognition

Investigations
- CBC, electrolytes, Ca^{2+}/albumin, Mg^{2+}, PO_4^{3-}, creatinine, LFTs (INR, bilirubin), vitamin B_{12}, folate, TSH, lipid profile
- if indicated by assessment, can consider urinalysis, ESR, CXR

Treatment
- direct treatment of underlying causes, encourage meals with family, friends or caregivers ("social eating")
- dietary modification: high calorie foods, oral nutritional supplementation with high protein supplementation preferred: patient specific meal replacement products (e.g. Ensure™, Glucerna™, Nepro™), vitamins/minerals (e.g. vitamin B12, calcium, vitamin D, thiamine)
- referral: speech language pathologist, nutritionist

Presbycusis

- see Otolaryngology, OT19

Presbyopia

- see Ophthalmology, OP8

Pressure Injuries

- see Plastic Surgery, *Pressure Ulcers*, PL17

Definition
- previously termed pressure ulcers/injuries, also termed decubitus ulcers
- any lesion caused by unrelieved pressure resulting in damage of underlying tissue; usually develops over bony prominences

Risk Factors
- extrinsic: friction, pressure, shear force, moisture
- intrinsic: immobility, malnutrition, comorbidities (e.g. DM, PVD, vasculitis, immunodeficiency, CHF), sensory loss
- geriatric: age-related skin changes, bedbound, cognitive impairment, chronic illness



Risk Assessment and Prevention of Pressure Ulcers
Ann Intern Med 2015;162:359-369
The American College of Physicians (ACP) strongly recommends advanced static mattresses or advanced static overlays for patients who are at an increased risk of developing pressure injuries. The ACP also recommends against using alternating air mattresses or alternating air overlays.

Table 5. NPIAP Staging System for Pressure Injuries

Stage 1	Localized area of nonblanchable erythema of intact skin (appearance may vary in darkly pigmented skin) Changes in sensation, temperature, or firmness may precede visual changes Colour changes do not include purple or maroon discolouration (may indicate deep tissue penetration injury)
Stage 2	Partial thickness loss of skin with exposed dermis Wound bed is viable, pink or red, moist, and may present as a serum-filled blister Adipose and deeper tissue not visible
Stage 3	Full thickness loss of skin; adipose tissue visible Slough and/or eschar may be visible Granulation tissue and epibole (rolled wound edges) often present
Stage 4	Full thickness skin and tissue loss Exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone Slough or eschar can be present on some parts of the wound bed Epibole, undermining, and/or tunneling often present
Unstageable Pressure Injury	Full-thickness skin and tissue loss; extent of tissue damage cannot be determined due to obstruction by slough or eschar
Deep Tissue Pressure Injury	Intact or nonintact skin with localized nonblanchable maroon or purple discolouration, or epidermal separation revealing dark wound bed or blood-filled blister Pain and temperature changes may precede skin colour changes Injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface

Source: Edsberg LE, Black JM, Goldberg M, et al. Revised National Pressure Ulcer Advisory Panel Pressure Injury Staging System: Revised Pressure Injury Staging System. J Wound Ostomy Continence Nurs 2016;43(6):585-597

Complications

- noninfectious: amyloidosis, heterotopic bone formation, perineal urethral fistula, pseudoaneurysm, Marjolin ulcer, systemic complications of topical treatment, complications of oral/IV treatments
- infectious: bacteremia/sepsis, cellulitis, osteomyelitis, septic arthritis, sinus tracts, abscess, endocarditis, meningitis

Prevention

- barrier cream to sacral area
- pressure reduction
  - frequent repositioning (q2 h in bed, q1 h in chair)
- support services (alternating-pressure mattresses/overlays, low-air-loss beds)
- optimizing nutritional status, encouraging mobility, and managing incontinence
- use validated pressure injury risk assessment (head-to-toe) tools on admission for those identified to be at risk for skin breakdown

Treatment

- optimize nutritional status
- minimize pressure on wound
- analgesia
- all ulcers with necrosis warrant debridement (mechanical, enzymatic, and autolytic are non-urgent forms of debridement, whereas sharp debridement is performed urgently due to risk of sepsis or cellulitis)
- dressing application (exudate absorbing, barrier products to reduce friction)
- maintain moist wound environment to enable re-epithelialization
- treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
- swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
- referral to Wound Care or Plastic Surgery
- consider other treatment options:
  - negative pressure wound therapy/vacuum-assisted closure
  - biological agents: application of fibroblast growth factor or platelet-derived growth factor to wound
  - non-contact normothermic wound therapy
  - electrotherapy

Driving Competency

Reporting Requirements

- physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia, and Alberta, where it is discretionary
- British Columbia, Ontario: must refer for re-test at ≥80 yr
- in the U.S., varies by state

Conditions That May Impair Driving

Table 6. Conditions That Impair Driving

Alcohol	Patients with history of impaired driving and those with a high probability of future impaired driving should not drive until further assessed
	Alcohol dependence or alcohol use disorder: if suspected, should be advised not to drive
	Alcohol withdrawal seizure: must (1) receive favourable report from addictions counsellor post-treatment and (2) be in remission and/or remained abstinent for 12 mo
Blood Pressure Abnormalities	HTN: sustained BP >170/110 should be evaluated carefully
	Hypotension: sustained BP <90/60; if syncopal, discontinue driving until syncope is treated and preventable
Cardiovascular Disease	Suspected asymptomatic CAD or stable angina: no restrictions
	STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for 1 mo following hospital discharge
	NSTEMI with minor LV damage, unstable angina: no driving for 48 h if PCI or 7 d if no PCI performed
Cerebrovascular Conditions	TIA: should not be allowed to drive until a medical assessment is completed
	Stroke: should not drive for at least 1 mo; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual, or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure
COPD	Mild/moderate impairment: no restrictions
	Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen
Cognitive Impairment/Dementia	Moderate to severe dementia is a contraindication to driving, defined as the "inability to independently perform 2 or more IADLs or any basic ADL"
	Patients with mild dementia should be assessed; if indicated, refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 mo
	Poor performance on MMSE, clock drawing, or Trails B suggests a need to investigate driving ability further
	MMSE score alone (whether normal or low) is insufficient to determine fitness to drive
Diabetes	Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular, or cerebrovascular disease)
	Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo
Drugs	Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants
	Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving
Hearing Loss	Effect of impaired hearing on ability to drive safely is controversial
	Acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves
Musculoskeletal Disorders	Physician's role is to report etiology, prognosis, and extent of disability (pain, range of motion, coordination, muscle strength)
Postoperative	Outpatient, conscious sedation: no driving for 24 h
	Outpatient, general anesthesia: no driving for ≥24 h
Seizures	First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head
	Epilepsy: can drive if seizure-free for 6 mo, on medication that does not impair ability to drive, and physician has insight into patient compliance (Ontario guideline)
Sleep Disorders	If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive
Visual Impairment	Visual acuity: contraindicated to drive if <20/50 with both eyes examined simultaneously
	Visual field: contraindicated to drive if <120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving

Key Factors to Consider in Older Drivers
SAFEDRIVE
Safety record
Attention (e.g. concentration lapses, episodes of disorientation)
Family observations
Ethanol use
Drugs
Reaction time
Intellectual impairment
Vision/Visuospatial function
Executive functions (e.g. planning, decision-making, self-monitoring behaviours)
Geriatrics 1996;51:36-45

Cognitive Tests and Determining Fitness to Drive in Dementia: A Systematic Review
J Am Geriatr Soc 2016;64(9):1904-1917
Purpose: To examine the relationship between cognitive tests and driving to determine whether a cognitive assessment can be implemented as a tool to examine driver safety.
Methods: Systematic review of 28 studies investigating the relationship between cognitive functioning and driving in individuals with dementia.
Results: Composite batteries comprising multiple individual tests from different cognitive domains consistently predicted driving performance for individuals with dementia. Scores on individual tests or tests of a single cognitive domain did not predict driver safety.
Conclusions: While studies consistently found composite batteries predicted driving performance, these tests were not clinically usable as they lacked the ability to discriminate between safe and unsafe drivers. Need development of a reliable, valid composite battery that can correctly determine driver safety in patients with dementia.

Hazards of Hospitalization

Table 7. Recommendations for Sequelae of Hospitalization in Older Patients

Sequelae	Recommendations
Malnutrition	No dietary restrictions (except diabetes and salt restriction if applicable), assistance, dentures if necessary, sitting in a chair to eat
Urinary Incontinence	Medication review, remove environmental barriers, discontinue use of catheter
Depression	Routine screening
Adverse Drug Event	Medication review
Confusion/Delirium	Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints
Pressure Injuries	Reactive air surface support services, daily inspection, repositioning every 2 h, nutrition
Infection	Early mobilization, remove unnecessary IV lines, catheters, NG tubes
Falls	Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review
Hypotension/Dehydration	Early recognition and repletion (ideally oral rehydration, if possible), access to water
Diminished Aerobic Capacity/Loss of Muscle Strength/ Contractures	Early mobilization
Decreased Respiratory Function	Incentive spirometry, physiotherapy
Functional Decline	Structured exercise, progressive resistance training, walking programs

Bell SP, Vasilevskis EE, Saraf AA, et al. Geriatric Syndromes in Hospitalized Older Adults Discharged to Skilled Nursing Facilities. J Am Geriatr Soc 2016;64(4):715–722

Healthcare Institutions

Table 8. Classification of Healthcare Services and Institutions

Institution/Service	Description
Home and Community Support Services	At-home support services offered to patients living at home independently or under the care of family members. These include professional healthcare services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks)
Rehabilitation	Healthcare services offered in an institution to optimize patients' function, independence, and quality of life
Residential	Divided into short (<60-90 d/yr) and long (indefinite) stay
a) Older adults Affordable Housing	Seniors who live independently and manage their own care, but prefer to live near other older adults; usually has accessibility features; rent is adjusted based on income
b) Retirement Home	Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned
c) Supportive Housing	Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment; may offer physiotherapy and rehabilitation services
d) Long-term Care/Skilled Nursing Facility	Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy, and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital
e) Hospice	Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤3 mo

- names of community healthcare institutions, types of facilities, and services offered vary between geographical locations
- factors to consider when referring to community services and institutions: level and type of support required, income/socioeconomic status, social supports and/or degree of social isolation, other social determinants of health creating potential barriers to care

Geriatric Pharmacology

Pharmacokinetics

Table 9. Age-Associated Pharmacokinetics

Parameter	Age Effect	Implications
Absorption (less significant)	Increased gastric pH, decreased splanchnic blood flow, GI absorptive surface and dermal vascularity, delayed gastric emptying. However, appropriate absorption of most oral drugs is seen in healthy older-aged patients except for drugs with extensive first pass metabolism; reduced absorption may be related to patient comorbidities	Comorbidities, drug-drug, and drug-food interactions are more likely to affect absorption
Distribution	Increased total body fat Decreased lean body mass and total body water Increased α1-glycoprotein Decreased albumin	Lipophilic drugs have a larger volume of distribution Decreased volume of distribution of hydrophilic drugs Increased binding of basic drugs Decreased binding of acidic drugs
Metabolism (aging effect less significant)	Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)	Lower doses may be therapeutic
Elimination	Decreased renal blood flow, glomerular filtration rate, tubular secretion Overall reduction in renal function by 30-50%	Lower doses may be therapeutic

Pharmacodynamics

Drug Sensitivity
- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, anticholinergics, digoxin, and narcotics
- decreased sensitivity to β-blockers and β-adrenergic stimulants, though may have increased sensitivity

Decreased Homeostasis
- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

Polypharmacy



New medications: Start Low, Go Slow! Avoid starting 2 drugs at the same time.

Definition
- prescription, administration, or use of more medications than are clinically indicated

Epidemiology
- in Canada, >60% of older adults reported using ≥5 medications
- hospitalized older adults are given an average of 10 medications during admission

Risk Factors for Polypharmacy
- patient-level risk factors: age, female sex, cognitive impairment, low health literacy, frailty, mental health conditions, multiple chronic conditions, lack of primary care physician, residing in LTC, multiple pharmacies
- systems-level risk factors: multiple prescribers, poor documentation systems, automated refill systems, lack of systematic medication review

Risk Factors for Non-Compliance
- greater number of medications (compliance with 1 medication is 80%, but drops to 25% with ≥6 medications)
- increased dosing frequency, complicated container design, financial constraints, and cognitive impairment



Adverse drug reactions in older adults may present as delirium, falls, fractures, urinary incontinence/retention, or fecal incontinence/impaction. Any new symptom in older adult could be medication related until proven otherwise.

Adverse Drug Reactions (ADRs)
- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in older adults
  - intrinsic: comorbidities (>5), age >85, low BMI, age-related changes in pharmacokinetics and pharmacodynamics, CrCl <50 mL/min
  - extrinsic: number of medications (>9 medications, >12 doses/d), multiple prescribers, unreliable drug history, prior ADR

- prescribing cascade: process whereby an ADR is misinterpreted as a new medical condition, and a subsequent drug is prescribed to treat the initial drug-induced event. Providers should ask themselves:
  - is the new drug being prescribed to address an adverse event from a previously prescribed drug therapy?
  - is the initial drug therapy really needed, especially if leading to a drug cascade?
  - do the benefits of the initial drug therapy outweigh the harms?

Preventing Polypharmacy

- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical comorbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication

Inappropriate Prescribing in Older Adults

Epidemiology

- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

Beers Criteria

- a list of medications to avoid in adults ≥65 yr due to safety concerns
- 2019 update lists drugs that are inappropriate in most older adults, those that should typically be avoided with certain conditions, drugs to use with caution, drug-drug interactions, and drug dose adjustment based on kidney function
- examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives

STOPP/START Criteria

- another screening tool for potentially inappropriate prescribing in older adults
- STOPP: Screening Tool of Older Person's Prescriptions
  - systems-based list of medications contraindicated in adults ≥65 yr in the context of their diagnoses
- START: Screening Tool to Alert physicians to Right Treatment
  - systems-based list of medications indicated in adults ≥65 yr in the context of their diagnoses
- older adults are often under-treated (ACEI, ASA, β-blockers, thrombolytics, oral anticoagulants)



Principles for Prescribing in Older Adults

CARED
Caution/Compliance
Age (adjust dosage for age)
Review regimen regularly
Educate
Discontinue unnecessary medications
Geriatric Pearls. Philadelphia: FA Davis Company, 1999



Inappropriate prescribing in older persons: A systematic review of medications available in different criteria
Arch Gerontol Geriatr 2017;68:55-61
Purpose: Comprehensive review of all potentially inappropriate medications for older persons, included in prescribing criteria of the last decade.
Results: From 778 articles, 14 criteria were included in the final analysis, including a total of 729 medication classes among all analyzed criteria. Diazepam was included in all 14 criteria, followed by amitriptyline in 13 criteria and doxepin in 12 criteria. Benzodiazepines, antihistamines, and antipsychotics were the most common drugs reported as potentially inappropriate for older adults, among final criteria.
Conclusion: Benzodiazepines, NSAIDs, antihistamines, and antipsychotics were the most common drugs reported as potentially inappropriate for older persons.

Common Medications

Table 10. Common Medications

Drug Name	Brand Name	Dosing Schedule	Indications	Contraindications	Side Effects	Mechanism of Action
Cognitive Enhancers						
donepezil	Aricept®	5-10 mg PO once daily	Moderate to severe dementia of Alzheimer's type	Known hypersensitivity, caution in untreated obstructive airway disease, cardiac conduction abnormalities, active PUD or occult GI bleed, seizure disorder, syncope NYD	N/V, diarrhea, anorexia, insomnia, fatigue, muscle cramps, syncope, bradycardia (uncommon), heart block (uncommon)	Reversible inhibition of acetylcholinesterase
galantamine	Reminyl®	8-12 mg PO BID	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, caution in untreated obstructive airway disease, cardiac conduction abnormalities, active PUD or occult GI bleed, seizure disorder, syncope NYD	N/V, diarrhea, anorexia, weight loss, headache, dizziness, syncope, heart block (rare), seizure (rare), delirium (rare)	Reversible inhibition of acetylcholinesterase
rivastigmine	Exelon®	1.5 mg PO BID (starting) up to 6-12 mg PO BID	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, severe hepatic disease, caution in untreated obstructive airway disease, cardiac conduction abnormalities, active PUD or occult GI bleed, seizure disorder, syncope NYD	N/V, diarrhea, headache, dizziness, anorexia, insomnia, weight loss, delirium, heart block (rare)	Acetylcholinesterase inhibition (reversible but very slow)
memantine	Ebixa®/Namenda® (Can)/(U.S.)	5 mg PO once daily (starting) up to 10 mg PO BID	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, conditions that alkalinize urine, caution in renal failure, seizures	Dizziness, headache, hypertension, constipation, confusion, hallucinations	NMDA-receptor antagonist
Laxatives						
bran	All-Bran®	1 cup PO once daily	Constipation		Bloating, flatus	Bulk-forming laxative
psyllium	Metamucil® Prodiem® Plain®	3.4 g PO once daily to TID	Constipation, hypercholesterolemia	N/V, abdominal pain, obstruction if another medication is taken within 2 h	Bloating, flatus	Bulk-forming laxative
lactulose	Chronulac® Cephulac® Kristalose®(U.S.) Acilac®; Apo-Lactulose®; Laxilose®; PMS-Lactulose® (Can)	15-30 cc PO once daily/BID and 5-10 mL PO BID for 2-4 wk for bowel evacuation after barium	Constipation, hepatic encephalopathy, bowel evacuation following barium exam	Patients on low galactose diets, abdominal pain, N/V	Flatus, cramps, nausea, diarrhea	Osmotic laxative
PEG 3350 (polyethylene glycol)	Lax-A-Day®, RestoraLAX®, Pegalax® (Can) Gavilax®, Healthylax® (U.S.)	17 g PO once daily (~1 heaping tablespoon) dissolved in 1 cup (250 mL) of beverage	Constipation, bowel prep (different dosing schedule)	Known/suspected bowel obstruction, known hypersensitivity, renal impairment	Abdominal cramps, bloating of the stomach, diarrhea, flatulence, nausea	Osmotic laxative
senna	Senokot®/Ex-lax®	2-4 tablets PO once daily or 10-15 mL syrup once daily/BID. Dosing should be the smallest required to pass soft stool	Constipation	Known/suspected bowel obstruction or abnormal constriction, atonic bowel, IBD, abdominal pain NYD, rectal bleeding NYD, severe dehydration	Abdominal cramps, N/V, diarrhea, urine and/or fecal discolouration	Stimulant laxative
bisacodyl	Dulcolax®	5-15 mg PO (10 mg PR)	Constipation	Acute GI diseases (e.g. appendicitis, diarrhea), ileus, obstruction, abdominal pain, N/V, severe dehydration, and ulcerative proctitis and/or anal fissures if PR	Abdominal cramps, pain, diarrhea, dehydration, dizziness, N/V	Stimulant laxative
Parkinsonian Agents – see Neurology, Table 26, N57						

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in older adults

Landmark Geriatric Medicine Trials

Trial Name	Reference	Clinical Trial Details
FRAILTY		
Gait Speed and Survival in Older Adults, Studenski et al. 2011	JAMA 2011;305:50-58	**Title:** Gait Speed and Survival in Older Adults **Purpose:** Evaluate the relationship between gait speed and survival. **Methods:** Pooled analysis of 9 cohort studies of adults >65 yr with baseline gait speed data, followed up for 6-21 yr. The main outcomes were survival and life expectancy. **Results:** The overall 5-yr survival was 84.8% and 10-yr survival was 59.7%. Gait speed was associated with survival in all studies (pooled hazard ratio per 0.1 m/s, 0.88; 95% CI 0.87 to 0.90; P<0.001). Survival increased across the range of gait speeds with significant increments at 0.1 m/s. **Conclusions:** Gait speed was associated with 10-yr survival in all studies, with considerable variability in predicted 10-yr survival across the range of gait speeds, at 75 yr.
Frailty in Older Adults: Evidence for a Phenotype, Fried et al. 2001	J Gerontol A Biol Sci Med Sci 2001;56(3): M146-56	**Title:** Frailty in Older Adults: Evidence for a Phenotype **Purpose:** Develop phenotype of frailty as a dinical syndrome. **Methods:** Baseline and annual follow-up for outcomes of incident disease, hospitalization, falls, disability, and mortality in an original cohort of 4735 participants and later-recruited cohort of 582 African American participants. All participant data from the prospective observational Cardiovascular Health Study. **Results:** Frailty may be defined as the presence of three or more of: unintentional weight loss (10 lbs in past yr), self-reported exhaustion, weakness (grip strength), slow walking speed, low physical activity. Frailty is associated with increased risk of comorbidity and disability. **Conclusions:** Frailty in community-dwelling older adults may be defined as above. While comorbidity is a risk factor for frailty and disability is an outcome of frailty, frailty itself does not equal comorbidity or disability. Assessment for frailty is vital in identifying patients at increased risk for comorbidity and disability.
REHAB-AF	NEJM 2021;385:203-216	**Title:** Physical Rehabilitation for Older Patients Hospitalized for Heart Failure **Purpose:** Investigate interventions to address physical frailty in older patients hospitalized for acute decompensated heart failure. **Methods:** Multicenter, randomized, controlled trial to evaluate transitional, tailored, progressive rehabilitation intervention, including four physical-function domains initiated during or soon after heart failure hospitalization and continued post-discharge for 36 sessions. Primary outcome was Short Physical Performance Battery score, and secondary outcome was 6 month rehospitalization rate. **Results:** Older adults hospitalized for acute decompensated heart failure produce improved clinical outcomes when treated with this rehabilitation intervention program.
DELIRIUM		
Delirium is a Strong Risk Factor for Dementia in the Oldest-Old: A Population-Based Cohort Study, Davis et al. 2012	Brain 2012;135(9):2809-16	**Title:** Delirium is a Strong Risk Factor for Dementia in the Oldest-Old: A Population-Based Cohort Study **Purpose:** Use a true population sample to determine if delirium is an incident risk factor for incident dementia and cognitive decline. **Methods:** 553 individuals aged >85 yr were used to assess associations between delirium and incident dementia, as well as decline in MMSE scores. The relationship between dementia common neuropathological markers was modelled and stratified. **Results:** Delirium increased the risk of incident dementia (OR 8.7; 95% CI 2.1 to 35), worsened dementia severity (OR 3.1; 95% CI 1.5 to 6.3) and deterioration in global function score (OR 2.8; 95% CI 1.4 to 5.5). Delirium was associated with a loss of 1.0 more MMSE points per yr (95% CI 0.11 to 1.89) than those with no history of delirium. **Conclusions:** Delirium is a strong risk factor for incident dementia and cognitive decline in elderly patients
A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients, Inouye et al. 1999	NEJM 1999;340:669-676	**Title:** A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients **Purpose:** Evaluate the effectiveness of a multicomponent strategy for delirium prevention among older inpatients. **Methods:** A total of 852 inpatients ≥70 yr were included in the study. In lieu of randomization, prospective individual matching was used to compare patients admitted to an intervention unit vs. one of two usual care units. In the intervention unit, the multicomponent approach sought to address cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. **Results:** Delirium developed in 9.9% of patients in the intervention unit, vs. 15% in the usual care unit (95% CI 0.39 to 0.92). Total number of days with delirium (105 d vs. 161 d, P=0.02) and total number of delirium episodes (62 vs. 90, P=0.03) were both lower in the intervention unit. **Conclusions:** A multicomponent intervention model aimed at addressing risk factors for delirium in hospitalized older adults is effective at reducing delirium incidence and delirium duration.
FALLS		
PROFET	Lancet 1999;353:93-97	**Title:** Prevention of Falls in the Elderly Trial (Profet): A Randomised Controlled Trial **Purpose:** Assess the benefit of a structured interdisciplinary assessment of people who have fallen. **Methods:** Patients >65 yr presenting to ED with a fall were randomized to the intervention group (detailed medical and OT-therapy assessment with referral if indicated) or to a control group (usual care only). **Results:** The risk of falling was significantly lower in the intervention group compared to the control group (OR 0.39; 95% CI 0.23 to 0.66) as was the risk of fall recurrence (OR 0.33; 95% CI 0.16 to 0.68). **Conclusions:** Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment.
NEUROCOGNITIVE DISORDERS		
Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease, Howard et al. 2012	NEJM 2012;366:893-903	**Title:** Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease **Purpose:** Assess the benefits of cholinesterase inhibitors for the long-term treatment of moderate-severe Alzheimer's disease. **Methods:** 295 community-dwelling patients with moderate-severe Alzheimer's disease treated with donepezil were randomized to either continue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. The primary outcomes were SMMSE scores and Bristol Activities of Daily Living (BADLS) scores. **Results:** Patients assigned to continue donepezil, compared to those who discontinued, had a 1.9 higher average SMMSE score (95% CI 1.3 to 2.5). The score on the BADLS was lower (less impairment) by 3.0 points (95% CI 1.8 to 4.3) (P<0.001 for both comparisons). Patients who received memantine, compared with placebo, had a 1.2 higher average SMMSE score (95% CI 0.6 to 1.8, P <0.001) and BADLS score that was 1.5 points lower (95% CI 0.3 to 2.8; P=0.02). **Conclusions:** Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer's disease.

Trial Name	Reference	Clinical Trial Details
HYPERTENSION IN THE ELDERLY		
Syst-Eur	Lancet 1997;350:757-64	**Title:** Randomised Double-blind Comparison of Placebo and Active Treatment for Older Patients with Isolated Systolic Hypertension. The Systolic Hypertension in Europe (Syst-eur) Trial Investigators **Purpose:** Investigate whether active treatment could reduce CV complications of isolated systolic HTN. **Methods:** Patients >60 yr were randomly assigned to nitrendipine 10-40 mg daily with the possible addition of enalapril 5-20 mg daily and hydrochlorothiazide 12.5-25 mg daily, or to matching placebos. Combined fatal and nonfatal stroke was the primary endpoint. **Results:** Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patient-years (43% reduction; P=0.003). Nonfatal stroke reduced by 44% (P=0.007) and nonfatal cardiac endpoints decreased by 33% (P=0.03). All-cause mortality was not influenced. **Conclusions:** Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications.
HYVET	NEJM 2008;358:1887-98	**Title:** Treatment of Hypertension in Patients 80 Years of Age or Older **Purpose:** Determine whether treatment of hypertension is beneficial in patients >80 yr. **Methods:** 3845 patients >80 yr and a sustained sBP >160 mmHg were randomized to receive indapamide SR 1.5 mg or matching placebo. The ACEI perindopril 2 or 4 mg was added if necessary, to achieve the target BP of 150/80 mmHg. The primary endpoint was fatal or nonfatal stroke. **Results:** The mean BP at 2 yr was 15.0/6.1 mmHg lower in the active-treatment group than in the placebo group. Active treatment was associated with a 30% reduction in the rate of death from stroke (95% CI 1 to 62; P=0.05), a 21% reduction in all-cause mortality (95% CI; 4 to 35; P=0.02). Fewer adverse events were reported in the active-treatment group. **Conclusions:** Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults >80 yr is beneficial.
INAPPROPRIATE PRESCRIBING IN THE ELDERLY		
EMPOWER	JAMA Intern Med 2014;174:890-98	**Title:** Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education: The Empower Cluster Randomized Trial **Purpose:** Compare the effect of direct-to-consumer education against usual care on benzodiazepine discontinuation in older adults. **Methods:** 303 long-term users of benzodiazepines aged 65-95 were randomized to the educational intervention (deprescribing patient empowerment intervention explaining risks of benzodiazepine use and a stepwise taper protocol) or the 'wait list' control. Primary outcomes were benzodiazepine discontinuation after 6 mo. **Results:** At 6 mo, 27% of patients in the intervention group had discontinued benzodiazepines, compared with 5% in the control group (risk difference 23%; 95% CI 14% to 32%). **Conclusions:** Direct-to-consumer education describing the risks of benzodiazepine use and a stepwise tapering protocol effectively elicits shared decision making and discontinuation of medications that increase the risk of harm in older adults.
STOPP and START	Int J Clin Pharmacol Ther 2008;46:72-83	**Title:** STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation **Purpose:** Validate a new screening tool of older persons' prescriptions, incorporating criteria for potentially inaccurate prescriptions (called STOPP), and criteria for appropriate prescriptions (called START). **Methods:** A Delphi consensus technique was used to obtain validity from an 18-member expert panel. Inter-rater reliability was assessed by determining the kappa-statistic on 100 datasets. **Results:** STOPP consists of 65 clinically significant criteria for potentially inappropriate prescriptions; START consists of 22 evidence-based prescribing indicators. **Conclusions:** STOPP/START is a valid, reliable, and comprehensive screening tool that enables the prescribing physician to appraise an older patient's prescription drugs in the context of his/her concurrent diagnoses.

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GY Gynecology

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Acronyms

ACEI	angiotensin converting enzyme inhibitors	GA	gestational age	IVM	in vitro maturation		quantification
AFP	α-fetoprotein	GIFT	gamete intrafallopian transfer	JRA	juvenile rheumatoid arthritis	PV	per the vagina administration
AIS	androgen insensitivity syndrome	GnRH	gonadotropin-releasing hormone	LEEP	loop electrosurgical excision procedure	RPR	rapid plasma reagin
AMH	anti-müllerian hormone	GTD	gestational trophoblastic disease	LHRH	luteinizing hormone-releasing hormone	RR	risk ratio
ARB	angiotensin II receptor blockers	GTN	gestational trophoblastic neoplasia	LMP	last menstrual period	SCC	squamous cell carcinoma
ASCUS	atypical squamous cells of undetermined significance	HERS	heart and estrogen/progestin replacement study	LN	lymph node	SERM	selective estrogen receptor modulator
AUB	abnormal uterine bleeding	HMG	human menopausal gonadotropin	LNMP	last normal menstrual period	SHBG	sex hormone binding globulin
BMD	bone mineral density	HPO	hypothalamic-pituitary-ovarian	LSIL	low grade squamous intraepithelial lesion	SHG	sonohysterography
BSO	bilateral salpingo-oophorectomy	HPV	human papillomavirus	LVSI	lymphovascular space involvement	SPRM	selective progesterone receptor modulator
BUC	buccal administration	HRT	hormone replacement therapy	MHT	menopause hormone therapy	SSRIs	selective serotonin reuptake inhibitor
BV	bacterial vaginosis	HSG	hysterosalpingography	MRKH	Mayer-Rokitansky-Küster-Hauser	TAH	total abdominal hysterectomy
CA-125	cancer antigen 125	HSIL	high grade squamous intraepithelial lesion	MTX	methotrexate	TET	tubal embryo transfer
CAH	congenital adrenal hyperplasia	HSV	herpes simplex virus	NK	natural killer	TH	total hysterectomy
CHC	combined hormonal contraception	IBD	inflammatory bowel disease	OCP	oral contraceptive pill	TOT	tension-free transobturator tape
CMV	cytomegalovirus	ICSI	intracytoplasmic sperm injection	OGTT	oral glucose tolerance test	TVT	tension-free vaginal tape
CRP	C-reactive protein	ITP	immune thrombocytopenic purpura	PCOS	polycystic ovarian syndrome	TZ	transformation zone
DES	diethylstilbestrol	IUD	intrauterine device	PG	prostaglandin	UAE	uterine artery embolization
DHEA	dehydroepiandrosterone	IUI	intrauterine insemination	PID	pelvic inflammatory disease	VIN	vulvar intraepithelial neoplasia
DMPA	depot medroxyprogesterone acetate or Depo-Provera®	IUS	intrauterine system	PMB	postmenopausal bleeding	VTE	venous thromboembolism
DUB	dysfunctional uterine bleeding	IVDU	intravenous drug use	PMDD	premenstrual dysphoric disorder	VWD	von Willebrand disease
DVT	deep venous thrombosis	IVF	in vitro fertilization	PMN	polymorphonuclear neutrophils	W/D	withdrawal
EPC	emergency postcoital contraception			PMS	premenstrual syndrome	WHI	Women's Health Initiative
ESR	erythrocyte sedimentation rate			POP-Q	pelvic organ prolapse	ZIFT	zygote intrafallopian transfer

Basic Anatomy Review

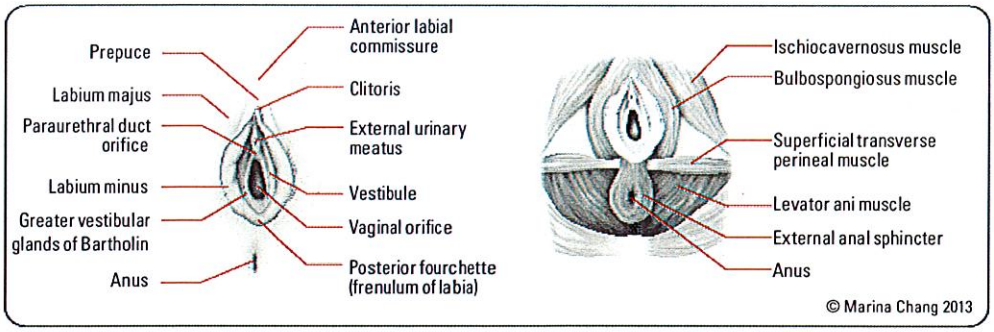


Figure 1. Vulva and perineum

A. External Genitalia

- blood supply: internal pudendal artery, superficial external pudendal artery (labia majora)
- sensory innervation: pudendal nerve
- lymphatic drainage: superficial inguinal lymph nodes, deep inguinal lymph nodes (clitoris)

B. Vagina

- muscular canal extending from cervix to vulva, anterior to rectum, and posterior to bladder
- lined by rugated, stratified squamous epithelium
- upper vagina separated by cervix into anterior, posterior, and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical, and middle rectal arteries

C. Uterus

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus, made up of the isthmus, fundus, and body
    - blood supply: uterine artery (branch of the internal iliac artery, anterior division)
  - cervix
    - blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs, and four paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals (canal of Nuck), then terminate in the labia major
    - function: anteversion/suspension
    - blood supply: Sampson's artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - function: mechanical support for uterus, prevent prolapse, and contain autonomic nerve fibres

- cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
  - function: mechanical support, prevent prolapse
- broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics. Within the broad ligament, the uterine artery anastomoses with the ovarian artery

- infundibulopelvic ligament (suspensory ligament of the ovary): continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
- position of the uterus
  - **anteverted** (majority), retroverted, neutral
  - **anteflexed** (more common), retroflexed

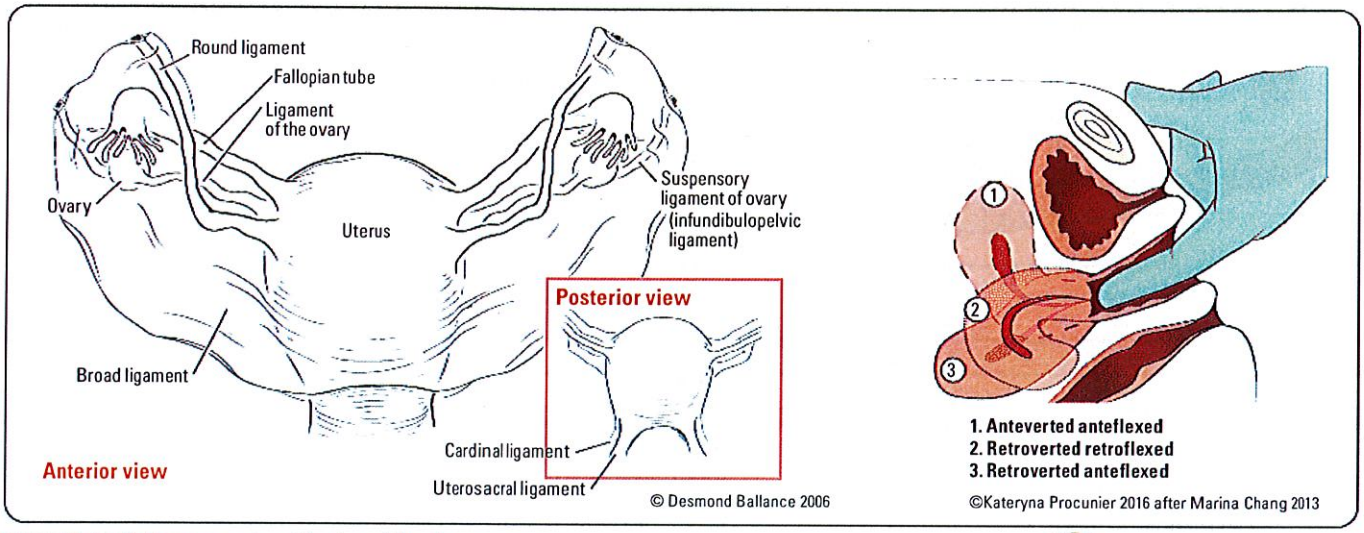


Figure 2. Genital organs and positioning of the uterus

D. Fallopian Tubes

- 8-14 cm muscular tubes extending laterally from the uterus to the ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. Ovaries

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off of aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

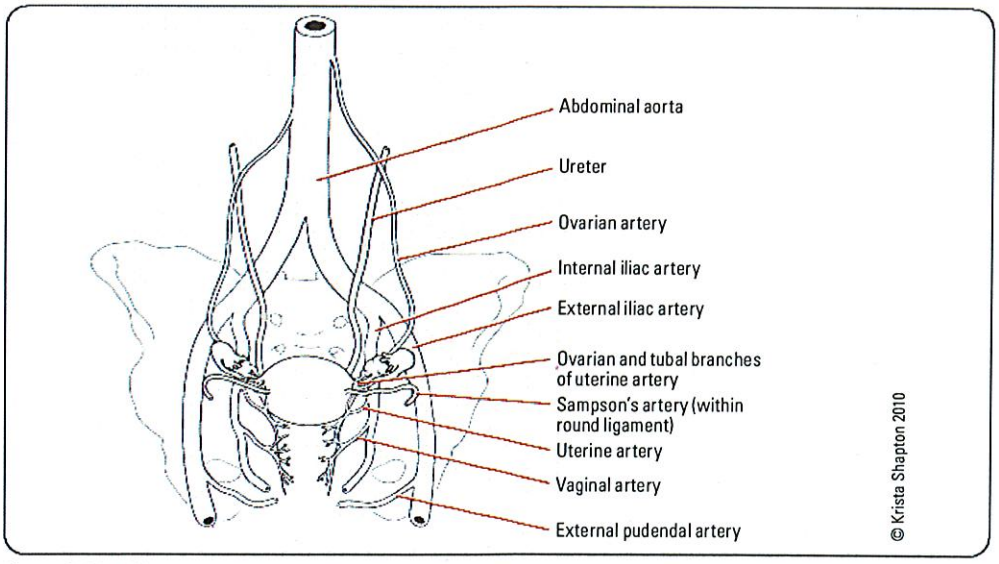


Figure 3. Vascular supply

Determination of Uterine Position by Clinical Exam

- If cervix faces anteriorly (under the urethra/pubic symphysis and less easily accessible), i.e. toward bladder more likely **RETROVERTED UTERUS**
- If cervix faces posteriorly (easily accessible), i.e. toward sacrum or rectum, more likely **ANTEVERTED UTERUS**
- If uterus is palpable with the abdominal hand on bimanual exam, more likely **ANTEVERTED UTERUS**
- If uterus is palpable behind the cervix in the posterior fornix, more likely **RETROVERTED UTERUS**

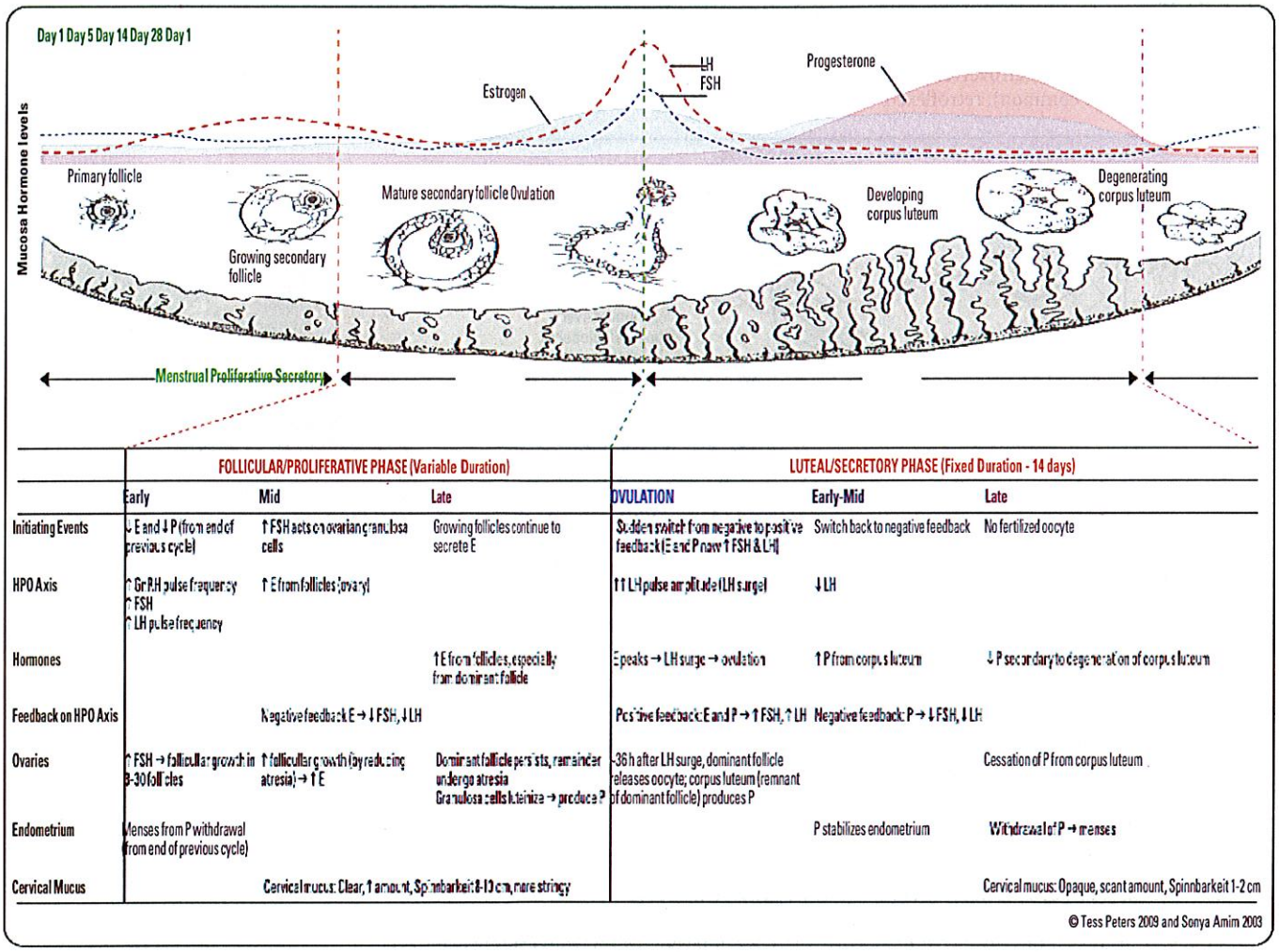
"Water Under the Bridge"
The ureters run inferior to the uterine arteries

Common Anatomy Questions in the OR

What is the origin of the left and right ovarian arteries?
Descending aorta
What are the drainage sites for the left and right ovarian veins?
Left to left renal vein, right to inferior vena cava
What is the most common place to locate the ureter?
In the pelvic brim, the ureter passes over the iliac vessels. The ureter can also be found in the medial leaf of the broad ligament where the ureter passes under the uterine artery
Which artery runs through the round ligament?
Sampson's artery

Menstruation

Menstrual Cycle



	FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)			LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)		
	Early	Mid	Late	OVULATION	Early-Mid	Late
Initiating Events	↓ E and ↓ P (from end of previous cycle)	↑ FSH acts on ovarian granulosa cells	Growing follicles continue to secrete E	Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH)	Switch back to negative feedback	No fertilized oocyte
HPO Axis	↑ GnRH pulse frequency ↑ FSH ↑ LH pulse frequency	↑ E from follicles (ovary)		↑↑ LH pulse amplitude (LH surge)	↓ LH	
Hormones			↑ E from follicles, especially from dominant follicle	E peaks → LH surge → ovulation	↑ P from corpus luteum	↓ P secondary to degeneration of corpus luteum
Feedback on HPO Axis		Negative feedback: E → ↓ FSH, ↓ LH		Positive feedback: E and P → ↑ FSH, ↑ LH	Negative feedback: P → ↓ FSH, ↓ LH	
Ovaries	↑ FSH → follicular growth in 8-30 follicles	↑ follicular growth (by reducing atresia) → ↑ E	Dominant follicle persists, remainder undergo atresia Granulosa cells luteinize → produce P	~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P		Cessation of P from corpus luteum
Endometrium	Menses from P withdrawal (from end of previous cycle)				P stabilizes endometrium	Withdrawal of P → menses
Cervical Mucus		Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy				Cervical mucus: Opaque, scant amount, Spinnbarkeit 1-2 cm

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CHARACTERISTICS
- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

ESTROGEN
ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle

Estrogen effects
- On the follicles in the ovaries: reduces atresia
- On the endometrium: proliferation of glandular and stromal tissue
- On all target tissues: decreases estrogen receptors

PROGESTERONE
PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle)

Progesterone effects
- On the endometrium: cessation of mitoses (stops building endometrium up), "organization" of glands (initiates secretions from glands), inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues: decrease estrogen receptors (the "anti-estrogen" effect), decrease progesterone receptors

Figure 4. Events of the normal menstrual cycle
E = estrogen; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HPO = hypothalamic-pituitary-ovarian; LH = luteinizing hormone; P = progesterone

Stages of Puberty

- see Pediatrics, P7
- adrenarche: increased secretion of adrenal androgens; usually adarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height veloc following breast bud ling

Stages of Puberty

"Boobs, Pubes, Grow, Flow"
Thelarche, Pubarche, Growth spurt, Menarche

Premenstrual Syndrome

Definition

- physiological and emotional disturbances that occur 1-2 wk prind last until a few day s after onset of menses; common symptoms include depression, rfulness, and mood s vings
- synonyms: "ovarian cycle syndrome," "menstrual molimina"

Etiology

- multifactorial: not completely understood; genetics likely pla
- CNS-mediated neurotransmitter (serotonin, dopamine, GAB with sex steroids (progesterone, estrogen, and testosterone)
- serotonergic dysregulation – currently most plausible theory

Diagnostic Criteria for Premenstrual Syndrome

- at least one affective and one somatic symptom during the 5 s in each of the three rior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxie ocial withdrawal
  - somatic: breast tenderness or swelling, abdominal bloat swelling of extremitie s, joint or muscle pain, weight gain, fatigue
- symptoms relieved within 4 d of onset of menses and do not ast day 13 of cycle
- symptoms present in the absence of any pharmacologic therngestion, drug, or alc hol use
- symptoms occur reproducibly during 2 cycles of prospective
- patient suffers from identifiable dysfunction in social or occrmance
- consider a PRISM (Prospective Record of the Impact and Sexual Symptoms) calen ar to monitor symptoms and confirm diagnosis particularly with ent

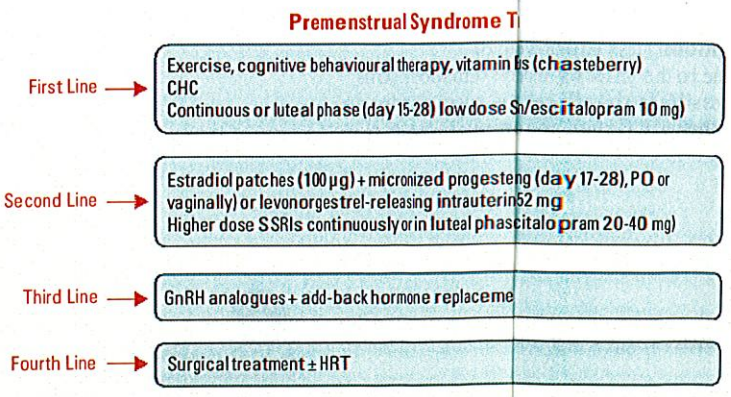


Figure 5. Royal College of Obstetricians and Gynecologists (RCO treatment of premenstr ual syndrome
Adapted from source: Management of Premenstrual Syndrome. Brit J Obstet Gynec 201

Premenstrual Dysphoric Disorder

Definition

- PMDD is similar to PMS but causes more severe symptoms of functioning

Clinical Features

- irritability and depressed mood
- breast pain and abdominal bloating

Diagnostic Criteria for Premenstrual Dysphoric Dis

- at least 5 of the following 11 symptoms during most menstr last year (with at least of the first 4)
  - depressed mood or hopelessness
  - anxiety or tension
  - affective instability

Tanner Stage

Thelarche
1. None
2. Breast bud
3. Further enlargement of areolae and breasts with no separation of contours
4. 2° mound of areolae and papilla
5. Areolae recessed to general contour of breast

Pubarche
1. None
2. Downy hair along labia only
3. Darker/coarse hair extends over pubis
4. Adult-type hair with no thigh involvement
5. Adult hair in distribution and type, extends over thighs. Not all patients achieve Tanner Stage 5. For image see Pediatrics, P38

  - anger or irritability
  - decreased interest in activities
  - difficulty concentrating
  - lethargy
  - change in appetite
  - hypersomnia or insomnia
  - feeling overwhelmed
  - physical symptoms: breast tenderness/swelling, headaches, joint/muscle pain, bloating, or weight gain
- symptoms cause significant distress and/or interfere with social or occupational functioning
- symptoms must be present during the week prior to menses and resolve within a few days after onset of menses
- may be superimposed on other psychiatric disorders, provided it is not merely an exacerbation of another disorder

Common Investigations and Procedures

Imaging

Ultrasound

- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1500 (β-hCG must be ≥6500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, and ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterise fibroids
  - detection of deep infiltrating endometriosis
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal patients

Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
- pre-treatment with misoprostol (Cytotec®) is optional (less effective in postmenopause)
- more invasive procedure (i.e. D&C) may be done in the office or operating room ± hysteroscopy (this may be required if endometrial biopsy is not possible in the office setting or if there is suspicion for an endometrial polyp/intrauterine pathology or other risk factors for endometrial hyperplasia/cancer)
- detection rate of >97% for endometrial biopsy
- indications
  - AUB/PMB
    - age >40
    - risk factors for or history of endometrial cancer
    - failure of medical treatment
    - significant intermenstrual bleeding
    - consider in patients with infrequent menses suggesting anovulatory cycles
    - obesity

Hysterectomy

Indications

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)
- venous thromboembolism

No. 377 – Recommendations for Hysterectomy for Benign Gynaecological Indications in the SOGC Clinical Practice Guidelines
J Obs Gyn Can 2019; 41(4): 543-557
Summary:

1. Hysterectomy should be approached by either vaginal, laparoscopic, or open routes.
2. Correction of preoperative anemia (Hb <120 g/L), preoperative antibiotic prophylaxis, and measures to decrease risk of venous thromboembolism are recommended.
3. In patients with endometriosis, full excision of local endometriosis should be performed concurrently.
4. Opportunistic salpingectomy can be considered at the time of hysterectomy, but the planned surgical approach should not be changed for this sole purpose.
5. Urinary tract injury is a known complication of hysterectomy and there should be a low threshold for further investigation in cases where injury is suspected – consider routine cystoscopy.
6. Patients should be counseled about the benefits and risks of removing the ovaries, the risk of ovarian cancer vs. the long-term health implications of earlier menopause.

Approaches (www.tvasurg.com)

1. open (abdominal approach): uterus removed via transverse (Pfannenstiel, Maylard) or midline laparotomy
2. minimally invasive approaches
   - vaginal hysterectomy: entire procedure performed through the vagina; no abdominal incisions
   - laparoscopic-assisted vaginal hysterectomy: vascular pedicles are divided by a combination of laparoscopic and vaginal approaches
   - total laparoscopic hysterectomy: all vascular pedicles including the colpotomy approached laparoscopically and removed through the vagina or a mini-laparotomy
   - robotic: a type of laparoscopic approach; may be advantageous in patients with a high BMI, but more costly

Table 1. Classification of Hysterectomy

Classification	Tissues Removed	Indications
Subtotal Hysterectomy	Uterus	Inaccessible cervix (e.g. adhesions) Patient choice/preference
Total Hysterectomy (TH) (extrafascial simple hysterectomy/type 1) ± Bilateral Salpingectomy	Uterus, cervix, uterine artery ligated at uterus ± fallopian tubes	Uterine fibroids Endometriosis Adenomyosis Heavy menstrual bleeding DUB Tubes often removed opportunistically if already doing hysterectomy
Total Hysterectomy (TH) (extrafascial simple hysterectomy/type 1) and Bilateral Salpingo-Oophorectomy (BSO)	Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries	Endometrial cancer Malignant adnexal masses Consider for endometriosis Any indication for hysterectomy in a postmenopausal patient
Modified Radical Hysterectomy (type 2)	Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, midpoint of uterosacral ligaments, and upper 1-2 cm vagina	Cervical cancer (up to stage 1B1)
Radical Hysterectomy (type 3)	Uterus, cervix, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum), and upper 1/3-1/2 vagina	Cervical cancer

Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

With Secondary Sexual Development		Without Secondary Sexual Development	
Normal Breast and Pelvic Development	**Normal Breast, Abnormal Uterine Development**	**High FSH (Hypergonadotropic Hypogonadism)**	**Low FSH (Hypogonadotropic Hypogonadism)**
Hypothyroidism Hyperprolactinemia PCOS Hypothalamic dysfunction	Androgen insensitivity Anatomic abnormalities Müllerian agenesis, uterovaginal septum, imperforate hymen	Gonadal dysgenesis Abnormal sex chromosomes (Turner's XO) Normal sex chromosomes (46XX, 46XY)	Constitutional delay (rare in girls) Congenital abnormalities Isolated GnRH deficiency Pituitary failure (Kallmann syndrome, head injury, pituitary adenoma, etc.) Acquired endocrine disorders (type 1 DM) Pituitary tumours Systemic disorders (IBD, JRA, chronic infections, etc.) Functional hypothalamic amenorrhea Asherman's Syndrome/uterine defect

Primary Amenorrhea
No menses by age 13 in absence of 2° sexual characteristics, or no menses by age 15 with 2° sexual characteristics, or no menses 2 yr after thelarche

Secondary Amenorrhea
No menses for >6 mo or 3 cycles after documented menarche

Most Common Causes of Primary Amenorrhea
1. Gonadal dysgenesis (e.g. Turner's Syndrome)
2. Functional hypothalamic amenorrhea
3. Mullerian agenesis

Table 3. Differential Diagnosis of Secondary Amenorrhea

With Hyperandrogenism	Without Hyperandrogenism
PCOS	Pregnancy
Autonomous hyperandrogenism (androgen secretion independent of the HPO axis)	Hypergonadotropic hypogonadism (i.e. primary ovarian insufficiency: high FSH, low estradiol)
Ovarian: tumour, hyperthecosis	Idiopathic
Adrenal androgen-secreting tumour	Autoimmune: type 1DM, autoimmune thyroid disease, Addison's disease, celiac disease
Late onset or mild congenital adrenal hyperplasia (rare)	Iatrogenic: cyclophosphamide drugs, radiation
	Hyperprolactinemia
	Endocrinopathies: most commonly hyper or hypothyroidism
	Hypogonadotropic hypogonadism (low FSH):
	Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan's syndrome
	Functional hypothalamic amenorrhea (often related to stress, excessive exercise and/or anorexia)

Functional hypothalamic amenorrhea is the most common cause of secondary amenorrhea

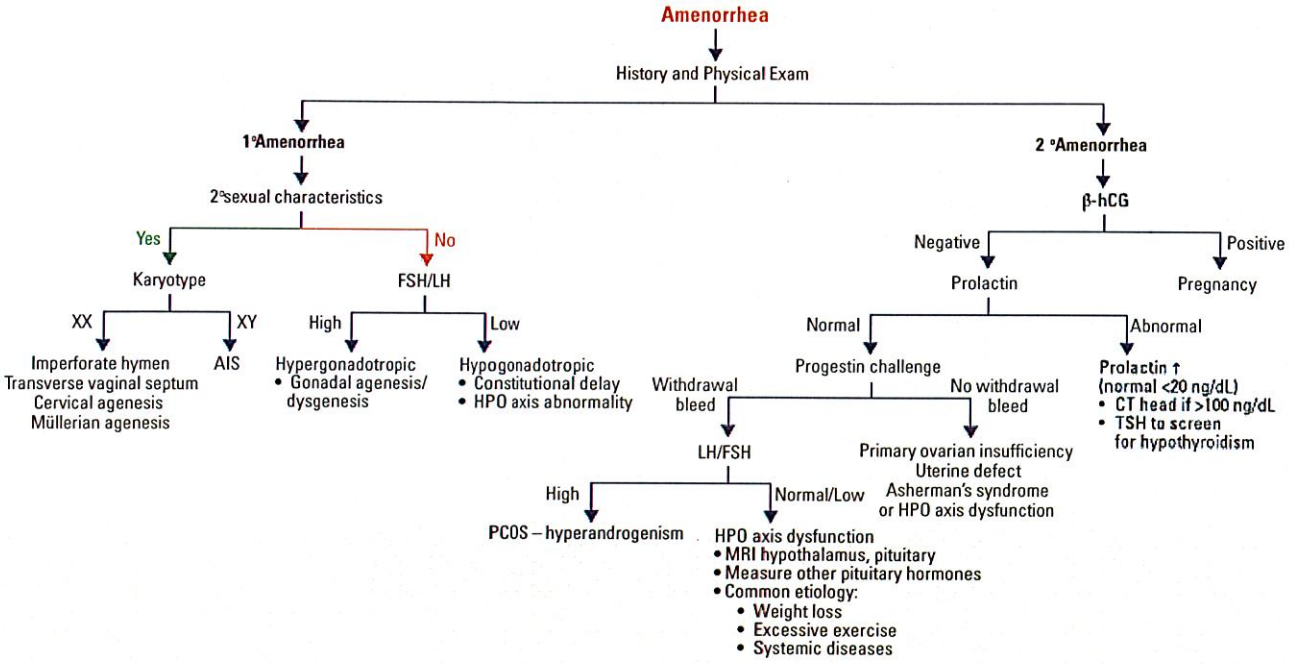


Figure 6. Diagnostic approach to amenorrhea

Investigations

- β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO once daily for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive W/D test
    - W/D bleed suggests presence of adequate estrogen to thicken the endometrium; thus W/D of progesterone results in bleeding
    - if no bleeding occurs, this may be secondary to inadequate estrogen (hypoestrogenism), excessive androgens or progesterones (decidualization), pregnancy, obstructive causes (e.g. cervical stenosis), or structural causes (e.g. uterine adhesions)
- karyotype: indicated if primary ovarian insufficiency or absent puberty
- U/S to confirm normal anatomy, identify PCOS (in adult population only)

Prolactinoma Symptoms
Galactorrhea, visual changes, headache

Treatment

Table 4. Management of Amenorrhea

Etiology	Management
1° AMENORRHEA	
AIS	Gonadal resection after puberty
	Psychological counselling
	Creation of neo-vagina with dilation
Anatomical	
Imperforate hymen	Surgical management
Transverse vaginal septum	Surgical management
Cervical agenesis	Suppression and ultimately hysterectomy
Müllerian dysgenesis (MRKH syndrome)	Psychological counselling
	Creation of neo-vagina with dilation
	Diagnostic study to confirm normal urinary system and spine
2° AMENORRHEA	
HPO axis dysfunction	Identify modifiable underlying cause
	Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work) Correct the problem (weight)
Hyperprolactinemia	MRI/CT head to rule out lesion
	If no demonstrable lesions by MRI:
	Bromocriptine, cabergoline if fertility desired
	Combined OCPs if no fertility desired
	Demonstrable lesions by MRI: surgical management
Polycystic ovarian syndrome	See *Polycystic Ovarian Syndrome, GY25*
Premature ovarian failure	Screen for DM, hypothyroidism, hypoparathyroidism, hypocortisolism
	Hormonal therapy with estrogen and progestin to decrease risk of osteoporosis; can use OCP after induction of puberty
Uterine defect	Evaluation with hysterosalpingography or sonohysterography
Asherman's syndrome	Hysteroscopy: excision of synechiae

2° amenorrhea is pregnancy until proven otherwise

Abnormal Uterine Bleeding

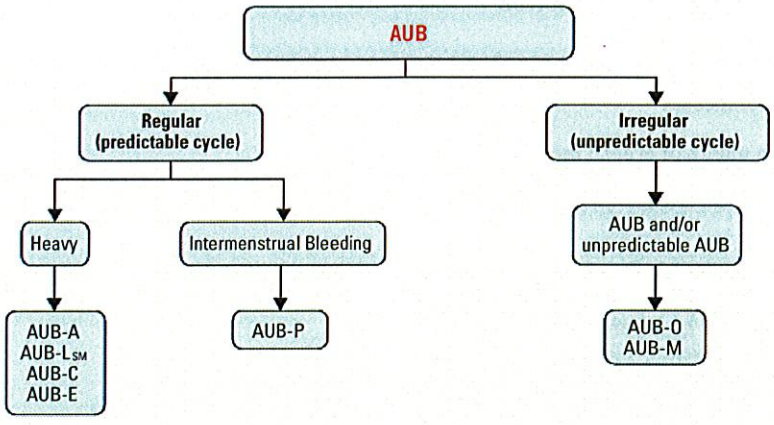


Figure 7. Diagnostic approach to abnormal uterine bleeding

The most common cause of postmenopausal bleeding is genitourinary syndrome of menopause (atrophy). However, endometrial cancer and hyperplasia must be ruled out with an endometrial biopsy before treatment for genitourinary syndrome of menopause (atrophy). 10% of post menstrual bleeding is endometrial cancer.

Approach

- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, impact on quality of life, and timing (inter- or premenstrual, or breakthrough)
- is it regular?
  - regular: cycle to cycle variability of <20 d – "Can you predict your menses within 20 days?"
  - irregular: cycle to cycle variability of ≥20 d
- is it heavy?
  - questions: How frequently do pads/tampons need to be changed? How saturated? Any clots?
  - ≥80 cc of blood loss per cycle or
  - ≥8 d of bleeding per cycle or
  - bleeding that significantly affects quality of life

Abnormal Uterine Bleeding
Change in frequency, duration, or amount of menstrual flow that affects quality of life.

- is it structural?
  - PALM (see *Table 5*)
- is it non-structural?
  - COEIN (see *Table 5*)

Table 5. Abnormal Uterine Bleeding – Etiologies, Investigations, and Management

Etiology	Investigations	Management
	STRUCTURAL	
Polyps (AUB-P)	Transvaginal sonography Saline infusion sonohysterography	Polypectomy (triage based on symptoms, polyp size, histopathology, and patient age)
Adenomyosis (AUB-A)	Transvaginal sonography MRI	See *Adenomyosis, GY13*
Leiomyoma (AUB-L) Submucosal (AUB-Lsm) Other (AUB-Lo)	Transvaginal sonography Saline infusion sonohysterography Diagnostic hysteroscopy MRI	See *Fibroids, GY14*
Malignancy and Hyperplasia (AUB-M)	Transvaginal sonography Endometrial biopsy for all patients >40 yr with AUB, for patients <40 yr with persistent AUB, or endometrial cancer risk factors	Dependent on diagnosis
	NON-STRUCTURAL	
Coagulopathy (AUB-C)	CBC, coagulation profile (especially in adolescents), VWF, Ristocetin cofactor, factor VII	Dependent on diagnosis (hormonal modulation (e.g. OCP), Mirena IUS, endometrial ablation)
Ovulatory Dysfunction (AUB-O)	Bloodwork: β-hCG, ferritin, prolactin, FSH, LH, serum androgens (free testosterone, DHEA, androstenedione), progesterone, 17-hydroxy progesterone, TSH, free T4 Pelvic ultrasound	See *Infertility, GY23*
Endometrial (AUB-E)	Endometrial biopsy	Tranexamic acid Hormonal modulation (e.g. OCP) Mirena IUS Endometrial ablation
Iatrogenic (AUB-I)	Transvaginal sonography (rule out forgotten IUD) Review OCP/HRT use Review medications (especially neuroleptic use)	Remove offending agent
Not Yet Classified (AUB-N)	–	–

Treatment

- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider AUB
- medical
  - mild AUB
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - combined hormonal contraceptive
    - progestins (Provera®) on first 10-14 d of each month or every 3 mo if AUB-O
    - Mirena® IUD
    - correct anemia - iron
  - acute, severe AUB
    - replace fluid losses, consider admission
      a) anti-fibrinolytic (e.g. Cyklokapron®) 500-1000 mg PO BID-TID prn (up to 4 g/d)
      b) anti-fibrinolytic (e.g. Cyklokapron®) 10 mg/kg IV q8 h and/or estrogen (Premarin®) 25 mg IV q4 h x 24 h with Gravol® 50 mg IV/PO q4 h (rarely used)
      c) tapering OCP regimen, 35 μg pill (often Marvelon) TID x 7 d then taper to 1 pill/d for 3 wk with Gravol® 50 μg IV/PO q4 h
      d) tapering OCP to 1 tab TID x 2 d → BID x 2 d → once daily (more commonly used) after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
      (e) medical (can also consider):
      - high dose progestins
      - GnRH agonists (e.g. Lupron®) with add-back Norlutate if taken for >6 mo
      - progesterone IUD (Mirena)
      - danazol (Danocrine®)
- surgical
  - polypectomy
  - myomectomy
  - uterine artery embolization
    - if finished childbearing
  - endometrial ablation
    - if finished childbearing
  - repeat procedure may be required if symptoms recur, especially if <40 yr
    - hysterectomy: definitive treatment

Dysmenorrhea

Etiology
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - PID
  - IUD (copper)
  - uterine polyps
  - foreign body

Primary Dysmenorrhea
Recurrent, crampy lower abdominal pain during menses in the absence of demonstrable disease

Secondary Dysmenorrhea
Pain during menses that can be attributed to an underlying disorder (i.e. endometriosis, adenomyosis, fibroids)

Table 6. Comparison of Primary and Secondary Dysmenorrhea

	Primary Dysmenorrhea	Secondary Dysmenorrhea
Features	Recurrent, crampy lower abdominal pain that occurs during menses in the absence of demonstrable disease	Similar features as primary dysmenorrhea but with an underlying disorder that can account for the symptoms, such as endometriosis, adenomyosis, or uterine fibroids
Signs and Symptoms	Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)	Same symptoms as primary dysmenorrhea Associated symptoms: dyspareunia, abnormal bleeding, infertility
Diagnosis	Assess for associated dyspareunia, abnormal bleeding, infertility (signs of 2° dysmenorrhea) Rule out underlying pelvic pathology and confirm cyclic nature of pain Pelvic examination not required; indicated for patients not responding to therapy or with signs of organic pathology	Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in patients <20 yr) U/S, laparoscopy, and hysteroscopy may be necessary to establish the diagnosis Vaginal and cervical cultures may be required
Treatment	Regular exercise, local heat NSAIDs: should be started before onset of pain CHCs with continuous or extended use: suppress ovulation/reduce menstrual flow	Treat underlying cause

Endometriosis

Definition
- the presence of endometrial tissue (glands and stroma) outside of the uterine cavity
- chronic condition, resolving only with menopause

Etiology
- not fully understood; proposed mechanisms include (combination likely involved):
  - retrograde menstruation (Sampson's theory)
  - immunologic: decreased NK cell activity limiting clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
  - extra-pelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Differential Diagnoses
- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy

Epidemiology
- incidence: 15-30% of premenopausal patients
- mean age at presentation: 25-30 yr
- regresses after menopause

4 "Dys" of Endometriosis
- Dysmenorrhea
- Dyspareunia (cul-de-sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)
- Dysuria (bladder involvement)

Risk Factors
- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – usually resolves with treatment of anomaly which relates to retrograde menses mechanism
- nulliparity
- age >25 yr
- early menarche (<11-13 y/o), shorter menstrual cycles (defined as ≤27 d)

Sites of Occurrence
- ovaries: 60% of patients have ovarian involvement
- broad ligament, vesicouterine fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs and diaphragm

Clinical Features
- may be asymptomatic and can occur with one of 3 presentations

1. **pain** (80%)
   - menstrual symptoms
     - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
     - secondary dysmenorrhea
     - sacral backache with menses
     - pain may eventually become chronic, worsening perimenstrually
     - deep dyspareunia
   - bowel and bladder symptoms
     - frequency, dysuria, hematuria
     - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)
2. **infertility** (25%)
   - 30-40% of patients with endometriosis will be infertile
   - 15-30% of those who are infertile will have endometriosis
3. **mass (endometrioma)** (20%)
   - endometrioma: an endometriotic cyst encompassing ovary
   - ovarian mass can present with any of above symptoms or be asymptomatic
   - physical examination:
     - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
     - fixed retroversion of uterus
     - firm, fixed adnexal mass

Investigations
- definitive diagnosis can be made based on:
  - direct visualization of lesions typical of endometriosis at laparoscopy (gold standard)
  - biopsy and histologic exam of specimens 2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125
  - may be elevated in patients with endometriosis but should NOT be used as a diagnostic test

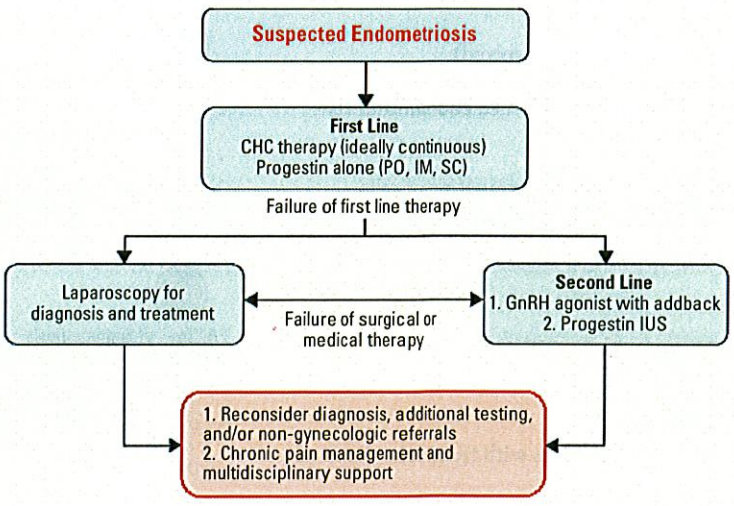


Figure 8. Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines for treatment of endometriosis

Long-Term Outcomes of Elagolix in Women with Endometriosis: Results from Two Extension Studies

Obstet Gynecol 2018;132:147-160

Purpose: An evaluation of the safety and efficacy of elagolix (a GnRH agonist) over 12 mo in women with endometriosis-associated pain.

Methods: A report of 2, double-blind, Phase III, placebo-controlled RCTs to evaluate two doses of elagolix over 12 mo of continuous treatment in patients with moderate to severe endometriosis-associated pain.

Results: In the first trial, 52.1% of women receiving 150 mg elagolix once daily had a clinical response with regards to dysmenorrhea and 67.8% had a response with regards to non-menstrual pelvic pain. In the higher dose group (200 mg q12 h), the response rate was 78.1% and 69.1%, respectively. These response rates were comparable in the second trial. Women who received elagolix had higher rates of hot flushes, higher serum lipids, and decreases in bone mineral density.

Conclusion: Both high and low doses of elagolix were effective in improving dysmenorrhea and non-menstrual pelvic pain in women with endometriosis-associated pain.

Endometriosis – Take Home Points

Suggestive history even with a negative exam should be considered adequate for a presumptive diagnosis

Pelvic pain that is not primary dysmenorrhea should be considered endometriosis until proven otherwise

Medical management is the mainstay of endometriosis

Consider surgery for patients who have not responded to medical management, fertility optimization, and/or large adnexal masses/adhesive disease causing obstruction. Medical management is often continued postoperatively

Treatment

- surgical confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)
- medical
  - medical suppression to prevent progression of disease, unless trying to conceive, which has not been proven in the literature
  - NSAIDs (e.g. naproxen sodium – Anaprox®). Avoid selective COX-2 inhibitors (celecoxib, rofecoxib, valdecoxib) in those who are attempting conception as some studies indicate these drugs can prevent or delay ovulation
  - 1st line
    - cyclic/continuous estrogen-progestin (OCP)
    - progestin (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®))
    - Mirena® IUS
  - 2nd line
    - GnRH agonist (e.g. leuprolide (Lupron®) or elagolix (Orlissa®)): suppresses pituitary gland and induces pseudomenopauses. Not a contraceptive
      - side effects: hot flashes, vaginal dryness, reduced libido
      - Lupron use >6 mo: include add-back progestin or estrogen to prevent decreased BMD, reduce vasomotor side effects
      - Orlissa® low dose (150 mg once daily) dose not require add-back progestin or estrogen. High dose (200 mg PO BID) dose require add-back
    - danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change (not commonly used due to side effects)
- surgical
  - limited to failure of medical treatment, or desire for definitive treatment
  - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: hysterectomy ± bilateral salpingo-oophorectomy
  - best time to become pregnant is immediately after conservative surgery
  - if patient is not planning to become pregnant postoperatively, suppress ovulation medically to prevent recurrence (not proven)
- above treatments are for the pain, not for the infertility associated with endometriosis, which usually involves surgery + assisted reproductive technologies. Also, management for endometriomas is surgical for symptomatic and expanding masses, but this can decrease ovarian reserve, so if it is asymptomatic and small (<5 cm), then no surgery is necessary

Adenomyosis

Definition

- synonym: "endometriosis interna" (uterine wall may be diffusely involved)



Adenomyosis
Extension of areas of endometrial glands and stroma into the myometrium

Epidemiology

- 15% of females >35 y/o; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 y/o (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features

- often asymptomatic
- heavy menstrual bleeding, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm
- Halban's sign: tender, softened uterus on premenstrual bimanual exam



Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI

Investigations

- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Treatment

- medical
  - iron supplements for anemia
  - analgesics, NSAIDs
  - Mirena® IUS
  - CHC, dinogest (Visanne®), medroxyprogesterone (Depo-Provera®) – limited evidence for efficacy
  - GnRH agonists (e.g. leuprolide (Lupron®), elagolix (Orlissa®))
  - danazol 100-200 mg PO once daily (trial x 4 mo)
- surgical
  - definitive: hysterectomy – treatment of choice in patients who have completed childbearing

Fibroids

Epidemiology
- diagnosed in approximately 40-50% of premenopausal patients >35 yr
- more common in Black patients, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential
- typically regress after menopause

Pathogenesis
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - fibroids can painfully degenerate, become calcified, develop sarcomatous component, or obtain parasitic blood supply

Classification
- International Federation of Gynecology and Obstetrics (FIGO) classifies fibroids by location and type
  - submucosal: grow within myometrium, can grow into endometrial cavity (FIGO type 0 - pedunculated, type 1 - <50% intramural, type 2 - ≥50% intramural)
  - intramural: most common, grow within the muscular wall of the uterus (FIGO type 3 - contacts endometrium and is 100% intramural, type 4 - intramural)
  - subserosal: grow from the serosa (FIGO type 5 - ≥ 50% intramural, type 6 - <50% intramural, type 7 - pedunculated)
  - cervical: located in cervix (FIGO type 8 - other)

Clinical Features
- majority asymptomatic, often discovered as incidental finding on pelvic exam or U/S (occur in 70-80% of women by age 50)
- symptoms classified into categories:
  - heavy or prolonged menstrual bleeding
    - AUB and menstrual cramps most common symptoms (26-29%) in symptomatic patients
  - pressure/bulk symptoms
    - pelvic pressure/heaviness
    - increased abdominal girth
    - urinary frequency, difficulty voiding
    - constipation, bloating (rare)
    - acute urinary retention (extremely rare, but surgical emergency!)
    - venous compression
  - reproductive dysfunction
    - infertility, recurrent pregnancy loss
    - pregnancy complications (fibroid degeneration, obstructed labour, malpresentation, difficult cesarean delivery)

Investigations
- bimanual exam: uterus asymmetrically enlarged
- diagnosis typically made based on pelvic exam and pelvic U/S
- pelvic and/or transvaginal U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating polyps from submucosal fibroids, assessing size and degree of submucosal component, or assessing presence of submucosal fibroids which may impact fertility, or for planning hysteroscopic resection
- diagnostic office hysteroscopy: can be used instead of a sonohysterogram in patients with suspected submucosal fibroids or those desiring fertility to visualize the endometrial cavity, helps with planning of hysteroscopic submucosal fibroid resection, and rules out small polyps not visualized on U/S
- pregnancy test: performed for all patients of reproductive age via urine or serum pregnancy test to rule out pregnancy prior to start of the procedure
- occasionally MRI is used for preoperative planning (e.g. before consideration of laparoscopic myomectomy)
- endometrial biopsy: used in patients with AUB to rule out endometrial hyperplasia or cancer (especially if age >40 yr or risk factors (type 2 DM, obesity, chronic anovulation))
- CBC: anemia (only found if associated with AUB/heavy menstrual bleeding)

Treatment
- only if symptomatic (heavy menstrual bleeding, bulk symptoms), rapidly enlarging, or submucosal and affecting fertility
- whether patient desires fertility is key in guiding treatment options
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant (follow-up U/S if symptoms progress-may remove at delivery if CD
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - CHC, hormonal IUS, or Depo-Provera®

Leiomyomata/Fibroids
Benign smooth muscle tumour of the uterus (most common gynecological tumour)

Submucosal leiomyomata are most symptomatic (bleeding, infertility)

Large fibroids can cause distressing bulk symptoms

The effect of pregnancy on fibroid size is variable

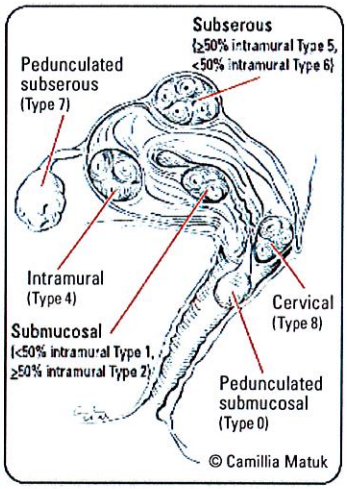


Figure 9. Possible anatomic locations of uterine leiomyomata

Uterine Artery Embolization for Symptomatic Uterine Fibroids
Cochrane DB Syst Rev 2014;12:CD005073
Purpose: To compare outcomes of UAE to other. medical or surgical therapies for symptomatic uterine fibroids. Primary outcomes were patient satisfaction and live birth rate.
Results: Seven RCTs with 793 women were included. There was no evidence of a difference in the primary outcomes or risk of major complications between the interventions. UAE was associated with a higher risk of minor complications and the need for additional surgical intervention within 2 yr.
Conclusions: No significant differences in patient satisfaction or major complications in UAE compared to surgical intervention. UAE is associated with an increased risk of surgical re-intervention.

  - GnRH agonist: leuprolide (Lupron®)
    - often used for 3 mo preoperatively to increase Hb and reduce fibroid size
    - reduces bleeding, shrinks fibroids, and corrects anemia
    - can be used long-term to bridge to menopause in combination with add-back progestin or estrogen
- interventional radiology approach: UAE occludes both uterine arteries, shrinks fibroids by 50% at 6 mo; improves heavy bleeding in 90% of patients within 1-2 mo; not an option in patients considering childbearing
  - higher risk of surgical re-intervention than with surgical approaches
  - should not be considered in patients planning future pregnancies due to potential for pregnancy complications
  - patients can become septic while fibroid is degenerating and require emergency hysterectomy
  - best for bleeding symptoms and NOT bulk
- surgical approach
  - myomectomy (hysteroscopic, open, or laparoscopic)
  - hysteroscopic resection of fibroid and endometrial ablation for AUB-Lsm (ablation should not be performed in patients planning future pregnancies)
  - hysterectomy (see *Hysterectomy, GY6*)
  - note: traditionally avoid operating on fibroids during pregnancy (due to vascularity and potential pregnancy loss); expectant management is usually best but more recently becoming more common

Contraception

- see Family Medicine, FM23

Table 7. Classification of Contraceptive Methods

Type	Effectiveness (Perfect Use, Typical Use*)
Physiological	
Withdrawal/coitus interruptus	96%, 77%
Rhythm	76%
Method/calendar/mucus/symptothermal	98% (first 6 mo postpartum)
Lactational amenorrhea	15%
Abstinence of all sexual activity	100%
Barrier Methods	
Condom alone	98%, 82%
Spermicide alone	82%, 72%
Sponge	
Parous	80%, 76%
Nulliparous	91%, 88%
Diaphragm with spermicide	94%, 88%
Female condom	95%, 79%
Cervical cap	
Parous	74%, 68%
Nulliparous	91%, 84%
Hormonal	
Combined (Estrogen and Progesterone)	
OCP	99.7%, 92%
NuvaRing®	99.7%, 92%
Transdermal (Ortho Evra®)	99.7%, 92%
Progesterone-Only	
Progestin-only injection (Depo-Provera®)	99.7%, 97%
Mirena® IUS	99.9%
Etonogestrel implant (NEXPLANON®)	99%
Copper IUS	99.3%
Surgical	
Tubal ligation	99.65%
Vasectomy	99.9%
Emergency Postcoital Contraception (EPC)	
Yuzpe® method	98% (within 24 h), decreases by 30% at 72 h
Plan B® levonorgestrel only	98% (within 24 h), decreases by 70% at 72 h
Postcoital IUD	99.9% (within 7 d)
Ella®	99.9% (within 7 d)

*Effectiveness: percentage of patients reporting no pregnancy after 1 yr of use



Counselling the Adolescent about Contraception
More than 80% of adolescent pregnancies are unintended. The one-year risk of pregnancy for patients engaging in contraception is 85%. The Canadian Paediatric Society endorses long-acting reversible contraceptives (LARCs; subdermal contraceptives and intrauterine contraceptives) as first line options for Canadian youth

Hormonal Methods

Combined Oral Contraceptive Pills

- daily pill with a 4-7 d placebo or pill free break to allow for withdrawal bleed. This is an apparent period, originally devised for women to hide contraception from others, and is not the same as menstruation (shorter pill free intervals result in fewer unintended pregnancies)
- estrogen: suppresses FSH and follicular development
- progestin: prevents LH surge, suppresses ovulation, thickens cervical mucus, decreases tubal motility, decidualizes endometrium
- most contain low dose ethinyl estradiol (10-35 μg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone). Pills vary by amount of ethinyl estradiol (maintains integrity of endometrium) and type of progestin (contraception action)
- failure rate (0.3-8.0%) depending on compliance
- monophasic formulations have the same amount of progestin throughout cycle while triphasic formulations have a varying amount of progestin throughout cycle
- can be prescribed for continuous or extended use. Continuous use involves taking a pill every day without using placebo pills, thus without withdrawal bleeding. Extended cycle preparations are also possible where withdrawal bleeds occur at less frequent intervals
- side effects: breast tenderness, nausea, bloating, unscheduled bleeding, amenorrhea. No clear evidence of weight gain
- risks: increased risk of venous thromboembolism, hypertension, and stroke in susceptible individuals. Unclear associations for elevated cancer risks
- non-contraceptive benefits: decreased menstrual bleeding, decreased acne, decreased progression of endometriosis as a result of inhibiting ovulation, decreased risk of ovarian and endometrial cancers

Transdermal (Ortho Evra®)

- patch that is changed every week for 3 consecutive weeks then left off for a week to allow for menstruation
- continuous release of norelgestromin 6 mg and ethinyl estradiol 0.60 mg into bloodstream
- can also be used in a continuous or extended fashion
- applied to lower abdomen, back, upper arm, buttocks, NOT breasts
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in patients >90 kg
- side effects: irregular uterine bleeding (worse at initiation), local skin irritation, breast tenderness, uncommonly mood disturbances
- should not be used in patients with skin hypersensitivity, exfoliative dermatologic disorders, or patients treated for Hepatitis C with obmitasvir, paritaprevir or ritonavir due to risk of reducing efficacy of the contraceptive

Contraceptive Ring (Nuva Ring®)

- thin flexible plastic ring that is inserted into the vagina by the patient and left there for 3 wk then removed and discarded. A new ring is then inserted 7 d later to allow for menstruation; releases etonogestrel 120 μg/d and estradiol 15 μg/d
- can also be used in a continuous or extended fashion
- as effective as OCP in preventing pregnancy (98%)
- side effects: vaginitis, vaginal discharge, mild breast tenderness, mild nausea
- associated with less breakthrough bleeding than other methods
- risk of toxic shock is rare

Starting Hormonal Contraceptives

- thorough history and BP measurement (post-pandemic SOGC guidelines do not require BP reading anymore to allow for virtual appointments)
- pelvic exam not required as STI screening can be done by urine, and pap smear screening does not start until >25 yr
- can start at any time during cycle but ideally within 5 d of LMP
- follow-up visit 3 mo after hormonal contraceptives prescribed
- generally recommended to use back-up contraception for 7 d, particularly if initiated >5 days from LMP

Table 8. Combined Estrogen and Progestin Contraceptive Methods

Advantages	Side Effects	Contraindications
Highly effective Reversible Cycle regulation Decreased dysmenorrhea and heavy menstrual bleeding (less anemia) Decreased benign breast disease and ovarian cyst development Decreased risk of ovarian and endometrial cancer Increased cervical mucus which may lower risk of STIs Decreased PMS symptoms Less acne Osteoporosis protection (possibly) Patient controlled	**Estrogen-related** Nausea Breast changes (tenderness, enlargement) Fluid retention/bloating/edema Weight gain (rare) Migraine, headaches Thromboembolic events Liver adenoma (rare) Breakthrough bleeding (low estradiol levels) **Progestin-related** Amenorrhea/breakthrough bleeding Headaches Breast tenderness Increased appetite Decreased libido Mood changes HTN Acne/oily skin* Hirsutism* *Androgenic side effects may be minimized by prescribing formulations containing desogestrel, norgestimate, drospirenone, or cyproterone acetate	**Absolute** 4 wk postpartum (breastfeeding) or <21 d postpartum (not breastfeeding) Major surgery with prolonged immobilization Known/suspected pregnancy Undiagnosed abnormal vaginal bleeding Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis Cerebrovascular or coronary artery disease Estrogen-dependent tumours (breast, uterus) Impaired liver function associated with acute liver disease Congenital hypertriglyceridemia Smoker age >35 yr Migraines with focal neurological symptoms (excluding aura) Uncontrolled HTN **Relative** Migraines (non-focal with aura <1 h) DM complicated by vascular disease SLE Controlled HTN Hyperlipidemia Sickle cell anemia Gallbladder disease **Drug Interactions/Risks** Rifampin, phenobarbital, phenytoin, griseofulvin, primidone, and St. John's wort can decrease efficacy of CHC requiring use of back-up method No evidence of fetal abnormalities if conceived on OCP No evidence that OCP is harmful to nursing infant but may decrease milk production

Table 9. Selected Examples of OCPs

Type	Active Compounds (estradiol and progestin derivative)	Advantages	Disadvantages
Lolo®	ethinyl estradiol 10 µg and norethindrone acetate 1 mg	Lowest estrogen dose (10 µg) OCP Least estrogen side effects 25% experience amenorrhea	Low-dose pills can often result in Low-dose pills can often result in breakthrough bleeding If this persists for longer than 3 mo, patient can be switched to an OCP with higher estrogen content Still effective with breakthrough bleeding
Alesse®	ethinyl estradiol 20 µg and levonorgestrel 0.5 mg	Low dose (20 µg) OCP Less estrogen side effects	Low-dose pills can often result in breakthrough bleeding If this persists for longer than 3 mo, patient can be switched to an OCP with higher estrogen content Still effective with breakthrough bleeding
Tri-cyclen®	ethinyl estradiol 35 µg and norgestimate 0.180/0.215/0.250 mg Triphasic oral contraceptive (graduated levels of progesterone)	Low androgenic activity can help with acne, as do all OCPs	Unlike monophasic OCP, triphasic OCPs cannot be used for continuous menstrual suppression as it will result in breakthrough bleeding
Yasmin® and Yaz®	Yasmin®: ethinyl estradiol 30 µg + drospirenone 3 mg (a new progestin) Yaz®: ethinyl estradiol 20 µg + drospirenone 3 mg – 24/4-d pill (4 d pill free interval) Drospirenone has antimineralocorticoid activity and antiandrogenic effects	Decreased perception of cyclic weight gain/bloating Fewer PMS symptoms Improved acne	Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency) Check potassium if patient also on ACEI, ARB, K+-sparing diuretic, heparin

Missed Combined OCPs

Miss 1 pill in <24 h
- Take 1 pill ASAP, and the next pill at the usual time

Miss ≥1 pill in a row in 1st wk
- Take 1 pill ASAP, and continue taking 1 pill daily until the end of the pack
- Use back-up contraception for 7 d; EPC may be necessary

Miss <3 pills in 2nd or 3rd wk of cycle
- Take 1 pill ASAP, and continue taking 1 pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- No need for back-up contraception

Miss ≥3 pills during the 2nd or 3rd wk
- Take 1 pill ASAP, and continue taking 1 pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- Use back-up contraception for 7 d; EPC may be necessary

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations. J Obstet Gynaecol Can 2008;30:1050-1062.

PROGESTIN-ONLY METHOD

Progestin-Only Pill

- progesterone-only pill taken daily with no pill free interval
- Slynd®: 4m g drospirenone - best for patients who need to avoid estrogen. Allows for 24 h missed-pill window. Formulated with 24 active pills and 4 placebo pills
- advantages: patient controlled, does not impact breast milk supply
- disadvantages: must take at exactly the same time every day so compliance can be challenging but has a 24 h missed pill window

Irregular breakthrough bleeding often occurs in the first few mo after starting OCP; usually resolves after three cycles

Progestin-only contraceptives must be taken at the same time every day

Progesterone Intrauterine System (IUS)

- small device left inside uterus typically left up to 5 yr, current FDA approved for up to 8 yrfor contraception
- Mirena IUS: levonorgestrel 52 μg - better for women patients with very heavy or painful periods, parous patients, 20% amenorrhea rate
- Kyleena IUS: levonorgestrel 19.5 μg - best for nulliparous people who want a light period every month and are mainly looking for birth control
- advantages: convenient, low hormone dose, minimal side effects, no effect on breast milk, quick return to fertility once removed
- disadvantages: insertion can be uncomfortable, must be inserted and removed by a doctor, rarely can have uterine perforation or IUS expulsion
- very effective reversible contraception; more likely to be an ectopic pregnancy if conception occurs due to efficacy at preventing intrauterine pregnancy. Lower absolute risk of ectopic pregnancy compared to other contraceptive methods

Depo-Provera®

- injectable depot medroxyprogesterone acetate 150 mg IM every 12 wk (convenient dosing)
- advantages: suppresses ovulation, complete amenorrhea in 70% of women after 1-2 yr of use, does not affect breast milk, effective for dysmenorrhea
- disadvantages: breakthrough bleeding, weight gain, controversial decreased bone density (often reversible), restoration of fertility may take up to 1-2 yr
- not recommended for long-term usage

Nexplanon®

- 4 cm long etonogestrel 68 mg implant that is placed in the inner arm and lasts for a maximum of 3 yr
- advantages: does not affect breast milk, do not have to put something in uterus, good bleeding and pain control, no change in bone density, quick return to fertility once removed
- disadvantages: breakthrough bleeding, weight gain

Table 10. Progestin-Only Contraceptive Methods

Indications	Mechanism of Action	Side Effects	Contraindications
Does not affect breast milk supply Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease) Women intolerant of estrogenic side effects of combined OCPs	Progestin prevents LH surge Thickening of cervical mucus Decreases tubal motility Endometrial decidualization Ovulation suppression – oral progestins do not consistently suppress ovulation compared to combined OCPs	Irregular menstrual bleeding Weight gain Headache Breast tenderness Mood changes Functional ovarian cysts Acne/oily skin Hirsutism	**Absolute** Current breast cancer Known/suspected pregnancy Undiagnosed vaginal bleeding Benign or malignant liver tumours, severe cirrhosis, or acute liver disease

Continuous or Extended Cycle vs. Cyclic Use of Combined Hormonal Contraceptives for Contraception
Cochrane Database Syst Rev 2014:7
Purpose: Systematic review of RCTs assessing the efficacy and side effects of cyclic administration vs. extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combination oral contraceptives (COC).
Results: The initial review published in 2012 identified 12 RCTs that ultimately showed no difference between groups with regards to efficacy (pregnancy rates), safety, and compliance rates. Continuous or extended COCs were shown to reduce menstrual symptoms (headaches, tiredness, bloating, and menstrual pain). In addition, 11 of 12 studies reported similar or improved bleeding patterns with continuous or extended cycles.
Conclusions: This recently published updated systematic review identified a further 4 RCTs, however, results did not change.

Intrauterine Device

Table 11. IUS Contraceptive Methods

Mechanism of Action	Benefits of all IUS	Risks of all IUS	Side Effects	Contraindications
Copper-Containing IUS (Nova-T®): mild foreign body reaction in endometrium, toxic to sperm and alters sperm motility **Progesterone-Releasing IUS (Mirena®, Kyleena®):** decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation	Return to baseline fertility after removal is very fast No estrogen (doesn't affect breastfeeding, can use if smoker, hypertension, previous VTE) Lasts 5 yr but can be removed before that if desired Can insert immediately after placental delivery and post abortion	Insertion is uncomfortable Must be inserted and removed by a doctor Infection (especially if multiple partners and within first 10 d of insertion) Uterine wall perforation on insertion (1/10000) Expulsion (5% in the 1st yr, greatest in the 1st mo) Chance of pregnancy very low, but if pregnant, higher relative risk of an ectopic pregnancy or miscarriage IUS do not protect against STIs*	**Copper IUS:** increased blood loss and duration of menses, dysmenorrhea, increased vaginal discharge **Progesterone IUS:** spotting, bloating, headache, acne, breast tenderness, nausea, headaches, ovarian cyst formation, vaginal discharge, and/or mood changes. Usually very mild	**Absolute** **Both Copper and Progesterone IUS** Known or suspected pregnancy Undiagnosed genital tract bleeding Acute or chronic PID Lifestyle risk for STIs Known distorted uterine cavity Immediately post-septic abortion **Copper IUS** Known allergy to copper or Wilson's disease **Relative** **Both Copper and Progesterone IUS** Valvular heart disease PMHx of PID or ectopic pregnancy Presence of prosthesis Abnormalities of uterine cavity Intracavitary fibroids Cervical stenosis Immunosuppressed individuals (e.g. HIV) Abnormalities of uterine cavity (excluding distorted uterine cavity) Copper IUS – severe dysmenorrhea or heavy menstrual bleeding

*Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

Emergency Postcoital Contraception

Table 12. Emergency Postcoital Contraceptive (EPC) Methods

Method	Mechanism of Action	Side Effects	Contraindications
HORMONAL			
Yuzpe Method Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg levonorgestrel 500 µg) Can substitute with any OCP as long as it contains ethinyl estradiol 100 µg 2% overall risk of pregnancy Used within 72 h of unprotected intercourse ideally within 24 h intercourse, limited evidence of benefit up to 5 d Efficacy decreased with time (e.g. less effective at 72 h than 24 h)	Unknown; theories include: Suppresses ovulation or causes deficient luteal phase Alters endometrium to prevent implantation Affects sperm/ova transport	Nausea (due to estrogen; treat with Gravol®) Irregular spotting	Pre-existing pregnancy (although not teratogenic) Caution in women with contraindications to OCP (although no absolute contraindications)
"Plan B™" Use within 72 h of unprotected intercourse, can use up to 5 d after levonorgestrel 750 µg q12 h for 2 doses (can also take 2 doses together) Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method No estrogen thus very few contraindications/side effects (less nausea) Less effective if >75 kg, not recommended if >80 kg	Same as above	Same as above	Same as above but no caution in women with contraindications to OCP
Ulipristal (Ella™) 30 mg PO within 5 d of unprotected intercourse	Selective Progesterone Receptor Modulator (SPRM) with primarily antiprogestin activity: may delay ovulation by up to 5 d	Headache, hot flashes, constipation, vertigo, endometrial thickening	Same as above but no caution in women with contraindications to OCP Need to delay the restart of Combined OCP by 14 d
NON-HORMONAL			
Postcoital IUD (Copper) Insert up to 7 d postcoitus Prevents implantation 1% failure rate Can use for short duration in higher risk individuals	See *Table 11*, GY18	See *Table 11*, GY18	See *Table 11*, GY18

Follow-up
- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counselling

Termination of Pregnancy

Indications
- patient desires an end to pregnancy
- may be for medical reasons (health of patient, disorders of pregnancy, or fetal anomaly) or a variety of social reasons, including patient

Legal Considerations
- no current law in Canada concerning abortion. Access to abortion is provincially regulated and highly variable
- CPSO: a physician must provide a referral for abortion services regardless of personal beliefs, but is not compelled to personally perform the procedure

Rates
- 13.1 abortions in 1000 women 15-44 yr in Canada (2017 CIHI data)
- worldwide: 56 million induced abortions per yr; half are unsafe (WHO data)
- maternal mortality almost zero where induced abortion is safe and legal; rises to 100 maternal deaths in 100000 live births in sub-Saharan Africa and other countries where abortion is illegal and unsafe
- in Canada, 91% of induced abortions occur <12 wk GA; much less common after 24 wk GA (usually only for maternal/fetal reasons)

Methods of Induced Abortion
- medical
  - gold standard up to 9 wk GA
  - mifepristone and misoprostol 95-98% effective up to 49 d after LMP
  - mifepristone (200 mg PO on 1st d) blocks the progesterone receptor (progesterone required in early pregnancy), alters the endometrium, induces bleeding and causes the cervix to soften
  - misoprostol (800 mg PV/BUC on 2nd or 3rd d) is a synthetic prostaglandin that stimulates uterine contractions and expulsion of the products of conception
  - can also use misoprostol alone or methotrexate and misoprostol (with lower success rates of 90-95%)

  - good follow-up and back-up access to D&C required if medical abortion fails
  - side effects: bleeding (self-limited) and pain (while tissue passes) are expected side effects, as well as nausea, diarrhea, and chills/fever due to prostaglandin effects
  - contraindications:
    - absolute: ectopic pregnancy, chronic adrenal failure, ambivalence
    - relative: unconfirmed GA, IUD in situ, long term steroid therapy, bleeding disorder/anticoagulation, porphyria
  - between 14-24 wk GA medical induction of labour (misoprostol followed by oxytocin) is an option, whereas after 24 wk GA induction of labour is the only option
- surgical
  - <14 wk GA:
    - manual vacuum aspiration – up to 12 wk GA with handheld aspiration device
    - suction dilatation + aspiration ± curettage – may involve presurgical preparation of cervix with laminaria tents and/or misoprostol
  - 14-24 wk GA:
    - dilatation and evacuation - presurgical preparation of cervix required with laminaria tents
  - pain or discomfort during procedure mitigated by use of appropriate analgesia/sedation/anesthesia (including paracervical blocks)
  - rare complications (1-5%): laceration of cervix, infection/endometritis, retained products of conception, ongoing pregnancy
  - very rare complications (0.1-2%): hemorrhage, perforation of uterus, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), future preterm birth (controversial and likely only with repeated abortion)
- counselling
  - counselling options always provided including possibility of carrying pregnancy with/without adoption
  - offer future contraception (most effective way to prevent unintended pregnancies) and family planning services
  - ensure follow-up

Pregnancy-Related Complications

First Trimester Bleeding

Prevalence
- first trimester (T1) vaginal bleeding or spotting is common, occurring in 25% of pregnancies

Approach to the Patient with Bleeding in First Trimester

History
- risk factors for ectopic pregnancy (see *Ectopic Pregnancy, GY21*)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

Physical
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness, cervical motion tenderness)

Investigations
- β-hCG
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Bleeding in Pregnancy Definitions

First trimester bleeding: vaginal bleeding within the first 14 wk

Second trimester bleeding: 14-28 wk

Differential Diagnosis

Physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial β-hCGs

Abortion (threatened, inevitable, incomplete, complete)

Abnormal pregnancy (ectopic, molar) (see *Hydatidiform Mole, GY53*)

Trauma (post-coital or after pelvic exam)

Genital lesion (e.g. cervical polyp, neoplasms)

Subchorionic hematoma

Non-OB/GYN related cause of bleeding (e.g. hemorrhoids)

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

Spontaneous Abortions

- see *Termination of Pregnancy, GY19* for therapeutic abortions

Table 13. Classification of Spontaneous Abortions

Type	History	Clinical and U/S Findings	Management (± Rhogam®)
Threatened	Bleeding ± cramping	Live fetus on U/S Cervix closed	Watch and wait <5% will go on to abort
Inevitable	Bleeding and cramping ± rupture of membranes	Fetus low in uterus on U/S Cervix open	a) Watch and wait b) Misoprostol 800 µg PV now and 800 µg PV 24 h later c) D&C
Incomplete	Bleeding and cramps ± passage of tissue noticed	Residual tissue in uterus on U/S Cervix open	a) Watch and wait b) Misoprostol 800 µg PV now and 800 µg PV 24 h later c) D&C
Complete	Bleeding and complete passage of sac and placental tissue	Empty uterus on U/S Cervix closed, no bleeding	No management needed
Missed	No bleeding (fetal death in utero)	No fetal heart rate on U/S, fetus and sac still in uterus Cervix closed, no bleeding	a) Watch and wait b) Mifepristone 200 mg PO followed by misoprostol 800 µg PV 24 h later c) D&C
Recurrent	≥3 consecutive spontaneous abortions		Evaluate mechanical, genetic, environmental, and other risk factors
Septic	Contents of uterus infected – very rare	Tissue in uterus on U/S Foul discharge	a) IV broad spectrum antibiotics b) D&C 24 h after antibiotics c) Misoprostol 800µg PV 24 h later

Management of Abortions

Always rule out an ectopic pregnancy

Always check Rh; if negative, give Rhogam®

Always ensure patient is hemodynamically stable

Pregnancy failure can be diagnosed on U/S based on findings of crown-rump length ≥7 mm and no heartbeat, mean sac diameter of ≥7 mm and no embryo, absence of embryo with heartbeat ≥2 wk after a scan that showed a gestational sac without a yolk sac, or absence of embryo with heartbeat ≥11 d after a scan that showed a gestational sac with a yolk sac

Ectopic Pregnancy

Definition

- embryo implants outside of the endometrial cavity

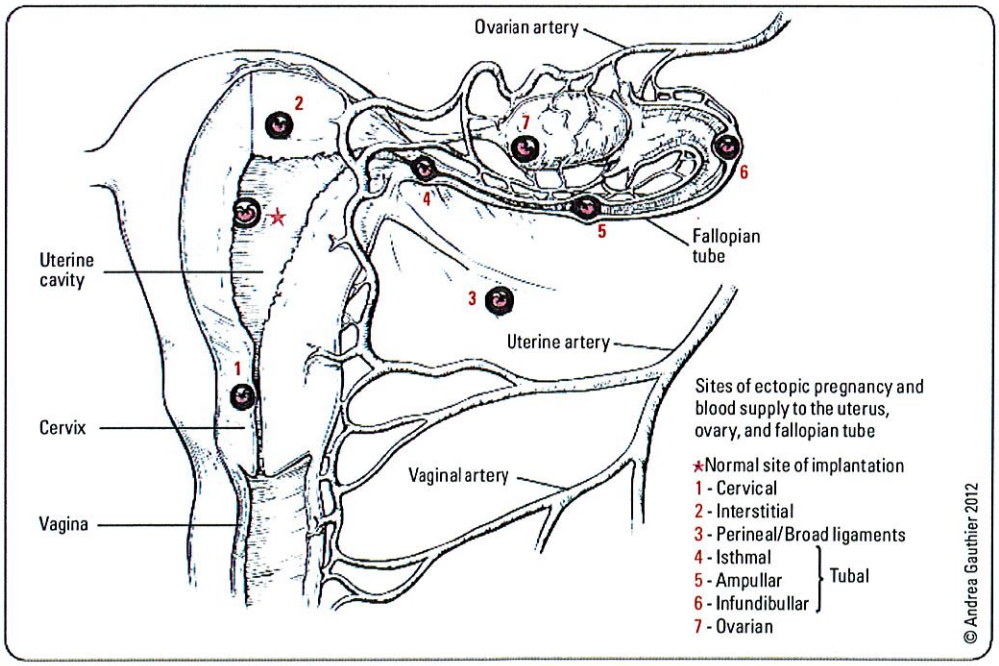


Figure 10. Sites of ectopic pregnancy implantation
ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of maternal death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

Etiology

- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle

- transmigration of fertilized ovum to contralateral tube
- major cause is disruption of normal tubal anatomy (infection, surgery, congenital differences, tumours)

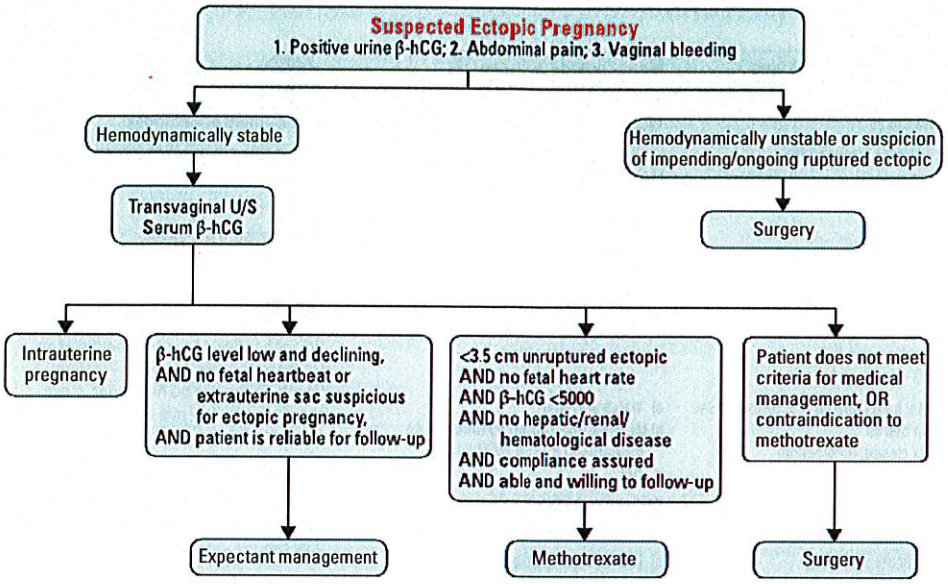


Figure 11. Algorithm for suspected ectopic pregnancy

Risk Factors

- previous ectopic pregnancy
- gynecologic
  - current IUD use – overall risk of pregnancy very low, but increased risk of ectopic pregnancy if pregnancy occurs
  - history of PID (especially infection with *C. trachomatis*), salpingitis, gonorrhea, chlamydia
  - infertility
- infertility treatment (IVF pregnancies following ovulation induction (7% ectopic rate))
- previous procedures
  - any surgery on fallopian tubes (for previous ectopic pregnancy, tubal ligation, tubal reconstruction, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
- *in utero* diethylstilbestrol (DES) exposure
- regular vaginal douching
- increased age

Investigations

- serial β-hCG levels; normal doubling time with intrauterine pregnancy is every 48 h in the first 8 wk
  - rise in β-hCG <35% every two days across 3 measurements is consistent with a non-viable pregnancy
  - prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - extra-uterine gestational sac with a yolk sac or embryo, regardless of cardiac activity, is diagnostic
  - specific suggestive, but not diagnostic, finding on transvaginal U/S is a tubal ring
- suspect ectopic pregnancy in case of empty uterus by transvaginal U/S with β-hCG >2000-3000 mIU/mL
- laparoscopy (sometimes used for definitive diagnosis)

Treatment

- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable, however, patient must be reliable to follow-up with weekly β-hCG
  - 15% risk of persistent trophoblast if salpingostomy, must monitor β-hCG titres weekly until they reach non-detectable levels
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence



Contraindications to Methotrexate Therapy in the 2021 SOGC Clinical Practice Guidelines on Management of Pregnancy of Unknown Location, Tubal and Nontubal Ectopic Pregnancies.
J Obs Gyn Can 2021; 43(5): 614-630

1. Hemodynamic instability or any signs of hemorrhage or tubal rupture
2. Unwilling or unable to adhere to methotrexate protocol and follow-up
3. Clinically significant abnormalities in renal or liver function
4. Hematologic disorders or bone marrow suppression
5. Active pulmonary disease
6. Peptic ulcer disease
7. Hypersensitivity to methotrexate
8. Immunosuppression or immunodeficiency
9. Chronic infection
10. Heterotopic pregnancy with coexisting viable intrauterine pregnancy
11. Breastfeeding

Note - cannot conceive for 3 mo after methotrexate therapy due to high teratogenicity



Salpingostomy Versus Salpingectomy in Women with Tubal Pregnancy (ESEP study): An Open-Label, Multicentre, Randomized Controlled Trial
Lancet 2014; 383:1483-1487

Purpose: Determine whether tube preserving salpingostomy offers favorable future fertility compared to salpingectomy in patients surgically treated for tubal pregnancies.
Methods: In this international RCT, patients with confirmed tubal pregnancy and healthy contralateral tube were randomized to salpingostomy (n=215) and salpingectomy (n=231). The primary outcome was ongoing pregnancy by natural conception.
Results: The primary outcome was present in 60.7% of patients in the salpingostomy group and 56.2% of patients in the salpingectomy group (p = 0.678). Persistent trophoblast was more frequent in the salpingostomy group with 7% of patients compared to <1% of patients in the salpingectomy group.
Conclusions: For pregnant patients requiring surgical treatment for tubal pregnancy, and that have a healthy contralateral tube, salpingostomy does not increase fertility prospects.



DDx of Lower Abdominal Pain
Urinary tract: UTI, kidney stones
GI: diverticulitis, appendicitis
Gynecological: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related



Any patient with a uterus presenting with abdominal pain, vaginal bleeding, and amenorrhea is an ectopic pregnancy until proven otherwise



More than half of patients with ectopic pregnancy have no risk factors

- consider Rhogam® if Rh-negative
- patient may require laparotomy if unstable, extensive abdominal surgical history, etc.

- medical = methotrexate
  - folic acid reductase inhibitor affecting rapidly dividing cells
  - use 50 mg/m²body surface area; given as a one time IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
  - follow β-hCG levels on days 4 and 7 after injection, and then weekly until β-hCG is non-detectable
  - plateaued or rising levels suggest persistent trophoblastic tissue requiring further treatment
  - 82-95% success rate, but up to 25% will require a second dose
  - administer a second dose if β-hCG does not decrease by at least 15%
  - tubal patency following methotrexate treatment approaches 80%
  - stop prenatal vitamins as folic acid will decrease efficacy of methotrexate
- expectant management is an option for patients who are clinically stable, reliable for follow-up, understand the risk of tubal rupture, and have β-hCG levels that are low and declining

Presentation of Ectopic Pregnancy Ruptures

Acute abdomen with increasing pain

Abdominal distention

Shock

Prognosis

- 9% of maternal deaths during pregnancy attributed to ectopic pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

Infertility

Epidemiology

- 10-15% of couples, must investigate both members of the couple

Female Factors

Infertility: inability to conceive or carry to term a pregnancy after 1 yr of regular, unprotected intercourse
Primary infertility: infertility in the context of no prior pregnancies
Secondary infertility: infertility in the context of a prior conception
Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr

Etiology

- increasing age
- chemotherapy
- ovulatory dysfunction (15-20%)
  - three groups of ovulatory disorders
    - hypogonadotropic hypogonadal (hypo-hypo; low gonadotropins, low gonadal hormones) anovulation (5-10%): excessive exercise, low body weight
    - normogonadotropic normoestrogenic anovulation (70-85%): PCOS
    - hypergonadotropic hypoestrogenic anovulation (10-30%): primary gonadal failure, gonadal dysgenesis
  - hypothalamic (hypothalamic amenorrhea)
    - stress, poor nutrition, excessive exercise (even with presence of menstruation), history of eating disorders
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - primary ovarian insufficiency
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, diabetes, Cushing's syndrome, renal/hepatic failure)
  - congenital (Turner's syndrome, gonadal dysgenesis, gonadotropin deficiency)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligation/occlusion (previous ectopic pregnancy)
- uterine factors (<5%)
  - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure, intrauterine adhesions (e.g. Asherman's syndrome), submucosal fibroids/polyps
  - infection (endometritis, pelvic tuberculosis)
- cervical factors (5%)
  - hostile or acidic cervical mucus, anti-sperm antibodies
  - structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

When Should Investigations Begin?

- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo of regular unprotected intercourse
- >40 yr: immediately

Earlier if:

- History of PID
- History of infertility in previous relationship
- Prior pelvic surgery
- Chemotherapy/radiation in either partner
- Recurrent pregnancy loss
- Moderate-severe endometriosis

Ethical Considerations in Infertility Treatment

Infertility demands non-judgmental discussion

Ethical issues surrounding surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial

If the physician finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

Investigations

- ovarian factors
  - day 3: FSH, LH, estradiol, TSH, prolactin, free and total testosterone, androstenedione, DHEAS, free testosterone
  - day 21-23: high serum progesterone levels confirm ovulation

- general health: CBC, Fe, HbA1c
- any day of cycle: anti-mullerian hormone (AMH) – a test of ovarian reserve, the higher the number the better

• tubal factors
- hysterosalpingogram (HSG) – dye insufflated into uterus and x-ray taken
  - shows uterine cavity shape and if tubes are patent
  - can be therapeutic – opens fallopian tube
- sonohysterogram (SHG) – saline insufflated into uterus and U/S done
  - shows uterine cavity shape and if tubes are patent
  - can be therapeutic and opens the tubes
- laparoscopy with dye insufflation (or tubal dye test) rarely done as diagnostic

• peritoneal/uterine factors
- HSG/SHG, hysteroscopy

• other
- karyotype

Treatment

• lifestyle modifications (quit smoking/cannabis, reduce caffeine/alcohol intake, healthy diet, exercise, etc.)
- education: time intercourse relative to ovulation (have sex every other day from 4 d prior to 2 d following presumed ovulation)

• medical
- ovulation induction
  - clomiphene citrate (Clomid®): estrogen antagonist used in anovulatory patients
    - blocks brain's perception of circulating estrogen, resulting in increased release of FSH and LH which can help to induce ovulation (better results if anovulatory)
  - letrozole: aromatase inhibitor; may be associated with a higher rate of live births in patients with PCOS
- may add:
  - bromocriptine (dopamine agonist) or carbamazepine (anticonvulsant) if elevated prolactin
  - metformin (for PCOS)
  - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
  - anticoagulation and ASA (81 mg PO once daily) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
  - thyroid replacement to keep TSH <2.5

• procedural
- artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
- sperm washing
- IVF
- intrafallopian transfer (IFT)
- GIFT*: immediate transfer with sperm after oocyte retrieval
- ZIFT*: transfer after 24 h culture of oocyte and sperm
- TET*: transfer after >24 h culture
- ICSI
- IVM
- ± oocyte or sperm donors
- ± pre-genetic screening for single gene defects in karyotype of zygote
- hysteroscopy

*not performed in Canada

• surgical
- salpingectomy
- tubuloplasty (extremely rare)
- lysis of adhesions

Male Factors

• see Urology, U24

Etiology

• varicocele (>40%)
• idiopathic (>20%)
• obstruction (~15%)
• cryptorchidism (~8%)
• immunologic (~3%)
• exogenous androgens

Investigations

• semen analysis and culture

Normal Semen Analysis (WHO lower reference limits)
- Must be obtained after 2-7 d of abstinence
- Volume 1.5 cc
- Count 15 million/cc
- Vitality 58% live
- Motility 32% progressive, 40% total (progressive + non-progressive)
- Morphology 4.0% normal

Polycystic Ovarian Syndrome

Etiology

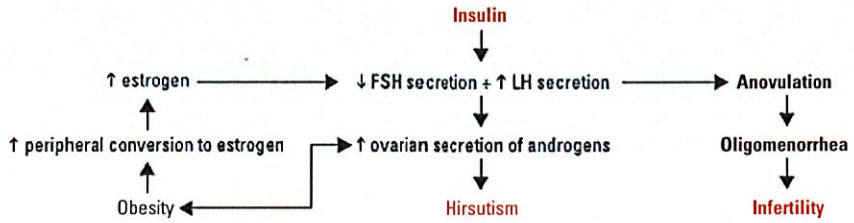


Figure 12. Pathophysiology of polycystic ovarian syndrome

Polycystic Ovarian Syndrome
HHAIIR-AN
Hirsutism, HyperAndrogenism, Infertility, Insulin Resistance, Acanthosis Nigricans

Diagnosis

- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence – hirsutism or acne
    - biochemical evidence – raised free testosterone
  - polycystic ovaries on U/S (not appropriate in adolescents)

PCOS may be confused with
- Late onset CAH (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

Clinical Features

- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis as adolescence resembles PCOS
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- acanthosis nigricans: darkening of skin folds in intertriginous zones (indicative of insulin resistance)
- insulin resistance occurs in both lean and obese patients
- FHx of DM

Clinical Signs of Endocrine Imbalance
- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- DM (10%)

Investigations

- assess BMI, BP, and fasting lipid profile at presentation
  - goal: identify hyperandrogenism or chronic anovulation and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, TSH, free T4
  - 17-hydroxyprogesterone, LH:FSH >2:1 (LH is chronically high with FSH mid-range or low (low sensitivity and specificity))
  - increased DHEAS, androstenedione, and free testosterone (most sensitive)
- transvaginal or transabdominal U/S: polycystic-appearing ovaries
  - "string of pearls" – 12 small follicles 2-9 mm or increased ovarian volume (>10 cc)
- tests for insulin resistance or glucose tolerance
  - 75 g OGTT every other year (particularly if obese)
- consider endometrial biopsy if long-standing abnormal uterine bleeding to rule out hyperplasia
- rule out other causes of abnormal bleeding

Long-Term Health Consequences
- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Subfertility
- Obesity
- Sleep apnea

Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - hormonal IUS, combined hormonal contraception or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if T2DM or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- infertility
  - medical induction of ovulation: letrozole, clomiphene citrate, human menopausal gonadotropins (HMG (Pergonal®)), LHRH, recombinant FSH, and metformin
    - metformin may be used in conjunction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary - rarely done
  - bromocriptine (if hyperprolactinemia)
- hirsutism
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-α reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone (androgen receptor inhibitor)

Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies
J Obstet Gynaecol Can 2008;8:671-679
At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on the basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multifactorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.

Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 4.0-4.5
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Non-Physiologic Discharge

- etiology
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen vascular disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features: irritation, pruritus, discharge, vulvar erythema, vaginal bleeding (can be due to Group A *Streptococcus* and *Shigella*)
- etiology
  - non-specific vulvovaginitis is responsible for 25-75% of vulvovaginitis in prepubertal patients
  - there are a number of potential factors in children that increase the risk of vulvovaginitis:
    - lack of labial development
    - non-estrogenized, thin mucosa
    - more alkaline pH (pH >7) than postmenarchal patients
    - obesity
    - poor hygiene (proximity of anus to vagina)
    - foreign bodies (most commonly toilet paper)
    - irritation by bubble baths, shampoos, perfumed soaps, and chemicals
  - localized skin disorders: lichen sclerosis, condyloma acuminata
  - trauma: accidental straddle injury, sexual abuse
  - infectious
    - pinworms
    - *Candida* (if using diapers or chronic antibiotics)
    - Group A *Streptococcus, S. aureus*, and *Shigella*
    - discovery of STI should raise suspicion of sexual abuse
  - other
    - polyps, tumour (ovarian malignancy)-RARE
    - psychosomatic vaginal complaints (specific to vaginal discharge)
    - endocrine abnormalities (specific to vaginal bleeding)
    - blood dyscrasia (specific to vaginal bleeding)
    - other systemic diseases: measles, chickenpox, scarlet fever, Epstein-Barr Virus, *Mycoplasma* pneumonia-induced rash and mucositis, Stevens-Johnson syndrome, Crohn's disease, and Kawasaki disease have all been associated with vulvovaginal signs and symptoms
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
  - pH, wet-mount, and KOH smear in postpubertal adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, use sitz baths, use mild detergent, urinate with legs spread apart, no nylon tights, no tight-fitting clothes, no sleeper pajamas, avoid bubble baths, eliminate fabric softener, avoid prolonged exposure to wet bathing suits) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified



Vulvovaginitis
Vulvar and vaginal inflammation



Vulvar Hygiene
Recommend wipe front to back, wash vulva only with water, avoid daily pantyliners, avoid douching, no need for "feminine cleansers/sprays/powders," use gentle laundry detergents for underwear, cotton underwear, no underwear at night



Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality

Clinicians who treat adolescents must be aware of federal, state, and provincial laws related to adolescent consent and confidentiality

Clinicians must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice



Most common gynecological problem in prepubertal patients is non-specific vulvovaginitis, not yeast

Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls

	Pinworms	Lichen Sclerosis	Foreign Body
Diagnosis	Cellophane tape test	Area of white patches and thinning of skin (figure of 8)	Careful examination with or without sedation
Treatment	Empirical treatment with mebendazole (anthelmintic)	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

INFECTIOUS VULVOVAGINITIS

Table 15. Infectious Vulvovaginitis

	Candidiasis	Bacterial Vaginosis (BV)	Trichomoniasis
Organisms	*Candida albicans* (90%) *Candida glabrata* (<5%) *Candida tropicalis* (<5%)	Replacement of vaginal Lactobacillus with: *Gardnerella vaginalis* *Mycoplasma hominis* *Anaerobes: Prevotella, Mobiluncus, Bacteroides*	*Trichomonas vaginalis* (flagellated protozoan)
Risk Factors	Immunosuppression (DM, AIDS, etc.) Recent antibiotic use Increased estrogen levels (e.g. pregnancy, OCP)	High frequency of vaginal intercourse Smoking Douching	Sexual transmission
Discharge	Whitish, "cottage cheese," minimal	Grey, thin, diffuse, fishy smelling	Yellow-green, malodourous, diffuse, frothy
% asymptomatic	20% asymptomatic	50-75% asymptomatic	25% asymptomatic
Signs/Symptoms	Intense pruritus Swollen, inflamed genitals Vulvar burning, dysuria, dyspareunia	Fishy odour, especially after coitus Absence of vulvar/vaginal irritation	Petechiae on vagina and cervix Occasionally irritated, tender vulva Dysuria, frequency, dyspareunia
pH	≤4.5	≤4.5	≤4.5
Saline Wet Mount	KOH wet mount reveals hyphae and spores	>20% clue cells = squamous epithelial cells dotted with coccobacilli (*Gardnerella*) Paucity of WBC Paucity of Lactobacilli Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)	Motile flagellated organisms Many WBC Inflammatory cells (PMNs) Can have positive whiff test
Treatment	Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments Only vaginal treatment in pregnancy Fluconazole 150 mg PO in single dose	No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure **Oral** Metronidazole 500 mg PO BID x 7 d* Oral treatment is best in pregnancy **Vaginal** Metronidazole 0.75% gel x 5 d once daily Clindamycin 2% 5 g intravaginally at bedtime for 7 d Probiotics (*Lactobacillus* sp.): oral or topical alone or as adjuvant	Treat even if asymptomatic Metronidazole 2 g PO single dose or metronidazole 500 mg BID x 7 d (alternative) Symptomatic pregnant women should be treated with metronidazole 2 g once
Other	Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole Routine treatment of partner(s) not recommended (not sexually transmitted)	Associated with recurrent preterm labour, preterm birth, and postpartum endometritis Routine treatment of partner(s) not recommended (not sexually transmitted)	Treat partner(s) (sexually transmitted)

* Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)

Sexually Transmitted Infections

- see Family Medicine, FM46

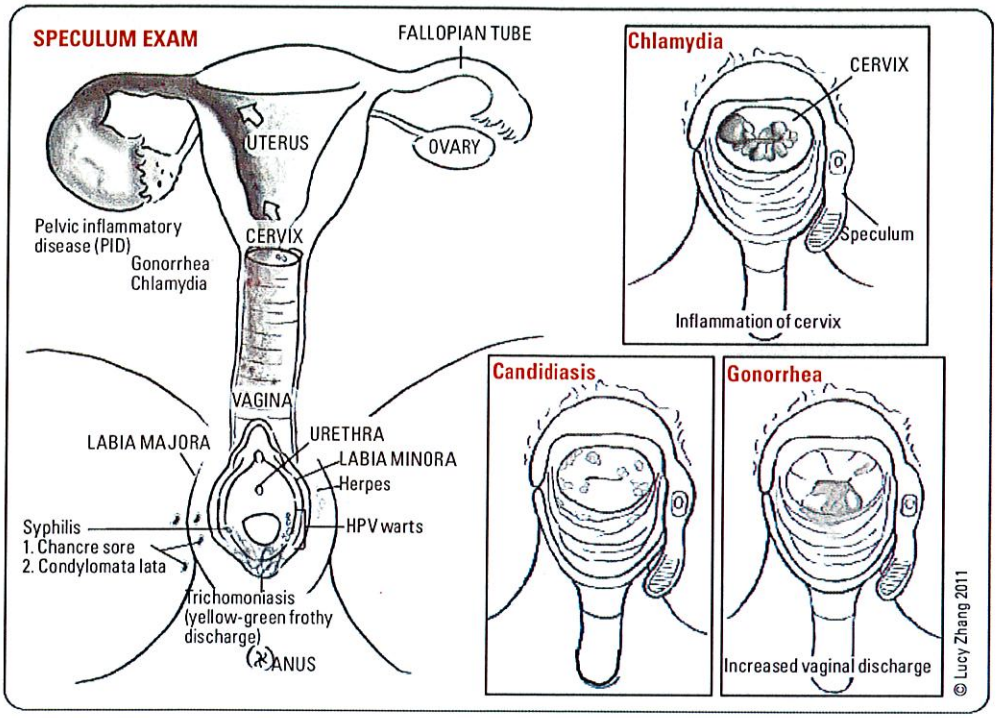


Figure 13. Speculum exam

CDC Notifiable Diseases
- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

Risk Factors for STIs
- History of previous STI
- Contact with infected person
- Sexually active individual <25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Social factors (homelessness, drug use)

TRICHOMONIASIS

- see *Infectious Vulvovaginitis, GY27*

CHLAMYDIA

Etiology
- *Chlamydia trachomatis*

Epidemiology
- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae* (patients with chlamydia should also be tested for gonorrhea)

Clinical Features
- asymptomatic (80% of patients)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

Investigations
- cervical culture or nucleic acid amplification test (can present in pharynx, rectum)
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and self-administered vaginal tests now available, which are equally or more effective than cervical culture

STI Testing
- Vaginal swab
- Tests for bacterial vaginosis, trichomoniasis, *Candida*
- Cervical swab
- Tests for gonorrhea and chlamydia

Treatment
- doxycycline 100 mg PO BID for 7 d or azithromycin 1 g PO in a single dose
  - doxycycline is contraindicated in the 2nd and 3rd trimesters of pregnancy
- reportable disease to public health
- test and provide empiric treatment to all sexual partners of the index case within 60 d prior to symptom onset or date of specimen collection (if the index case is asymptomatic)
- test of cure is recommended 3 wk after completion of treatment when compliance to treatment is suboptimal, an alternative treatment regimen is used, persistent symptoms, or the person is prepubertal or pregnant

Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant

Screening
- during pregnancy
- asymptomatic sexually active people under 25 yr
- neonates born to mothers with chlamydia
- any other people with risk factors for sexually transmitted and blood-borne infections

Complications
- PID: low-grade salpingitis and adhesions resulting in tubal obstruction
- infertility
- ectopic pregnancy
- chronic pelvic pain
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
- *Neisseria gonorrhoeae*
- symptoms and risk factors same as chlamydia

Investigations
- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

Treatment
- single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
  - if pregnant: above regimen or spectinomycin 2 g IM plus azithromycin 1 g PO (avoid quinolones)
  - also treat chlamydia, due to high rate of co-infection
- treat partners
  - reportable disease
  - screening as with chlamydia

HUMAN PAPILLOMAVIRUS

Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma
  - HPV is readily transmissible between opposite and same-sex partners through receptive and penetrative vaginal, anal and oral sex, and non-penetrative sex (digital-vaginal sex and skin-to-skin contact)
  - infection with one HPV type does not appear to provide protection against infection with related HPV types

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification (check pharynx too)
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cervical cytology by Pap test
  - koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- anogenital warts
  - patient administered
    - podofilox 0.5% solution or gel BID x 3 d in a row (4 d off) then repeat x 4 wk
    - imiquimod (Aldara®) 5% cream 3x/wk nightly x 16 wk
    - sinecatechins 10% ointment 0.5 cm strand TID x up to 16 wk, daily dose ≤ 250 mg (need not be washed off)
  - provider administered
    - cryotherapy with liquid nitrogen: repeat q1-2 wk
    - podophyllin resin in tincture of benzoin: weekly
    - trichloroacetic acid (TCA) (80-90%) or bichloroacetic acid weekly x 4-6 wk; safe in pregnancy
    - surgical removal/laser
- intraepithelial lesions and cancers (See *Gynecological Oncology, GY42*)



Genital Warts During Pregnancy
- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- Remove only if obstructing birth canal or risk of extensive bleeding
- Do not use imiquimod, podophyllin, or podofilox in pregnancy
- Baby at risk for juvenile respiratory papillomatosis, but condyloma dissection does not significantly reduce the risk



Human Rights in Health Equity: Cervical Cancer and HPV Vaccines
Am J Law Med 2009;35:365-387
- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries cervical cancer rates have risen or remained unchanged.
- It must be recognized that cervical cancer disparities between race groups, urban and rural residence, and high and low socioeconomic status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited healthcare settings, sexual health stigma, and related privacy concerns.



A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women
NEJM 2015;372:711-723
Purpose: To determine the efficacy and immunogenicity of the qHPV (types 6, 11, 16, 18) vs. 9vHPV (five additional types 31, 33, 45, 52, 58) vaccines.
Method: International randomized, double-blinded phase 2B-3 study of 9vHPV vaccine in 14215 women between ages of 16-26. Participants were randomized to the 9vHPV vaccine group or the qHPV vaccine group and each received a series of three IM injections (d 1, 2 mo, and 6 mo). Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue was obtained and used for HPV DNA testing/Pap smear.
Results: Rate of high-grade cervical, vulvar, or vaginal disease was 14.0 per 1000 person-yr in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1000 person-yr in the 9vHPV group and 1.6 per 1000 person-yr in the qHPV group (95% CI=80.9-99.8). Antibody responses to HPV-6, 11, 16, and 18 were not significantly different between the two vaccine groups although adverse events related to injection sites were more common in the 9vHPV group.
Conclusions: The 9vHPV vaccine was non-inferior to qHPV vaccine in preventing infection and disease related to HPV-6, 11, 16, and 18 and also covered additional oncogenic types HPV-31, 33, 45, 52, and 58 in a susceptible population.

Prevention
- vaccination: Gardasil®9, Gardasil®, Cervarix® (see *Table 28, GY49*)
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: average incubation is 4 d after exposure (range 2-12 d)
- prodromal symptoms: tingling, burning, and pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: common but less severe, less frequent, and shorter in duration (usually only HSV-2)

Investigations
- viral culture preferred in patients with ulcer present; however, decreased sensitivity as lesions heal
- HSV DNA PCR
- cytologic smear (Tzanck smear) shows multinucleated giant cells, limited use due to low sensitivity and specificity
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not routinely available in Canada)

Treatment
- first episode: acyclovir 200 mg PO five times daily x 7-10 d, famciclovir 250 mg PO TID x 7-10 d, or valacyclovir 1 g PO BID x 7-10 d
- recurrent episode: acyclovir 400 mg PO TID x 5 d, famciclovir 125 mg PO BID x 5 d, or valacyclovir 1 g PO once daily x 5 d
- daily suppressive therapy
  - consider for >6 recurrences per yr or recurrence every 2 mo
  - acyclovir 400 mg PO BID, famciclovir 250 mg PO BID, valacyclovir 500 mg PO once daily, or valacyclovir 1 g PO once daily
- severe disease: IV acyclovir 5-10 mg/kg q8 h x 2-7 d or until clinical improvement observed followed by oral antiviral therapy to complete 10 d of total therapy
- education regarding transmission: avoid sexual contact from onset of prodrome until lesions have cleared, use barrier contraception

SYPHILIS

Etiology
- *Treponema pallidum*

Classifications
- primary syphilis
  - 3-4 wk after exposure (median incubation 21 d)
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection, in 25% of patients with untreated primary syphilis
  - nonspecific symptoms: malaise, anorexia, headache, and diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, and limbs
  - condylomata lata: anogenital, broad-based, fleshy, grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis and general paresis
  - cardiovascular: aortic aneurysm and dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate, and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death



Epidemiology of Genital Ulcers

HSV	70-80%
1° Syphilis	5%
Chancroid *(Haemophilus ducreyi)*	<1%

Investigations
- aspiration of ulcer serum or node
- dark field microscopy (most sensitive and specific diagnostic test for syphilis): look for spirochetes
- non-treponemal screening tests (VDRL, RPR); non-reactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
- reportable disease, partners should be referred for treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1 wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units q4 h x 10-14 d
- screening
  - high-risk groups (partner with syphilis, HIV-infected individuals, high risk sexual behaviour, history of incarceration)
  - in pregnancy (see Obstetrics, *Infections During Pregnancy, OB32*)

Complications
- if untreated, 25-40% will experience late complications

HIV
- see Infectious Diseases, ID27

Bartholin Gland Abscess

Etiology
- follows the infection of an obstructed Bartholin duct
- most commonly *E. coli*, polymicrobial, *S. aureus*, and Group B *Strep*

Clinical Features
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

Treatment
- large mass >3 cm
  - 1st or 2nd episode: I&D under local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
  - recurrence after two failed attempts with Word catheter: marsupialization in ER under sedation, or under GA
- small mass <3 cm
  - I&D with Word catheter, sitz baths, warm compresses
- antibiotics: reserved for patients with recurrence, high risk of complicated infection, culture-positive MRSA, systemic infection

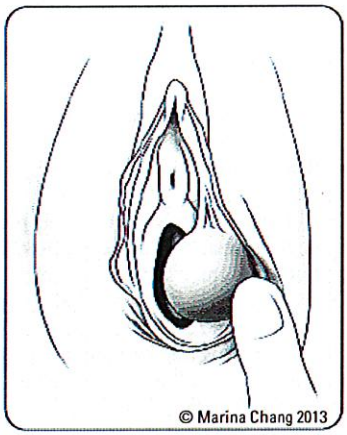


Figure 14. Bartholin gland abscess

Pelvic Inflammatory Disease

- infection of the upper genital tract (above the cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum ± contiguous structures that primarily affects young, sexually active women

PID accounts for up to 20% of all gynecological hospital admissions

Etiology

- microbial etiology unknown in most cases, often considered a polymicrobial infection
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
    - gonorrhea and chlamydia often co-exist
  - *M. genitalium*
  - *E. coli* and colonic anaerobes found in rare cases of PID in postmenopausal women
  - very rare pathogens: *M. tuberculosis, H. influenzae, S. pneumoniae,* and the agents of actinomycosis

Risk Factors

- age 15-25 yr
- multiple partners, STI in partner
- previous PID
- IUD (extremely rare, occurs within first 3 wk after insertion)

Clinical Features

- wide spectrum of clinical presentation: time course typically acute although many patients will have subclinical PID that does not prompt a patient to present for medical care but severe enough to cause significant sequelae (fertility issues)
- clinical diagnosis of PID: fever >38.3°C, lower abdominal pain and tenderness, and abnormal discharge (cervical or vaginal)
- uncommon: N/V, dysuria, and AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

Investigations

- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine routine and microscopy (R&M)
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - nucleic acid amplification tests (NAAT) for *N. gonorrhoeae, C. trachomatis, M. genitalium*
  - HIV testing and serologic testing for syphilis
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy
  - only done in patients that have failed outpatient treatment, symptoms not improving after 72 h of inpatient treatment, or unclear diagnosis
  - surgery has high specificity but low sensitivity

PID Diagnosis

Minimum diagnostic criteria

- Cervical motion tenderness
- Uterine tenderness
- Adnexal tenderness

Additional diagnostic criteria

- Oral temperature >38.3°C
- Leukocytosis on saline microscopy of vaginal secretions/wet mount
- Elevated ESR or CRP
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

Definitive diagnostic criteria

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal sonography or MRI showing thickened fluid-filled tubes, free fluid or tubo-ovarian complex
- Gold standard: laparoscopy demonstrating abnormalities consistent with PID

Treatment

- must treat with polymicrobial coverage
- percutaneous drainage of abscess under U/S guidance
- laparoscopic drainage when no response to treatment, surgical (salpingectomy, TAH/BSO) if failure
- consider removing IUD after a minimum of 24 h of treatment
- reportable disease, treat partners
- consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection

Table 16. Inpatient and Outpatient Management Options for Pelvic Inflammatory Disease

	Inpatient	Outpatient
Indications	Moderate to severe illness Atypical infection Adnexal mass, tubo-ovarian mass, or pelvic abscess Failed or cannot tolerate oral therapy Immunocompromised Pregnant Adolescent (first episode) Surgical emergency cannot be excluded (e.g. ovarian torsion) PID is secondary to instrumentation	Typical findings Mild to moderate illness Oral antibiotics tolerated Compliance ensured Follow up within 48-72 h (to ensure symptoms not worsening)
Antibiotic Regimen	Cefoxitin 2 g IV q6 h + doxycycline 100 mg PO/IV q12 h or Clindamycin 900 mg IV q8 h + gentamycin 2 mg/kg IV/IM loading dose then gentamicin/tobramicin 1.5 mg/kg q8 h maintenance dose Continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO BID to complete 14 d (add metronidazole 500 mg PO BID x 14 d in patients with tubo-ovarian abscess)	1st line: ceftriaxone 500 mg IM x 1 dose + doxycycline 100 mg PO BID x 14 d or cefoxitin 2 g IM x 1 dose + probenecid 1 g PO + doxycycline 100 mg PO BID ± metronidazole 500 mg PO BID x 14 d 2nd line: ofloxacin 400 mg PO BID x 14 d or levofloxacin 500 mg PO once daily x 14 d ± metronidazole 500 mg PO BID x 14 d

Complications of Untreated Pelvic Inflammatory Disease

- chronic pelvic pain
- persistent hydrosalpinx
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID: 13% infertility
  - 2 episodes of PID: 36% infertility
- bacteremia
- septic arthritis, endocarditis

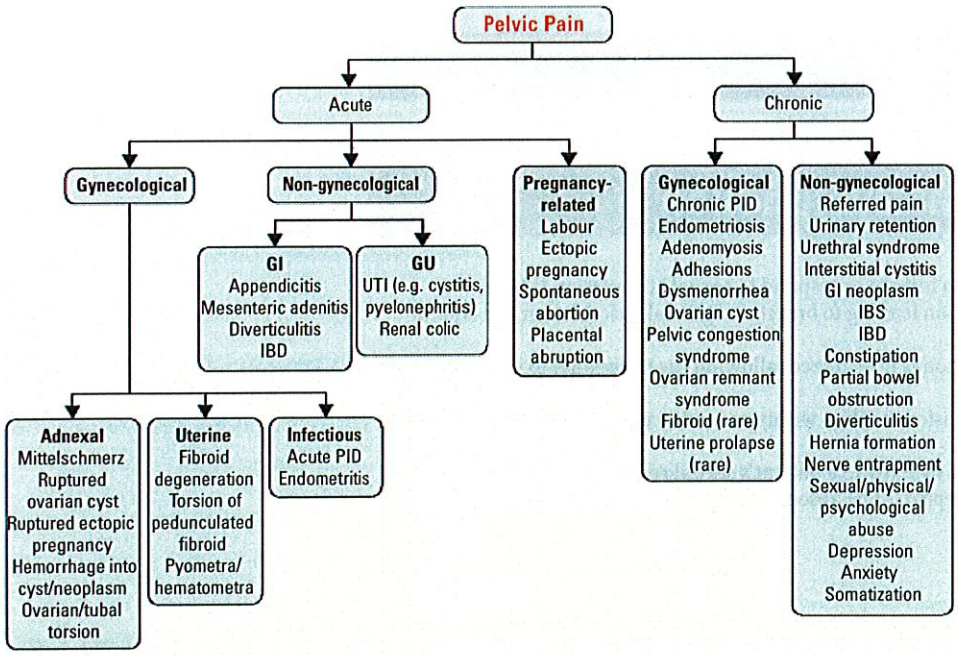


Figure 15. Approach to pelvic pain

Toxic Shock Syndrome (TSS)

- see Infectious Diseases, ID22
- Staphylococcal toxic shock syndrome (TSS) is a clinical illness characterized by rapid onset of fever, rash, hypotension, and multiorgan system involvement

Toxic Shock Syndrome
Multiple organ system failure due to *S. aureus* exotoxin (rare condition)

Risk Factors

- menstrual TSS
  - significantly decreased as a result of the withdrawal of highly-absorbent tampons and polyacrylate rayon-containing products from the market; however, tampon use remains a risk factor for TSS (high absorbency, tampons used continuously for more days of their cycle, and keeping a single tampon in place for a longer period of time)

- non-menstrual TSS (gynecologic)
  - diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
  - surgical and postpartum wound infections, mastitis, sinusitis, osteomyelitis, arthritis, burns, cutaneous lesions, etc.

Clinical Features
- sudden high fever/chills
- sore throat, headache, and diarrhea
- macular erythroderma followed by desquamation 1-2 wk later
- signs of multisystem organ failure
- refractory hypotension

Treatment
- treatment of shock
- remove potential sources of infection (foreign objects)
- surgical debridement (if warranted)
- adequate hydration
- empiric antibiotic therapy with vancomycin (load 20-35 mg/kg and maintenance 15-20 mg/kg q8-12 h) + clindamycin 900 mg IV q8 h + piperacillin-tazobactam 4.5 g IV q6 h
- continue combination therapy until patient is hemodynamically stable for at least 48-72 h

Surgical Infections

Postoperative Infections in Gynecological Surgery
- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, and discharge involving vaginal cuff
  - if fever and leukocytosis, treat with broad-spectrum ABx (i.e. clindamycin and gentamicin)
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General and Thoracic Surgery, *Postoperative Fever, GS8*

Sexual Abuse

- see Emergency Medicine, ER27 and Family Medicine, FM46

Sexuality and Sexual Dysfunction

SEXUAL RESPONSE
1. desire: energy that allows an individual to initiate or respond to sexual stimulation (libido)
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement (excitement)
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

Note: this framework cannot be applied consistently to a patient's sexual response. For many patients, the phases may vary in sequence, overlap, repeat, or be absent during some or all sexual encounters

SEXUAL DYSFUNCTION

Classification
- lack of desire (most common)
- lack of arousal
- anorgasmia
  - primary anorgasmia: never achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but unable to achieve orgasms presently
- dyspareunia: painful intercourse, can be superficial or deep

Etiology
- biological:
  - gynecological (e.g. pregnancy, childbirth, menopausal atrophy, endometriosis, prolapse, urinary incontinence)
  - urological (e.g. recurrent UTI, chronic renal failure)
  - vascular (e.g. peripheral vascular disease, CAD)
  - neurological dysfunction (e.g. nerve entrapment syndrome, spinal cord injury, multiple sclerosis, Parkinson's)

  - musculoskeletal (e.g. arthritis, mechanical back pain)
  - systemic health disorders (e.g. DM, thyroid disorders)
  - medication side effects (e.g. β-blockers, benzodiazepines, SSRIs, antipsychotics, oral contraceptives)
  - behavioural or lifestyle (e.g. smoking, alcohol consumption, opioids, obesity)
- psychological:
  - early events: history of sexual violence, unpleasant early sexual experiences, or growing up in a family or society that communicates no information or negative messages about female sexuality
  - current events: depression, anxiety, psychosis, fatigue, stress, or other mental health disorders
- relationship:
  - abuse
  - relationship distress
  - failure to engage in effective sexual stimulation

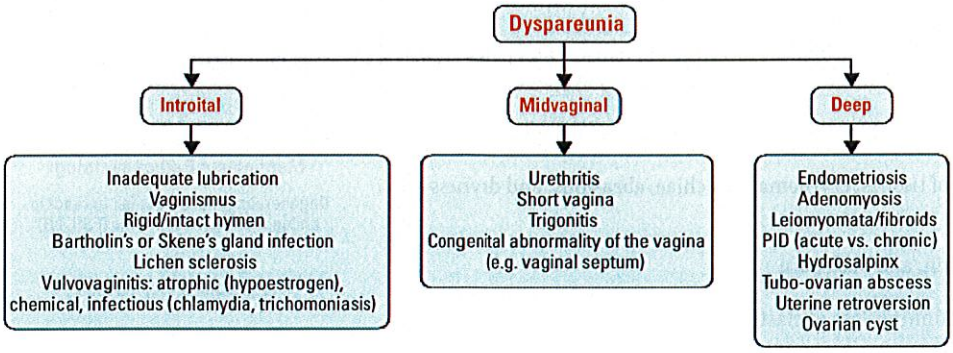


Figure 16. Approach to dyspareunia

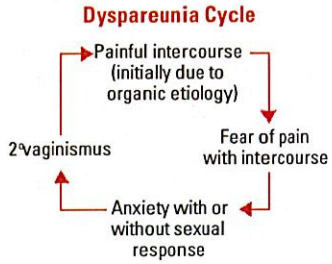


Figure 17. Dyspareunia cycle

Treatment

- general:
  - assess patient goals and construct a safety plan as needed
  - counselling
  - lifestyle changes
  - improve body image
- lack of desire:
  - biological: rule out other conditions/medication side effects; consider sildenafil for SSRI side effects; consider androgens (testosterone, DHEA), estrogens, tibolone in postmenopausal women; consider serotonergic and dopaminergic agents: flibanserin, bupropion, buspirone; consider bremelanotide
  - psychological: rule out/treat depression, other mental health issues
  - relationship: assess couple interaction and partner sexual function; treat partner and relationship conflict
- concerns with arousal/lubrication:
  - biological: non-hormonal, water-based lubricants; consider estrogen (topical cream, tablet, or ring) or coconut oil
  - psychological: address sexual anxieties
  - relationship: education regarding slowing of sexual response with aging
- anorgasmia:
  - biological: augment stimulation ± vibrator; consider androgens
  - psychological: sex education, anxiety reduction, and use of erotica
  - relationship: stimulation needs and helping patient teach partner what they need
- sexual pain disorders:
  - biological: rule out other conditions; topical estrogen if atrophy; consider nerve modulators (amitriptyline, gabapentin, or pregabalin); pelvic floor physiotherapy
  - psychological: sex therapy if vaginismus
  - relationship: rule out abuse (with patient alone)

Menopause

• see Family Medicine, FM43

Definitions

• lack of menses for 1 yr
• timing of menopause
  ▪ physiological; average age 51 yr (follicular atresia)
  ▪ premature ovarian insufficiency; before age 40 (autoimmune disorder, infection, Turner's syndrome)
  ▪ iatrogenic (surgical/radiation/chemotherapy)

Clinical Features

• associated with estrogen deficiency
  ▪ vasomotor instability (tends to dissipate with time)
    ◆ hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, and palpitations
  ▪ urogenital atrophy involving vagina, urethra, and bladder (genitourinary syndrome of menopause (GUSM))
    ◆ dyspareunia, pruritus, vaginal dryness, bleeding, post-coital bleeding, urinary frequency, urgency, and incontinence
    ◆ inspection may reveal: thinning of tissues, erythema, petechiae, abrasions, and dryness on speculum exam
  ▪ skeletal
    ◆ osteoporosis, joint and muscle pain, and back pain
  ▪ skin and soft tissue
    ◆ decreased breast size, and skin thinning/loss of elasticity
  ▪ psychological
    ◆ increased anxiety, depression, irritability, fatigue, decreased libido, and memory loss

Investigations

• for women with irregular cycles and menopausal symptoms:
  ▪ >45 yr: no testing necessary
  ▪ 40-45 yr: β-hCG, prolactin, TSH
  ▪ <40 yr: β-hCG, FSH, prolactin, TSH
• increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
• FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
• decreased levels of estradiol (later)

Treatment

• goal is for individual symptom management

Table 17. Treatment of Menopause

Vasomotor Instability	Vaginal Atrophy	Urogenital Health	Osteoporosis	Decreased Libido	CVD*	Mood and Memory
Menopause hormonal therapy (MHT) as first line, SSRI, venlafaxine, gabapentin, propanolol, clonidine, acupuncture, behavioural modifications	Local estrogen: cream (Premarin® or Estragyn Vaginal Cream®), vaginal suppository (VagiFem®), ring (Estring®), lubricants (Replens®), intravaginal laser	Lifestyle changes (weight loss, bladder training), pelvic floor exercises, local estrogen replacement, surgery	Calcium 1000-1500 mg once daily, vitamin D 800-1000 IU, weight-bearing exercise, smoking cessation, bisphosphonates (e.g. alendronate), SERMs (e.g.raloxifene (Evista®)), HRT (second-line treatment)	Vaginal lubricants, counselling, androgen-replacement testosterone cream or the oral form (Andriol®)	Manage CVD risk factors	Anti-depressants (first line), MHT (augments effect), CBT

*CVD (cardiovascular disease)

Menopause
Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins)

"Being in menopause"
Lack of menses for 1 yr

Perimenopause
Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset

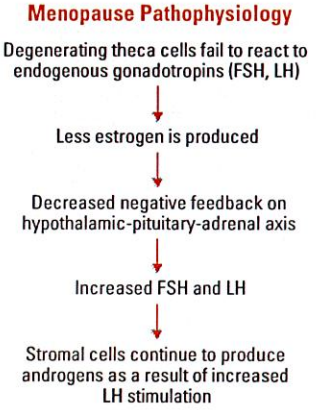


Figure 18. Menopause pathophysiology

85% of women experience hot flashes
20-30% seek medical attention
10% are unable to work

Menopause Hormone Therapy

- see Family Medicine, FM43

Treatment Guidelines

- primary indication is treatment of menopausal symptoms (vasomotor instability)
  - should not be prescribed if the only objective is the prevention of chronic disease
- before starting, review the benefits and risks (see *Table 18*) and contraindications with the patient
- use the lowest effective dose; patients with standard dose should be advised to lower dose after a few years
- patients receiving MHT must be evaluated annually
- decisions around duration of treatment should be individualized, but recommended to avoid treatment >5 yr with combination estrogen and progesterone treatment due to the duration-dependent risk of breast cancer
  - tapering and abruptly discontinuing MHT have similar impact on symptom recurrence, but for patients with a history of severe baseline vasomotor symptom, gradual tapering is probably preferable

Table 18. MHT Benefits vs. Risks

Benefits	Risks
Reduction of vasomotor symptoms Reduction of sleep problems Reduction of mood or anxiety problems Reduction of aches and pains Osteoporosis prevention and treatment Reversal of vulvar and vaginal atrophy (local estrogen therapy recommended if such atrophy is the only indication for therapy)	Thromboembolic events Stroke Breast cancer (increased risk after 4-5 yr with estrogen-progesterone regimens, no increased risk for at least 8 yr with estrogen-alone and no uterus regimens) Coronary heart disease (for women age >60 and those who are >10 yr after menopause) Endometrial hyperplasia and cancer (with estrogen-only regimens and uterus *in situ*)

MHT Components

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for patients overall, especially with hypertriglyceridemia or impaired hepatic function, smokers, and patients low-dose (preferred dose: Premarin® 0.3 mg/Estradot® patch 25 µg, can increase if necessary)
- progestin
  - given in combination with estrogen for patients with an intact uterus to prevent development of endometrial hyperplasia/cancer

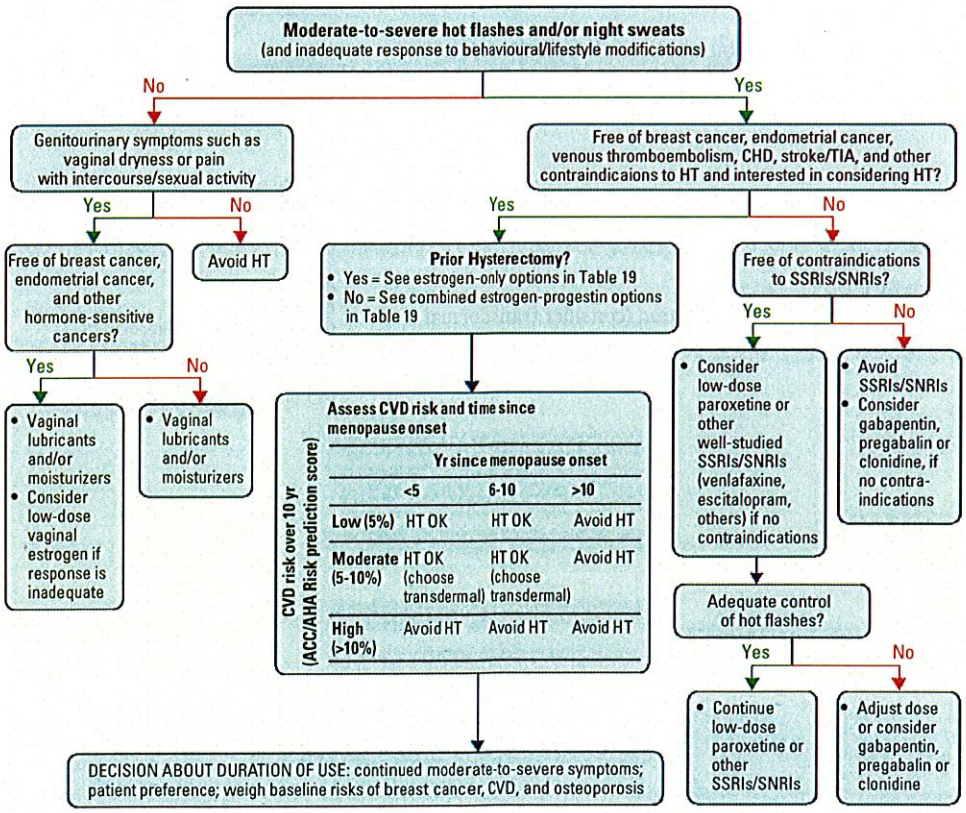


Figure 19. Hormone therapy in menopause

Long-Term Hormone Therapy for Perimenopausal and Postmenopausal Women
Cochrane DB Syst Rev 2017;1:CD004143
Purpose: To determine the effect of long-term HT (hormone therapy) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition, and quality of life (QOL) in perimenopausal and postmenopausal women, during HT use, and after cessation of HT.
Results: 22 studies with 43637 women included. Most studies included postmenopausal American women with at least some degree of comorbidity, with a mean participant age over 60 yr. Combined continuous HT: increased risk of coronary event after 1 yr (from 2/1000 to 3-7/1000), venous thromboembolism after 1 yr (2/1000 to 4-11/1000), stroke after 3 yr (6/1000 to 6-12/1000), breast cancer after 5.6 yr (19/1000 to 20-30/1000), gallbladder disease after 5.6 yr (27/1000 to 38-60/1000), and death from lung cancer after 5.6 yr use plus 2.4 yr additional follow up (5/1000 to 6-13/1000). Estrogen only HT: increased risk of venous thromboembolism after 1-2 yr use (2/1000 to 2-10/1000; after 7 yr, 16/1000 to 16-28/1000), stroke after 7 yr (24/1000 to 25-40/1000), and gallbladder disease after 7 yr use (27/1000 to 38-60/1000) but reduced the risk of breast cancer after 7yr (25/1000 to 15-25/1000 and clinical fracture after 7yr (141/1000 to 92-113/1000). Women >65 yr of age taking combined HT had shown an increase in the incidence of dementia after 4 yr use (9/1000 to 11-30/1000). For women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism at 1 yr (3/1000 to 3-29/1000).
Conclusions: HT may be contraindicated for some women with increased risk of cardiovascular disease, thromboembolic disease, and certain cancers such as breast cancer in women with a uterus. HT is not indicated for primary or secondary prevention of cardiovascular disease, dementia, or deterioration of cognitive function.

Osteoporosis is the single most important health hazard associated with menopause

Cardiovascular disease is the leading cause of death post-menopause

Increased risk of breast cancer (RR 1.3) is associated with estrogen+progesterone HRT, but not with estrogen-only HRT

All women taking HRT should have periodic surveillance and counselling regarding its benefits and risks

Table 19. Examples of MHT Regimens

MHT Regimen	Trade Names	Standard Doses
Estrogen-only – oral	Estrace®	17 β-estradiol 0.5-1 mg tablet daily
	Premarin®	CE 0.3-0.625 mg tablet daily
	Estragyn®	Esterified estrogens 0.3-0.625 mg cyclic
Estrogen-only – transdermal	Patches:	
	Estradot®, Sandoz Estradiol Derm®, Oesclim®, Climara®	17 β-estradiol 25-100 µg 1-2x/wk
	Gel:	
	Estrogel®	1-2 metered doses/actuation daily
	Divigel®	0.25-1 mg packets daily
Estrogen-only – vaginal	Cream:	
	Premarin®	CE 0.625 mg/g
	Estragyn®	Estrone 1 mg/g
	Inserts: Vagifem®	17 β-estradiol 10 µg
	Ring: Estring®	17 β-estradiol 2 mg
Combined E-P – oral	Activelle®	1 mg 17 β-estradiol/0.5 mg NEA
	Angeliq®	1 mg 17 β-estradiol/1 mg drospirenone
Combined E-P – transdermal	Patch: Estalis® (2 doses available)	17 β-estradiol/NEA: 50/140 mµg continuous 2x/wk 50/140 mµg or 50/250 mµg cyclic 2x/wk

CE = conjugated estrogen; E-P = estrogen-progestin; NEA = norethindrone acetate
Current common practice includes using the Mirena® IUD as the progesterone component (levonorgestrel 52 mg over 5 yr, approximately 20 µg/d)

Side Effects of MHT

- estrogen
  - breast tenderness
  - nausea
  - headache
  - bloating
- progestins
  - mood alterations
  - breast tenderness
  - bloating
  - sedation (micronized progesterone)

Contraindications to MHT

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - history of breast cancer
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis, or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, and impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials
JAMA 2013;310:1353-1368
Purpose: To report comprehensive findings from the 2 Women's Health Initiative (WHI) hormone therapy trials with extended post-intervention follow-up.
Methods: A total of 27347 postmenopausal women ages 50-79 were enrolled at 40 US centers. In the CEE+MPA trial, 16608 women, with intact uterus, received either continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg once daily) or placebo. In the CEE-only trial, 10739 women, with prior hysterectomy, received either CEE 0.625 mg once daily or placebo.
Results: Results all reported as difference between treatment and placebo in cases per 100000 person-yr, stratified by age.

	CEE + MPA trial		CEE alone trial	
CHD	50-59	5	50-59	-11
	60-69	0	60-69	-3
	70-79	19	70-79	7
Invasive breast cancer	50-59	6	50-59	-5
	60-69	8	60-69	-10
	70-79	15	70-79	-5
Stroke	50-59	5	50-59	-1
	60-69	11	60-69	18
	70-79	13	70-79	17
PE	50-59	6	50-59	3
	60-69	8	60-69	7
	70-79	18	70-79	-2
Colorectal cancer	50-59	-1	50-59	-3
	60-69	-8	60-69	-2
	70-79	-11	70-79	19
Hip fracture	50-59	-3	50-59	3
	60-69	-4	60-69	-6
	70-79	-14	70-79	-21

Absolute Contraindications to MHT

ABCD
Acute liver disease
Undiagnosed vaginal Bleeding
Cancer (breast/uterine), Cardiovascular disease
DVT (thromboembolic disease)

Urogynecology

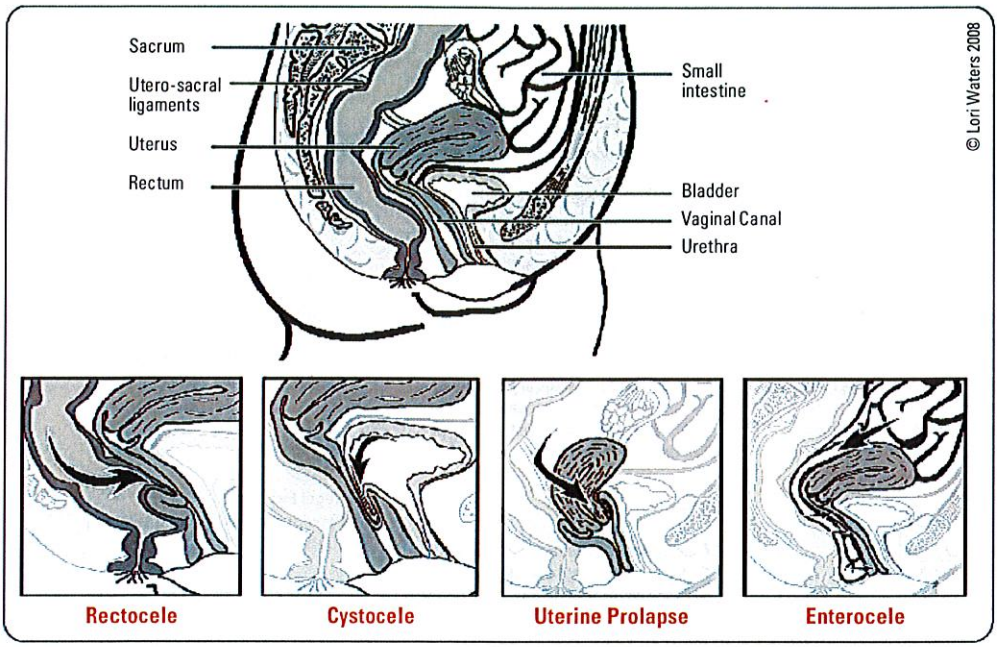


Figure 20. Pelvic anatomy

Pelvic Organ Prolapse

Etiology

- related to:
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - ethnicity (greater incidence in White women > Asian or African women)
  - connective tissue disorders

Pelvic Organ Prolapse
A weakening in the structures of the pelvic floor resulting in descent of one or more of the pelvic structures (bladder/rectum/small intestine/uterus) into the vagina

Diagnosis

- medical history
  - assess symptoms specific to prolapse: pressure, bulge
  - assess urinary, defecatory, and sexual concerns, which are often associated with pelvic organ prolapse
- physical exam (each component with patient relaxed and then while straining)
  - inspection in the dorsal lithotomy position
  - evaluate for apical prolapse with a bivalve speculum exam, then evaluate for anterior and posterior prolapse with the posterior blade of the bivalve speculum
  - use the POP-Q staging system to quantify stage of prolapse
  - evaluate for any coexisting pelvic abnormalities with a bimanual exam
  - test the strength of pelvic floor muscles with voluntary Kegel contractions
- ancillary studies
  - if continent with apical prolapse, consider clinical or urodynamic testing with and without reduction of prolapse to investigate for occult stress urinary incontinence
  - if voiding symptoms, consider post-void residual volume to evaluate urinary retention
  - if urgency or other UTI symptoms, consider urine microscopy and culture to test for UTI

POP-Q Staging of Pelvic Organ Prolapse
0 = no prolapse
1 = most distal portion of prolapse >1 cm above level of hymen
2 = most distal portion of prolapse is between 1 cm above or below the hymen
3 = most distal portion of prolapse >1 cm below level of hymen but no further than 2 cm less than the total vaginal length
4 = complete procidentia (uterus present with complete herniation of anterior, posterior, and apical compartments) or vault eversion (no uterus present with complete eversion of the anterior, posterior, and apical compartments), most distal prolapse protrudes 2 cm of total vaginal length

GENERAL CONSERVATIVE TREATMENT

- weight loss
- pelvic floor muscle training (e.g. Kegel exercises, pelvic physiotherapy)
- local vaginal estrogen therapy
- vaginal pessary (intravaginal devices that are either supportive or space-occupying)

The primary clinical features of pelvic organ prolapse are vaginal bulge and pressure

Table 20. Types and Management of Pelvic Organ Prolapse

Type	Clinical Features	Treatment
Anterior Vaginal Wall Prolapse (previously "cystocele") (protrusion of bladder into the anterior vaginal wall)	Frequency, urgency, nocturia Stress incontinence Incomplete bladder emptying ± associated increased incidence of UTIs (may lead to renal impairment)	General conservative treatment (see above) Anterior colporrhaphy ("anterior repair") Consider additional/alternative surgical procedure if documented urinary stress incontinence Can consider pessary
Posterior Vaginal Wall Prolapse (previously "rectocele") (protrusion of rectum into posterior vaginal wall)	Straining/digitation to evacuate stool Constipation	General conservative treatment (see above) Also laxatives and stool softeners Posterior colporrhaphy ("posterior repair"), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)
Uterine Prolapse (protrusion of cervix and uterus into vagina)	A type of apical prolapse Groin/back pain (stretching of uterosacral ligaments) Feeling of heaviness/pressure in the pelvis Worse with standing, lifting Worse at the end of the day Relieved by lying down Ulceration/bleeding (particularly if hypoestrogenic) ± urinary incontinence	General conservative treatment (see above) Vaginal hysterectomy ± surgical prevention of vault prolapse Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present Can consider pessary
Vault Prolapse (previously "enterocele", protrusion of apex of vaginal vault into vagina, post-hysterectomy, often containing small bowel)	A type of apical prolapse Same as uterine prolapse	General conservative treatment (see above) Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension

Surgery: native tissue repair vs. mesh reconstruction (usually reserved for severe, recurrent prolapse)



The only **true** hernia of the pelvis is an ENTEROCELE because peritoneum herniates with the small bowel



Kegel Exercises
Regular contraction and relaxation to strengthen pelvic floor muscles

Reverse Kegel Exercises
1 s contraction then 5 s of relaxation

Urinary Incontinence

• see Urology, U6

STRESS INCONTINENCE

Definition

- involuntary loss of urine with increased intra-abdominal pressure (cough, laugh, sneeze, walk, run)
- affects 4-35% of all women

Risk Factors for Stress Incontinence in Women

- increased age
- obesity
- pregnancy/vaginal delivery
- hypoestrogenic state (post-menopause)
- smoking/chronic cough
- neurological
- genetics
- high impact exercise

Diagnosis

- history
  - onset, frequency, severity, and pattern of urinary incontinence
  - frequency, dysuria, urgency, and nocturia
  - pads used per 24 h
  - obstructive urinary symptoms (incomplete voiding, hesitancy, straining, post-void dribbling, and recurrent UTI)
  - pelvic organ prolapse symptoms
  - neurological conditions/symptoms
  - obstetric history, and current menopause/hormone therapy status
  - medications (sedatives, diuretics, anticholinergic medications, and OTCs)
  - lifestyle risk factors (caffeine, smoking, weight, exercise, and occupation)
  - urinary diary
- physical exam
  - height, weight, and BMI
  - abdominal exam: scars, abdominal mass, and presence of a full bladder
  - neurological exam: S2-S4 sacral nerves (motor, sensory, and reflexes)
  - elderly: mini mental status exam, and observe mobility
  - pelvic exam: inspect vulva and urogenital epithelium, assess for signs of pelvic organ prolapse, and digital rectal exam to assess for anal sphincter tone and perineal sensation
  - standing stress test

- studies
  - urinalysis: hematuria, pyuria, glucosuria, proteinuria
    - hematuria/irritative voiding symptoms: cytology
    - pyuria/bacteria: urine culture
  - post-void residual
    - normal: ≤1/3 total volume
    - abnormal: >1/3 total volume (poor bladder contractility or bladder outlet obstruction)
  - urodynamic testing

Treatment
- for conservative management, see *Pelvic Organ Prolapse, GY39*
- procedures: vaginal laser, urethral bulking
- surgical
  - midurethral sling (TVT, TOT)
  - urethropexy (Burch procedure)
  - pubovaginal sling
  - urethral bulking

OVERACTIVE BLADDER

Definition
- symptom syndrome defined as "urgency, with or without urge urinary incontinence (UUI), usually with frequency and nocturia"
- 16% of all patients
- UUI: involuntary leakage with or immediately preceded by a strong desire to void
  - involuntary bladder contraction that overcomes the urethral sphincter mechanism OR
  - poor bladder compliance

Etiology
- idiopathic: congenital and aging
- medical: CHF, DM, and diuretics
- neurogenic: multiple sclerosis, Parkinson's, CVD, dementia, and spinal cord injury
- bladder outlet obstruction: previous bladder neck surgery and pelvic organ prolapse
- gynecologic: UTI, pregnancy, pelvic mass, and urethral diverticulum
- psychosomatic: habits, anxiety, and high fluid consumption

Diagnosis
- see *Stress Incontinence, GY40* for diagnosis

Treatment
- behaviour modification (reduce bladder irritants (caffeine, smoking, alcohol, acidic, spicy); adequate water intake; regular voiding schedule)
- bladder training with pelvic physiotherapist
- medications
  - anticholinergics
    - oxybutynin (oral: Ditropan®; patch: Oxytrol®; transdermal gel: Gelnique®)
    - tolterodine (Detrol®)
    - fesoterodine (Toviaz®)
    - solifenacin (Vesicare®)
    - trospium (Trosec®)
    - darifenacin (Enablex®)
  - β-adrenergic agonist: mirabegron (Myrbetriq®)
- procedures: sacral neuromodulation, detrusor botox injection

Gynecological Oncology

Pelvic Mass

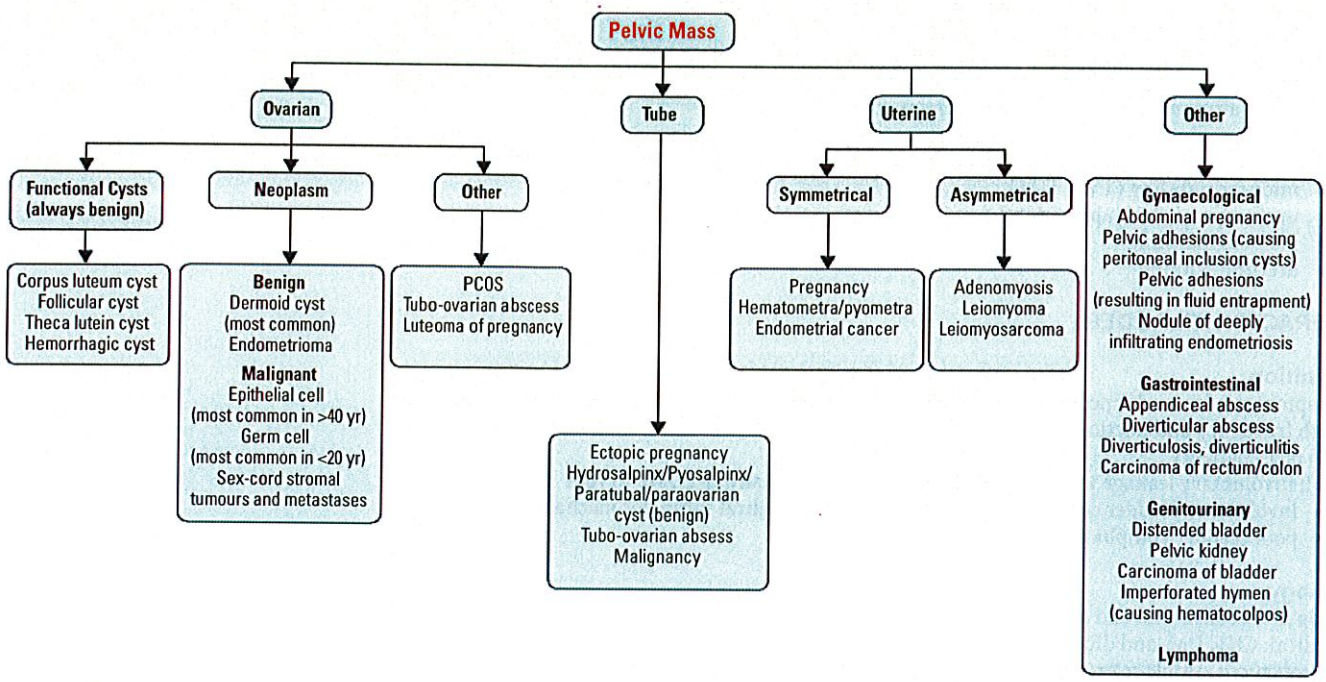


Figure 21. Differential diagnosis of pelvic mass

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology

- most common gynaecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of patients with a uterus develop endometrial carcinoma during their lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% 5 yr survival for all stages

Table 21. Features of Type I and Type II Endometrial Cancer

	Type I	Type II
Description	Estrogen-related (i.e. excess/unopposed estrogen): Endometrioid Includes well-differentiated (grade 1 and 2) endometrioid adenocarcinoma 80% of cases	Non-estrogen related: Non-endometrioid Includes serous, clear cell, grade 4 endometrioid and undifferentiated carcinomas, carcinosarcoma 20% of cases, poorer prognosis
Risk Factors (Increasing age and family history are risk factors for both types)	PCOS Diabetes mellitus Unbalanced HRT (balanced HRT is protective) Nulliparity or history of infertility related to anovulation Late menopause (>55 yr), early menarche Estrogen-producing ovarian tumours (e.g. granulosa cell tumours) HNPCC*/Lynch II syndrome Tamoxifen Prior pelvic radiation	Parous people More likely in Black patients Associated with p53 mutation, HER2 overexpression
Clinical Features	Postmenopausal bleeding AUB in premenopausal patients (menorrhagia, intermenstrual bleeding)	AUB

*HNPCC = Hereditary non-polyposis colorectal cancer

Incidence of Malignant Gynecological Lesions in North America
endometrium > ovary > cervix > vulva > vagina > fallopian tube

Risk Factors for Endometrial Cancer

COLD NUT
Cancer (ovarian, breast, colon)
Obesity
Late menopause
Diabetes mellitus
Nulliparity
Unopposed estrogen: PCOS, anovulation, HRT
Tamoxifen (chronic use)
(Genetic syndromes: Hereditary Nonpolyposis Colorectal Cancer (HNPCC) - Lynch II syndrome, Cowden syndrome)

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding and a thickness of more than 11 mm is considered abnormal in a postmenopausal woman without vaginal bleeding

Screening
- no known benefit for mass screening
- annual endometrial sampling starting at age 30-35 only for patients at high risk (HNPCC/Lynch II syndrome)
- routine pelvic ultrasound should not be used as a screening test (high false positive rates)

Investigations
- endometrial sampling in all suspected patients (office endometrial biopsy most commonly)
- hysteroscopy considered in patients with persistent uterine bleeding with benign sampling or inadequate sampling
- additional tumour markers, CT, MRI only in specific cases, such as high-grade tumours or suspected extrauterine spread

Table 22. FIGO Staging of Endometrial Cancer (2009)

Stage	Description	Stage	Description
I	Confined to corpus uteri including endocervical glandular involvement	IIIC	Metastasis to pelvic ± para-aortic LNs
IA	Less than 50% myometrial invasion	IIIC1	Positive pelvic LN
IB	More than 50% myometrial invasion	IIIC2	Positive para-aortic LN ± positive pelvic LNs
II	Invades cervical stroma, but does not extend beyond uterus	IV	Invades bladder ± bowel mucosa ± distant metastases (note: omental disease is stage IV)
III	Involves serosa, adnexa, vagina, or parametrium	IVA	Invades bladder ± bowel mucosa
IIIA	Invasion of serosa ± adnexae	IVB	Distant metastases, including intra-abdominal and intraperitoneal metastases, ± inguinal LNs
IIIB	Vaginal ± parametrial involvement		

FIGO: International Federation of Gynecology and Obstetrics

Treatment
- surgical: total hysterectomy + BSO
  - pelvic washings ± pelvic and para-aortic node dissection ± omentectomy in more advanced cases
  - goals: treatment, staging, determining need for adjuvant treatment
- adjuvant therapy: includes radiation and chemotherapy, depends on clinical and histological features
- hormone therapy: can be used in fertility-sparing treatments (e.g. progesterone IUD or oral progestins)

UTERINE SARCOMA
- rare; 3-9% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal, or myometrial tissues)
- behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5 yr survival is 35%
- vaginal bleeding is the most common presenting symptom

Table 23. Summary of Uterine Sarcoma Subtypes and Features

Type	Epidemiology	Features	Diagnosis	Treatment
PURE TYPE				
1. Leiomyosarcoma	Most common type of uterine sarcoma Average age of presentation is 55 yr, but may present in premenopausal patients Often coexists with benign leiomyomata (fibroids)	Histologic distinction from leiomyoma: 1. Increased mitotic count (>10 mitoses/10 high-power fields) 2. Tumour necrosis 3. Cellular atypia Rapidly enlarging fibroids in a premenopausal patient Enlarging fibroids in a postmenopausal patient	Often postoperatively after uterus removed for presumed fibroids Stage using FIGO 2009 staging for leiomyosarcomas and ESS	Hysterectomy ± BSO usually No routine pelvic lymphadenectomy Chemotherapy is used in cases of metastatic disease Radiation therapy does not improve local control or survival Poor outcomes overall, even for early-stage disease
2. Endometrial Stromal Sarcoma (ESS)	Usually presents in perimenopausal or postmenopausal patients with abnormal uterine bleeding	Abnormal uterine bleeding Good prognosis	Diagnosed by histology of endometrial biopsy or D&C Stage using FIGO 2009 staging for leiomyosarcomas and ESS	Hysterectomy & BSO (remove ovaries as ovarian hormones may stimulate growth) No routine pelvic lymphadenectomy Adjuvant therapy based on stage and histologic features (hormones and/or radiation) Hormonal therapy (progestins) may be used for metastatic disease
3. Undifferentiated Sarcoma	Rare; less common than leiomyosarcoma and ESS	Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack of smooth muscle or endometrial stromal differentiation Poor prognosis	Often found incidentally postoperatively for abnormal bleeding	Treatment primarily surgical Radiation and/or chemotherapy for advanced diseased or unresectable disease
MIXED TYPE				
4. Adenosarcoma	The rarest of the uterine sarcoma Mixed tumour of low malignancy potential	Present with abnormal vaginal bleeding Polypoid mass in uterine cavity	Mixture of benign epithelium with malignant low-grade sarcoma Often found incidentally at time of hysterectomy for PMB Stage using FIGO 2009 staging for adenosarcoma	Treatment is surgical with hysterectomy & BSO



Prognostic Factors
- FIGO stage (most important factor)
- Age
- Grade
- Histologic subtype
- Depth of myometrial invasion
- Presence of LVSI



Complications of Therapy

Surgical Complications
- Surgical site infection
- Lymphedema
- VTE
- Urinary retention
- UTI
- Pelvic lymphocyst
- Leg weakness
- Vaginal dryness

Radiation Complications
- Radiation fibrosis
- Cystitis
- Proctitis
- Long-term increase in other types of malignancy



Uterine Sarcoma – Presentation
Bleeding, abdominal distention, pelvic pressure



CA-125 is indicated for monitoring response to treatment

Table 24. FIGO Staging of Uterine Sarcoma (2009)

Stage	Description	Stage	Description
I	**Tumour limited to uterus**	III	**Tumour invades abdominal tissues**
IA	<5 cm	IIIA	One site
IB	>5 cm	IIIB	More than one site
II	**Tumour extends beyond uterus**	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IIA	To the pelvis, adnexal involvement	IV	**Distant spread**
IIB	To extra-uterine pelvic tissue	IVA	Tumour invades bladder and/or rectum
		IVB	Distant metastasis

Ovary

BENIGN OVARIAN TUMOURS

- see *Table 25, GY45*
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour (rare)

MALIGNANT OVARIAN TUMOURS

- see *Table 25, GY45*

Epidemiology

- lifetime risk 1.4%
- majority of ovarian cancer cases are detected in patients >50 yr
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 85% epithelial; 15% non-epithelial
- 10-15% of epithelial ovarian cancers are related to hereditary predisposition

Risk Factors (for epithelial ovarian cancers)

- early menarche and/or late menopause
- personal history of breast, colon, or endometrial cancer
- family history of breast, colon, endometrial, or ovarian cancer
- advanced age
- BRCA mutation (serous) and Lynch syndrome (non-serous, non-mucinous)
- use of fertility drugs (limited evidence)

Protective Factors (for epithelial ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use, 50% after 5 yr)
- pregnancy/breastfeeding

Prophylactic Measures

- prophylactic BSO in high-risk patients (i.e. BRCA mutation carriers)
- prophylactic salpingectomy in high-risk patients (i.e. BRCA mutation carriers who do not want oophorectomy yet)

Screening

- no effective method
- routine CA-125 or U/S not recommended

Clinical Features

- most patients with epithelial ovarian cancer present with advanced stage disease (i.e. stage IIIC high-grade serous histology)
- symptoms:
  - abdominal symptoms (nausea, bloating, pain, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
  - increased abdominal girth (from ascites or tumour itself)
  - urinary urgency and frequency
  - constipation



Ovaries are like GEMS
Germ cell
Epithelial
Metastatic
Sex cord stromal



Most (70%) epithelial ovarian cancers present at stage III disease



Ovarian Tumour Markers
Epithelial cell:
- CA-125 (serous and endometrioid)

Sex-cord stromal cell:
- Granulosa cell: inhibin
- Sertoli-Leydig: androgens

Germ cell:
- Dysgerminoma: LDH
- Yolk sac: AFP
- Choriocarcinoma: β-hCG
- Immature teratoma: none
- Embryonal cell: AFP + β-hCG



Diagnosis of ovarian tumours requires surgical pathology



Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise



Omental Cake: a term for ascites plus a fixed upper abdominal and pelvic mass; almost always signifies ovarian cancer



Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force
JAMA 2018;319(6):595-606
Purpose: To systematically review evidence on benefits and harms of ovarian cancer screening among average-risk, asymptomatic women.
Methods: Systematic review of RCTs of ovarian cancer screening in average-risk women that reported mortality or quality-of-life outcomes. Interventions included transvaginal U/S and/or CA-125 testing. Comparators were usual care or no screening.
Results: Four trials (n = 293587) were included. No trial found a significant difference in ovarian cancer mortality with screening. In two trials, screening led to surgery for suspected ovarian cancer in 1% of women without cancer and for transvaginal U/S with or without CA-125 screening in 3%, with major complications occurring in 3% to 15% of surgeries. Evidence of psychological harm was found in cases of repeat follow-up scans and tests.
Conclusions: Ovarian cancer mortality did not significantly differ between screened women and those with no screening or in usual care.

Treatment

- debulking surgery including total hysterectomy, BSO, omentectomy, and/or removal of all visible disease
- many epithelial ovarian cancers (i.e. serous ovarian carcinoma) are chemosensitive: treat with platinum-based chemotherapy + taxol
- neo-adjuvant chemotherapy (if needed) to shrink down tumours prior to debulking
- adjuvant chemotherapy to treat microscopic disease



Malignant Ovarian Tumour Prognosis

5 Yr Survival	
Stage I	75-95%
Stage II	60-75%
Stage III	23-41%
Stage IV	11%

Low Malignant Potential (also called "Borderline") Tumours

- a subcategory of epithelial ovarian cancer (~15% of all epithelial ovarian tumours)
- approximately one-third of tumours are identified in patients <40 yr
- pregnancy and breastfeeding are protective factors
- tumour cells with histologically malignant characteristics arise from the ovarian surface, but do not invade the ovarian stroma
- able to metastasize, but uncommon
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  - chemotherapy has limited benefit: can be treated with hormonal manipulation (letrozole)
  - young patients can be treated with fertility-sparing options such as cystectomy or unilateral salpingo-oophorectomy
- generally slow growing, excellent prognosis
  - 5 yr survival >99%
  - recurrences tend to occur late, may be associated with low-grade serous carcinoma

Table 25. Ovarian Tumours

Type	Description	Presentation	Ultrasound/Cytology	Treatment
FUNCTIONAL TUMOURS (all benign)				
Follicular Cyst	Follicle fails to rupture during ovulation	Usually asymptomatic May rupture, bleed, tort, infarct, causing pain ± signs of peritoneal irritation	4-8 cm mass, unilocular, lined with granulosa cells	Symptomatic or suspicious masses warrant surgical exploration Otherwise if <6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression): will prevent development of new cysts Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)
Corpus Luteum Cyst	Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic	More likely to cause pain than follicular cyst May delay onset of next period	Larger (10-15 cm) and firmer than follicular cysts	Same as for follicular cysts
Theca-Lutein Cyst	Due to atretic follicles, stimulated by abnormal β-hCG levels	Associated with molar pregnancy, ovulation induction with clomiphene		Conservative Cyst will regress as β-hCG levels fall
Endometrioma	See *Endometriosis, GY11*			
Polycystic Ovaries	See *Polycystic Ovarian Syndrome, GY25*			
BENIGN GERM CELL TUMOURS				
Benign Cystic Teratoma (dermoid)	Single most common ovarian germ cell neoplasm Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)	May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive yr	Smooth-walled, mobile, unilocular U/S may show calcification which is pathognomonic	Treatment usually laparoscopic cystectomy; may recur
MALIGNANT GERM CELL TUMOURS				
General Information	Rapidly growing, 2-3% of all ovarian cancers	Usually children and young women (<30 yr)		Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy
Dysgerminoma	Produces LDH	10-15% bilateral		When diagnosed at stage IA, no adjuvant treatment is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Immature Teratoma	No tumour marker identified	Almost always unilateral		When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated When diagnosed at Grade 2-3, either adjuvant chemotherapy or surgical staging is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Yolk Sac Tumour	Produces AFP	Abdominal pain and pelvic mass		High grade tumour can be treated with adjuvant chemotherapy or monitor AFP levels
Ovarian Choriocarcinoma	Produces β-hCG	Precocious puberty and irregular vaginal bleeding		High grade tumour usually treated with adjuvant chemotherapy

Table 25. Ovarian Tumours

Type	Description	Presentation	Ultrasound/Cytology	Treatment
EPITHELIAL OVARIAN TUMOURS (malignant or borderline)				
General Information	Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (including malignant tumours)		Varies depending on subtype	**Borderline** Cystectomy vs. unilateral salpingo-oophorectomy **Malignant** 1. Early stage (stage I): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy). Depending on histology, may require adjuvant chemotherapy 2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatin/paclitaxel vs. intraperitoneal chemotherapy (stage III) neoadjuvant chemotherapy with IV carboplatin/paclitaxel, followed by delayed debulking with further adjuvant IV chemotherapy
Serous	Most common ovarian tumour histology 50% of all ovarian cancers 75% of epithelial tumours 70% benign	20-30% bilateral	Lining similar to fallopian tube epithelium Often multilocular Histologically contain psammoma bodies (calcified concentric concretions)	See above
Mucinous	20% of epithelial tumours	Rarely complicated by Pseudomyxoma peritonei: implants seed abdominal cavity and produce large quantities of mucin	Resembles endocervical epithelium Often multilocular May reach enormous size	Poor response to chemotherapy If mucinous, remove appendix as well to rule out possible source of primary disease
Clear Cell	10% of epithelial tumours Can be found adjacent to endometriosis More common in the Asian population	More likely to be detected at an early stage	Contains glycogen-rich cells with clear cytoplasm and hobnail cells	Poor response to chemotherapy
Endometrioid	10% of epithelial tumours Can be found adjacent to endometriosis	Can be associated with endometrial neoplasm	Typically cystic or solid, unilateral, and confined to the ovary	Tend to respond well to chemotherapy
SEX CORD STROMAL OVARIAN TUMOURS				
Fibroma/Thecoma (benign)	From mature fibroblasts in ovarian stroma	Non-functioning Occasionally associated with Meig's syndrome (triad of benign ovarian tumour, ascites, and pleural effusion)		
Granulosa-Theca Cell Tumours (benign or malignant)	Tumour marker is inhibin	Estrogen-producing: feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding) Risk of endometrial cancer due to estrogen	Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies	Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
Sertoli-Leydig Cell Tumour (benign or malignant)	Can measure elevated androgens as tumour markers	Androgen-producing: virilizing effects (hirsutism, deep voice, recession of front hairline)		Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
METASTATIC OVARIAN TUMOURS				
From GI Tract, Breast, Endometrium, Lymphoma	4-8% of ovarian malignancies Krukenberg tumour: metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast primary tumour)	80% bilateral	Krukenberg tumours have "signet-ring" cells	

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
    - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for preoperative gynecologic oncology referral (see sidebar)
- physical exam findings largely dependent on stage of disease
- blood work: CBC, LFTs, electrolytes, Cr, tumour markers as appropriate (CA-125, inhibin, β-hCG, LDH, AFP, androgens, CEA, Ca19-9, estrogen)
- biopsy not recommended due to tumour spillage into peritoneum; if extensive disease, determine cytological diagnosis from paracentesis from ascites or tissue biopsy from peritoneal deposits or omental cake
- radiology
  - transvaginal U/S best to visualize ovaries
  - CT abdomen and pelvis to look for metastatic disease
  - bone scan or PET scan not indicated



Causes of Elevated CA-125

Age influences reliability of test as a tumour marker

50% sensitivity in early-stage ovarian cancer (poor), therefore not good for screening

Malignant

Gynecologic: ovary, uterus

Non-Gynecologic: pancreas, stomach, colon, rectum

Non-Malignant

Gynecologic: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID

Non-Gynecologic: cirrhosis, pancreatitis, renal failure

- try to rule out other primary source (if suspected), based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms: gastroscopy ± upper GI series
  - abnormal vaginal bleeding: endometrial biopsy to rule out concurrent endometrial cancer; abnormal cervix: need to biopsy cervix (not Pap smear); breast lesion identified or risk factors present: mammogram

Table 26. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2014)

Stage	Description
I	Growth limited to the ovaries
IA	1 ovary, no ascites, no tumour on external surface, capsule intact, negative washings
IB	2 ovaries, no ascites, no tumour on external surface, capsule intact
IC	1 or 2 ovaries with any of the following: surgical spill (IC1), capsule ruptured (IC2), tumour on ovarian surface (IC2), or malignant cells in ascites (IC3)
II	**Growth involving one or both ovaries with pelvic extension or primary peritoneal cancer**
IIA	Extension ± implants to uterus/tubes
IIB	Extension to other pelvic structures
III	**Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal nodes**
IIIA	Positive retroperitoneal LNs and/or microscopic metastasis beyond pelvis
IIIA1	Positive retroperitoneal LNs
IIIA2	Microscopic, extrapelvic peritoneal involvement ± positive retroperitoneal LNs
IIIB	Macroscopic peritoneal metastasis beyond pelvis ≤2 cm, ± positive retroperitoneal LNs. Includes extension to capsule of liver/spleen
IIIC	Same as above but peritoneal metastasis >2 cm
IV	**Distant metastasis beyond peritoneal cavity**
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis or metastasis to extra-abdominal organs (inguinal LNs and LNs outside of abdominal cavity included)

FIGO = International Federation of Gynecology and Obstetrics

A Risk of Malignancy Incorporating CA-125, Ultrasound, and Menopausal Status for the Accurate Preoperative Diagnosis of Ovarian Cancer
BJOG 1990;97:922-929
RMI = U x M x CA-125
Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 1 (for U/S scores of 0 or 1)
U = 4 (for U/S scores of 2-5)
Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI>200: gynecologic oncology referral is recommended

Optimal Primary Surgical Treatment for Advanced Epithelial Ovarian Cancer
Cochrane Database Syst Rev 2011;(8):CD007565
Summary: During primary surgery for stage III or IV epithelial ovarian cancer, all attempts should be made to achieve complete cytoreduction. When this is not achievable, optimal (<1 cm) residual disease should be the goal.
Methods: Identified 11 retrospective studies consisting of 4735 women using comprehensive search strategy.
Results:
1. When suboptimal (margins >1 cm) was compared with optimal (<1 cm) cytoreduction, the survival estimates were reduced but remained statistically in favour of the lower volume disease group.
2. No significant difference in overall survival between suboptimal and optimal cytoreduction.
3. Borderline difference in progression-free survival when residual disease >2 cm and <2 cm were compared (p=0.05).

Cervix

MALIGNANT CERVICAL LESIONS

Epidemiology
- majority are SCC (90%); adenocarcinomas increasing (10%); rare subtypes include small cell, adenosquamous
- 8000 deaths annually in North America
- average age at presentation: 50 yr; bimodal distribution (increased frequency in 40s and 60s)

Etiology
- at birth, the vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from columnar to squamous)
  - a new squamocolumnar junction forms as a result
- the TZ is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (e.g. HPV) to get dysplasia
- dysplasia progresses to carcinoma *in situ* (CIS), which further progresses to invasion of cervical tissues
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors
- HPV infection
  - see *Sexually Transmitted Infections, GY28*
  - high-risk of neoplasia associated with types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82
  - low-risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high-risk HPV types
- high-risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high-risk male partner

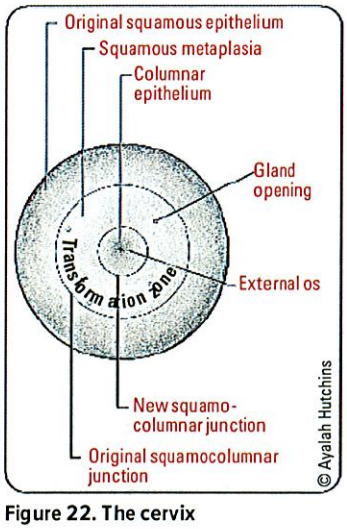


Figure 22. The cervix

Cervical cancer is most prevalent in developing countries and, therefore, is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies such as CT and MRI

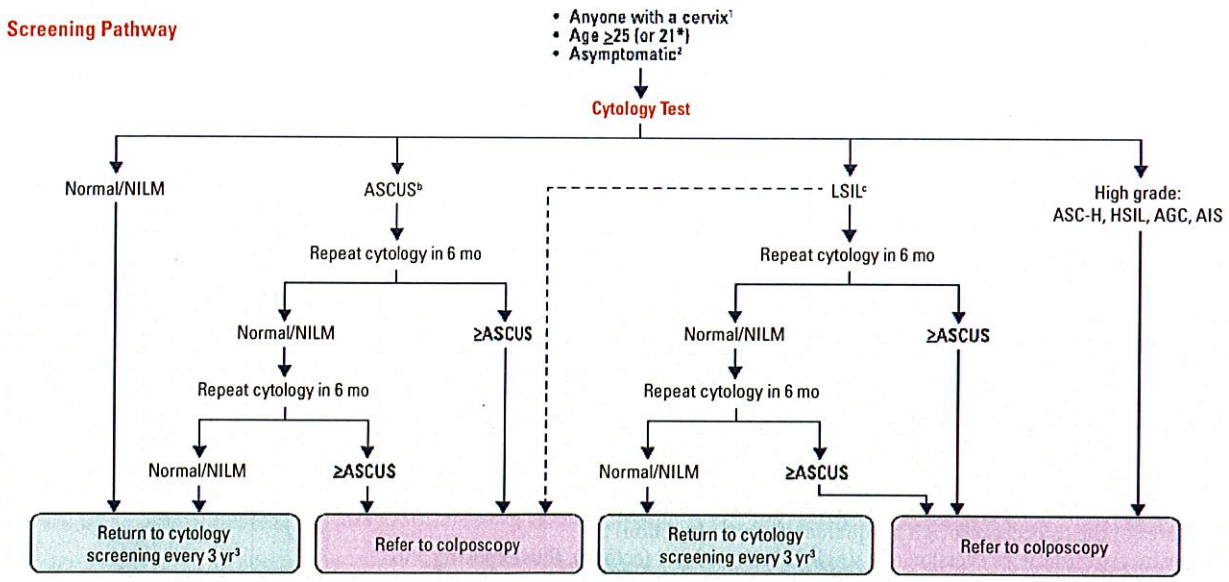
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
  - immigrant Canadians
  - Indigenous peoples in Canada
  - geographically-isolated Canadians
  - sex-trade workers
  - low socioeconomic status Canadians
  - immunocompromised individuals

Cervical Cancer Screening Guidelines (Pap Test)

- see Family Medicine, FM5

Clinical Features

- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic or exophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal, or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix



[1]These guidelines apply to anyone with a cervix including: women; pregnant people; transmen; non binary people; people who have undergone a subtotal hysterectomy; and people who have been vaccinated with the HPV vaccine
[2]Any visible cervical abnormalities or abnormal symptoms must be investigated. Consider referral to a specialist (e.g. colposcopist, gynaecologist, gynaeoncologist)
[3]Immunocompromised people may be at elevated risk and should receive annual screening
*Ontario Health (Cancer Care Ontario) is aware that the Screening Activity Report is not yet aligned with this guidance and will be updated with HPV implementation. Criteria for preventive care bonuses may not be updated during the interim period of changeover to HPV testing. Criteria for preventive care bonuses will be updated when HPV testing is implemented in screening
[b]HPV testing is not currently funded by the Ministry of Health. Primary care providers can consider HPV testing for those with ASCUS results on a patient pay basis or where available (i.e. in some hospital settings) for people ages 30 and older
[c]Repeat cytology or colposcopy are acceptable management options after the first LSIL result. Low grade abnormalities often regress on their own and may be best managed in surveillance, however colposcopy may be considered

Figure 23. Decision making chart for Pap test (not applicable for adolescents)

Adapted from: Ontario Cervical Screening Program. June 2020. Cervical screening guidelines unique to each province

Diagnosis

- colposcopy is a clinical procedure that facilitates identification and biopsy of suspicious cells
- in colposcopy:
  - apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
  - ECC if entire lesion is not visible or no lesion visible
  - diagnostic excision (LEEP) if:
    - unsatisfactory colposcopy (poor visualization/access to transformation zone)
    - discrepancy between cytology, colposcopy, and histological findings
    - positive findings/glandular abnormalities in endocervical curettage
    - suspicious for adenocarcinoma *in situ* (consider cold-knife conization)
    - recurrence of lesion post-ablation or excision
    - inability to rule out invasive disease, i.e. large lesions (lesions extending into endocervical canal, extending widely on cervix, or onto vaginal epithelium)
- consider cold-knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- any imaging modality or pathological findings are permitted for FIGO clinical staging

Table 27. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2018)

Stage	Description
I	**Confined to cervix**
IA	Diagnosed only by microscopy
IA1	Stromal invasion not >3 mm deep
IA2	3 mm to <5 mm deep
IB	Measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to cervix
IB1	Stromal invasion ≥5 mm deep and <2 cm wide
IB2	Stromal invasion ≥5 mm deep and ≥2 cm and <4 cm wide
IB3	≥4 cm in width
II	**Beyond uterus but not to the pelvic wall or lower 1/3 of vagina**
IIA	Limited to upper 2/3 of vagina, no obvious parametrial involvement
IIA1	Clinically visible lesion <4 cm wide
IIA2	Clinically visible lesion ≥4 cm wide
IIB	Obvious parametrial involvement, but not up to pelvic wall
III	**Extends to pelvic wall, and/or involves lower 1/3 of vagina, and/or causes hydronephrosis or non-functioning kidney, and/or involves pelvic and/or para-aortic lymph nodes**
IIIA	Involves lower 1/3 vagina but no extension into pelvic wall
IIIB	Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent
IIIC1	Pelvic lymph nodes metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	**Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (bullous edema does not permit a case to be allotted to stage IV)**
IVA	Spread of the growth to adjacent organs (bladder or rectum)
IVB	Distant metastases

Treatment: Prevention and Management

Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

Table 28. Comparison of Two Vaccines against Human Papillomavirus (HPV)

	Gardasil®*	Cervarix®
Viral Strains Covered	6, 11, 16, 18, 31, 33, 45, 52, and 58	16, 18
Route of Administration	IM	IM
Schedule of Dosing	2 Dose: Second dose administered 6-12 mo after first dose 3 Dose: 0, 2, 6 mo	0, 1, 6 mo
Side Effects	Local: redness, pain, swelling General: headache, low grade fever, GI upset	Local: redness, pain, swelling General: headache, low grade fever, GI upset
Approved Age	Females ages 9-45, males ages 9-45	Females ages 9-45
Contraindications	Pregnancy and breastfeeding (limited data)	

*Gardasil-9 also covers types 31, 33, 45, 52, and 58; also used to prevent genital warts

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. LSIL, HSIL, or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy

Cervical Cancer Prognosis 5 yr Survival	
Stage 0	99%
Stage I	75%
Stage II	55%
Stage III	30%
Stage IV	7%
Overall	50-60%

Final Efficacy, Immunogenicity, and Safety Analyses of a Nine-Valent Human Papillomavirus Vaccine in Women Aged 16-26 Years: A Randomised, Double-Blind Trial
Lancet 2017;390:2143-2159
Purpose: A nine-valent HPV vaccine (9vHPV) was developed which covers additional strains of HPV compared to the quadrivalent vaccine (qHPV). This study reported the efficacy of the 9vHPV vaccine.
Methods: A randomized double-blind efficacy trial comparing the nine-valent HPV vaccine (9vHPV) to the quadrivalent HPV vaccine (qHPV) in 14215 women. The primary outcomes were incidence of high-grade cervical, vulvar, and vaginal diseases related to HPV-31, 33, 45, 52, and 58 and non-inferiority of anti-HPV 6, 11, 16, and 18 mean titres.
Results: The incidence of high-grade cervical, vulvar, and vaginal disease was 0.5 cases per 10000 person-yr for the 9vHPV group compared to 19 cases per 10000 person-yr for the qHPV group. HPV 6, 11, 16, and 18 titres were non-inferior in the 9vHPV group compared to the qHPV group. There were no clinically meaningful differences in severe adverse effects between groups.
Conclusions: The 9vHPV vaccine is effective at preventing infection, cytological abnormalities, and high-grade lesions and may offer broader protection against HPV and cervical cancer compared to the qHPV vaccine.

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most patients will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease

Abnormal Pap Tests in Pregnancy

- incidence: 1 in 2200
- Pap test at initial prenatal visit if overdue for routine Pap test
  - if abnormal Pap or suspicious lesion, refer to colposcopy
  - if diagnostic conization required, should be deferred until T2 to minimize risk of pregnancy loss
  - if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
  - if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
    - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
    - recommendations in T2/T3: delay of therapy until viable fetus and C-section for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Table 29. Management of Abnormal Cervical Histology and Cervical Cancer

Histology Result from Colposcopy	Management
Normal	If histology results normal and cytology > LSIL, then repeat colposcopy in 6 mo
LSIL	**Women <25 yr** If cytology is LSIL, ASCUS, or normal, then annual Paps by primary care provider x 3 yr, followed by return to normal screening If cytology is HSIL, then consider pathology review, and/or reassessment every 6-12 mo in colposcopy **Women ≥ 25 yr** If HPV -: routine Pap screening every 3 yr If HPV +: follow-up colposcopy with cytology and HPV test (if 30 yr or older) in 1 yr
HSIL CIN II/CIN III	**Women ≥25 yr** Excisional procedures (e.g. cold knife, LEEP) or laser preferred Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage **Women <25 yr** Colposcopy every 6 mo for 2 yr or treatment may be acceptable based on patient preference
AIS	Repeat colposcopy + treatment (e.g. LEEP, cold-knife cone) ± endocervical curettage
Stage IA1 (no LVSI)	LEEP if future fertility desired (and lesion ≤2 cm) Simple hysterectomy if future fertility is not desired
Stage IA2, IB1, IB2	Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes or pelvic lymph node dissection) If high chance of adjuvant radiation then consider primary chemoradiation as more morbidity occurs from double-modality treatment (surgery and radiation) Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy Advantage is that ovaries can be spared if premenopausal, better sexual functioning For fertility preservation (if tumour <2 cm), may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease Chemoradiation therapy if adverse high-risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins or adverse cervical factors (2 or more): deep stromal invasion, size >4 cm, LVSI
Stages IB3 (>4 cm), II, III, IV	Primary chemoradiation therapy CT to assess extent of disease: evaluate pelvic and para-aortic nodes For positive nodes on PET: primary chemoradiation with extended field RT Hysterectomy generally not suggested following primary treatment with curative intent

Fallopian Tube

- least common site for carcinoma of the female reproductive system (0.3%)
- usually serous epithelial carcinoma
- new evidence shows that some serous ovarian cancers originate in the fallopian tube
- more common in fifth and sixth decade

Clinical Features

- classic triad present in minority of cases, but very specific
  - watery discharge (most specific): "hydrops tubae profluens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain

- most patients present with a pelvic mass (see *Pelvic Mass, GY42* and *Ovary, GY44* for guidelines regarding diagnosis/investigation)

Treatment
- same as for malignant epithelial ovarian tumours, see *Table 25, GY45*
- salpingectomy (removal of fallopian tubes to prevent ovarian cancer)

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is often necessary to make diagnosis and/or rule out malignancy:
  1. Lichen sclerosus
     - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
     - pruritus, dyspareunia, burning, bleeding, ulceration, excoriations
     - 'figure of 8' distribution
     - most common in postmenopausal patients but can occur at any age
     - patients should be monitored for malignancy, due to increased risk of SCC
     - treatment: high-potency topical steroid ointment (clobetasol), likely long-term treatment necessary
  2. Lichen simplex chronicus
     - surface of labia majora is thickened and hyperkeratotic, leather-like in appearance
     - most common symptoms: pruritus and burning, often at night
     - typically occurs in postmenopausal patients
     - treatment: medium-potency steroid ointment based on symptom severity + nighttime antihistamines
  3. Lichen planus
     - autoimmune disorder where T cells attack basal keratinocytes
     - peak incidence at age 30-60
     - 3 variants including erosive, papulosquamous, and hypertrophic
     - can extend into vaginal canal and cause loss of structure (desquamative vaginitis)
     - can have oral lichen planus in oral cavity
     - treatment: ultrapotent steroid ointment BID until plaques resolve, vaginal suppositories, or immunosuppressive therapies (e.g. cyclosporine) are all accepted



Any suspicious lesion of the vulva should be biopsied

Tumours
- papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%), usual or classical vulvar intraepithelial neoplasia (VIN)
    - more likely in younger patients
    - 90% of VIN contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy, differentiated VIN
    - usually postmenopausal patients
    - related to lichen sclerosis

Risk Factors
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
- progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)
- history of cervical cancer
- cigarette smoking
- immunodeficiency
- vulvar lichen sclerosus

Clinical Features
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus, or white, red, or skin coloured papules, nodules, or plaques most common
- less common: ulcer, bleeding, discharge, pain, and dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal, then spreading to pelvic nodes)
  - hematogenous

Investigations
- ± vulvar biopsy
- always biopsy any suspicious lesion
  - do not remove entire lesion during biopsy (allows for site identification through sentinel LN injection if malignant)

Prognosis
- depends on stage: particularly nodal involvement (single most important predictor followed by tumour size)
  - lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

Treatment
- FIGO Stage I (tumour confined to vulva; no extension to adjacent perineal structures): radical local excision
- FIGO Stage II (tumour of any size with extension to adjacent perineal structures, no nodal metastases): modified radical vulvectomy
- FIGO stage III-IV (extension to any of: proximal 2/3 of urethra, proximal 2/3 of the vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or large/distant nodal metastases): sentinel lymph node biopsy followed by surgical resection of residual primary and adjuvant chemotherapy or radiation

Vagina

BENIGN VAGINAL LESIONS
- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS

Epidemiology
- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr

Risk Factors
- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations
- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are metastatic from one of these sites)
- staging

Clinical Features

Table 30. Clinical Features of Malignant Vaginal Lesions

Type	Clinical Features
Vaginal Intra-Epithelial Neoplasia (VAIN)	Grades: analogous to cervical dysplasia
Squamous Cell Carcinoma (SCC)	Most common site is upper 1/3 of posterior wall of vagina Asymptomatic Painless vaginal discharge (often foul-smelling) and bleeding Vaginal bleeding especially during/post-coitus Urinary and/or rectal symptom 2° to compression
Adenocarcinoma	Most are metastatic, usually from cervix, endometrium, ovary, or colon Most primaries are clear-cell adenocarcinomas Two types: non-DES and DES syndrome

Treatment

- Stage I
  - radiation therapy: for tumours >2 cm diameter or tumour involvement of the middle or lower vagina
  - surgical excision: radical hysterectomy, upper vaginectomy, and bilateral pelvic lymphadenectomy
- Stage II-IV: primary radiation with or without chemotherapy

Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast
- GTD = abnormal, can be benign or lead to the malignant form, called GTN

Epidemiology

- 1/1000 pregnancies
- marked geographic variation (as high as 1/125 in Taiwan)
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (GTD)

Complete Mole

- most common type of hydatidiform mole
- risk factors
  - geographic (most common in those of South East Asian background)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency not proven)
  - prior molar pregnancy



With development of HTN early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

Partial (or Incomplete) Mole

- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations

Table 31. Features of Complete and Incomplete Hydatidiform Moles

	Complete	Incomplete
Pathology	Diffuse trophoblastic hyperplasia	Focal trophoblastic hyperplasia
Presence of Fetus	None	Associated with fetal tissue
Ultrasound Features	"Snowstorm" appearance due to swelling of villi	Degeneration of placenta Multiple echogenic regions Focal intrauterine hemorrhage
Genetics	Diploid Chromosomes completely of paternal origin	Triploid 1 set of maternal chromosomes 2 sets of paternal chromosomes
Clinical Presentation	Vaginal bleeding Uterine size large for dates Hyperemesis gravidarum Preeclampsia Hyperthyroid	Similar to spontaneous, threatened, missed abortion Vaginal bleeding
Risk of Progression of Malignancy	15-20%	<4%

Investigations

- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- CXR (may show metastatic lesions)
- features of molar pregnancies at high-risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts >6 cm in diameter

Treatment
- for GTD: suction D&C (or rarely hysterectomy)
- Rhogam® if Rh-negative
- for GTN: single agent (i.e. methotrexate, actinomycin D) or multi-agent (i.e. EMACO, EMA-EP) chemotherapy based on WHO scoring system

Follow-up
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), and then one month after for incomplete hydatidiform mole or monthly for 6 mo if complete hydatidiform mole
- reliable contraception required to avoid pregnancy during entire follow-up period
- women who become pregnant during the follow-up period should be referred to gynecologic oncology and maternal-fetal medicine specialists
- increase or plateau of β-hCG indicates GTN: single or multi-agent chemotherapy based on WHO scoring system (see *Table 32*)

Table 32. WHO Prognostic Score for GTD (2011)

	Score			
Prognostic Factor	**0**	**1**	**2**	**4**
Maternal Age	<40	≥40		
Antecedent Pregnancy	Mole	Abortion	Term	
Interval (End of Antecedent Pregnancy to Chemotherapy in Months)	<4	4-6	7-13	>13
HCG IU/L	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Number of Metastases	0	1-4	5-8	>8
Site of Metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Largest Tumour Mass		3-5 cm	>5 cm	
Prior Chemotherapy			Single drug	Two drugs

A score of 6 or less is considered low-risk GTD. A score of 7 or more is considered high-risk GTD. A score of ≥ 13 is considered ultra high-risk GTD. The prognostic factor score is recorded after the FIGO score stage, separated by a colon

GTN (MALIGNANT GTD)

GTN Diagnosis
- β-hCG rise >10% compared with previous levels over 2 wk (e.g. 3 levels measured on days 1, 8, and 15) OR
- β-hCG plateau: <10% change/plateau compared with previous levels over 3 wk (e.g. 4 levels measured on days 1, 8, 15, and 22) OR
- histologic diagnosis of choriocarcinoma OR
- metastatic disease OR
- β-hCG level ≥20 000 mIU/mL >4 wk post-evacuation

Invasive Mole or Persistent GTN
- development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often presents with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, miscarriage, therapeutic abortion, ectopic pregnancy, or normal pregnancy

Placental-Site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

Classification of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% of patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma, which tends toward early vascular invasion and widespread dissemination

- if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
  - lungs (80%): cough, hemoptysis, CXR lesion(s)
  - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
  - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
  - liver (10%): elevated LFTs, U/S, or CT findings
  - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
- highly vascular tumour, which is more likely to bleed and result in anemia
- all have rising or plateau of β-hCG
- classification of metastatic GTN
  - divided into good prognosis and bad prognosis
  - features of bad prognosis
    - long duration (>4 mo from antecedent pregnancy)
    - high pre-treatment β-hCG titre: >100000 IU/24 h urine or >40000 IU/L of blood
    - brain or liver metastases
    - prior chemotherapy
    - metastatic disease following term pregnancy
  - good prognosis characterized by the absence of each of these features

Investigations (for Staging)

- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis only
- if CXR shows lung metastasis then CT abdomen/pelvis, MRI brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
- ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases



Lungs are the primary site for malignant GTN metastases; when pelvic exam and CXR are negative, metastases are uncommon

Table 33. FIGO Staging and Management of Malignant GTN

Stage	Findings	Management
I	Disease confined to uterine corpus	Single agent chemotherapy for low-risk disease (WHO score ≤6) 1st line: pulsed actinomycin D (Act-D) IV q2 wk Alternatives: methotrexate (MTX)-based regimen 20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high-risk (WHO score ≥7) or if resistant to single-agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour
II	Metastatic disease to genital structures	As above
III	Metastatic disease to lungs with or without genital tract involvement	As above
IV	Distant metastatic sites including brain, liver, kidney, GI tract	Ultra high-risk patients should have low-dose induction chemotherapy weekly for 1-3 wk, followed by multi-agent chemotherapy

Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period, recommended combined OCP
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 6-12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

Common Medications

Table 34. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
acyclovir (Zovirax®)	Antiviral; inhibits DNA synthesis and viral replication	**First Episode:** 400 mg PO TID x 7-10 d **Recurrence:** 400 mg PO TID x 5 d	Genital herpes	**S/E:** headache, GI upset **D/I:** zidovudine, probenecid
bromocriptine (Parlodel®)	Dopaminomimetic, agonist at D2 Receptor and antagonist at D1 Receptor; acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin	**Initial:** 1.25-2.5 mg PO once daily at night with food **Then:** increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response **Usual Range:** 1.5-15 mg once daily For IVF: **Initial:** 1.25 mg/d PO between days 4-6 of follicular phase **Then:** 2.5 mg/d until 3 d after onset menstruation	Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF	**S/E:** N/V, headache, postural hypotension, somnolence **C/I:** uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding **D/I:** domperidone, macrolides, octreotide
clomiphene citrate (Clomid®)	Increases output of pituitary gonadotropins to induce ovulation	50 mg once daily x 5 d Try 100 mg or 160 mg once daily If ineffective 3 courses: adequate trial	Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy	**S/E:** Common: hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare: ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects **C/I:** pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding
clotrimazole (Canesten®)	Antifungal; disrupts fungal cell membrane	**Tablet:** 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose **Cream** (1 or 2%): 1 applicator intravaginally QHS x 3-7 d **Topical:** apply BID x 7 d	Vulvovaginal candidiasis	**S/E:** vulvar/vaginal burning
combined oral contraceptive pill (OCP)	Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration		Contraception Disorders of menstruation	See Tables 7-10, *GY15* and Table 12, *GY19*
dienogest (Visanne®)	Synthetic progestin	2 mg PO	Pelvic pain associated with endometriosis	**S/E:** changes to menstrual pattern, VTE **C/I:** pregnancy, lactation, liver disease/ malignancy, VTE disorders, cardiovascular disease, hormone-dependent tumours, undiagnosed AUB
doxycycline	Tetracycline derivative; inhibit protein synthesis	100 mg PO BID x ≥7 d	Chlamydia, gonococcal infection, syphilis	**S/E:** GI upset, hepatotoxicity **C/I:** pregnancy, severe hepatic dysfunction **D/I:** warfarin, digoxin
elagolix (Orlissa®)	Synthetic GnRH antagonist; induces reversible hypoestrogenic state	150 mg PO daily or 400 mg PO BID	Endometriosis, emerging evidence for fibroids, adenomyosis	**S/E:** hot flushing, nausea, headache **C/I:** pregnancy, osteoporosis, undiagnosed vaginal bleeding, severe hepatic dysfunction **D/I:** Organic Anion Transport Protein (OATP) 1B1 inhibitors
fluconazole (Diflucan®)	Antifungal; disrupt fungal cell membrane	150 mg PO x 1 dose	Vulvovaginal candidiasis unresponsive to clotrimazole	**S/E:** headache, rash, N/V, abdominal pain, diarrhea **D/I:** terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin
intrauterine device (IUD) **copper IUD (Nova-T®)** **progesterone-releasing IUD (Mirena®, Kyleena®)**	Copper IUD: mild foreign body reaction in endometrium, which is toxic to sperm and alters sperm motility Progesterone-releasing IUD: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last 3 yr; up to 5 yr (Copper IUD, Mirena®, Kyleena®)	Contraception Disorders of menstruation	See Tables 7-10, *GY15* and Table 12, *GY19*
leuprolide (Lupron®)	Synthetic GnRH antagonist; induces reversible hypoestrogenic state	3.75 mg IM q1 mo or 11.25 mg IM q3 mo Usually ≤6 mo, check bone density if >6 mo Retreatment with Lupron® alone not recommended because of effects on bone density	Endometriosis Leiomyomata DUB Precocious puberty	**S/E:** hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset **C/I:** pregnancy, undiagnosed vaginal bleeding, breastfeeding

Table 34. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
menotropin (Pergonal®)	Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development	75-150 IU of FSH and LH IM once daily x 7-12 d, then 10000 IU HCG 1 d after last dose	Infertility	**S/E**: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding
metronidazole (Flagyl®)	Bactericidal; forms toxic metabolites which damage bacterial DNA	2 g PO x 1 dose or 500 mg PO BID x 7 d	Bacterial vaginosis, trichomonas vaginitis	**S/E**: headache, dizziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V) **C/I**: pregnancy (1st trimester) **D/I**: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine
nexplanon (etonogestrel implant)	Releases progestin which causes decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last up to 3 yr	Contraception Disorders of menstruation	See Tables 7-10, *GY15* and Table 12, *GY19*
oxybutynin (Ditropan®)	Anticholinergic; relaxes bladder smooth muscle, inhibits involuntary detrusor contraction	5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d	Overactive bladder (urge incontinence)	**S/E**: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache **C/I**: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function
tolterodine (Detrol®)	Anticholinergic	1-2 mg PO BID	Overactive bladder (urge incontinence)	**S/E**: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain **C/I**: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function
tranexamic acid (Cyklokapron®)	Anti-fibrinolytic; reversibly inhibits plasminogen activation	1-1.5 g TID-QID for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk	Menorrhagia	**S/E**: N/V, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain **C/I**: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yr
ulipristal acetate (Fibristal®) -withdrawn from market in 2020 urofollitropin (Metrodin®)	Selective progesterone receptor modulator (SPRM)	5 mg PO once daily for max 3 mo; first tablet taken anytime during first 7 d of menstruation	Leiomyoma (preoperative)	**S/E**: headache, hot flushes, constipation, vertigo, endometrial thickening **C/I**: pregnancy, undiagnosed vaginal bleeding, any gynecological cancer
urofollitropin (Metrodin®)	FSH	75 IU/d SC x 7-12 d	Ovulation induction in PCOS	**S/E**: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding

Landmark Gynecology Trials

Trial Name	Reference	Clinical Trial Details
Endometrial Cancer		
PORTEC-3	LANCET 2019; 20(9):1273-1285	**Title:** Adjuvant Chemoradiotherapy versus Radiotherapy Alone in Women with High-Risk Endometrial Cancer (PORTEC-3): Patterns of Recurrence and Post-Hoc Survival Analysis of a Randomised Phase 3 Trial **Purpose:** To investigate the benefit of combined adjuvant chemotherapy and radiotherapy vs. pelvic radiotherapy alone for women with high-risk endometrial cancer. **Methods:** Women with high-risk endometrial cancer were randomly assigned to receive radiotherapy alone or chemoradiotherapy. The co-primary endpoints were overall survival and failure-free survival. Secondary endpoints included vaginal, pelvic, and distance recurrence. **Results:** At a median of 72.6 mo, 5 yr overall survival was 81.4% with chemoradiotherapy vs. 76.1% with radiotherapy, and 5 yr failure-free survival was 76.5% with chemoradiotherapy vs. 69.1% with radiotherapy. Distant metastases occurred in 78/330 women in the chemoradiotherapy group vs. 98/330 in the radiotherapy group. **Conclusions:** For women with stage 3 or serous endometrial cancers, or both, chemoradiotherapy should be recommended over radiotherapy alone.
Cervical Cancer		
LACC	NEJM 2018; 379:1895-1904	**Title:** Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer **Purpose:** To investigate survival outcomes after laparoscopic or robot-assisted radical hysterectomy (minimally invasive surgery) vs. open abdominal radical hysterectomy (open surgery). **Methods:** Patients with stage A1, IA2, or IB1 cervical cancer and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, were randomly assigned to undergo minimally invasive surgery or open surgery. **Results:** The rate of disease-free survival at 4.5 yr was 86% with minimally invasive surgery and 96.5% with open surgery, a difference of -10.6% (95% confidence interval [CI], −16.4 to −4.7). Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3 yr rate, 91.2% vs. 97.1%) and a lower rate of overall survival (3 yr rate, 93.8% vs. 99.0%). **Conclusions:** Among women with early-stage cervical cancer, minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy.
Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix	J Clin Oncology 2000; 18(8):1606-1613	**Title:** Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix **Purpose:** Determine whether adjuvant cisplatin-based chemotherapy (CT) in addition to pelvic radiation therapy (RT) has benefit for early stage, high risk cervical cancer. **Methods:** In this multi-center trial, patients with stage IA2, IB, and IIA cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy, with high-risk prognostic factors on surgical sample were randomized to CT+RT (n=127) and RT (n=116). Primary outcomes were progression free and overall survival. **Results:** 4-year progression free survival was 80% in the CT-RT group and 63% in the CT group. CT-RT improved both progression-free survival (HR, 2.01; p = 0.003) and overall survival (HR, 1.96; p = 0.007). **Conclusions:** CT+RT adjuvant therapy following radical surgery improved survival for high-risk, early-stage cervical cancer.
Ovarian Cancer		
LION	NEJM 2019; 380:822-832	**Title:** A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms **Purpose:** Clarify role for pelvic and para-aortic lymphadenectomy in surgical treatment of patients with advanced ovarian cancer. **Methods:** In this international, multi-center trial, patients with advanced epithelial ovarian cancer who underwent macroscopically complete resection and had negative lymph nodes before and during surgery, were randomized to lymphadenectomy (n=323) or no lymphadenectomy (n=324). The primary outcome was overall survival. **Results:** Median overall survival was 65.5 mo in the lymphadenectomy and 69.2 mo in the no lymphadenectomy (HR, 1.06; 95% CI, 0.83-1.34; p = 0.65). Incidence of repeat laparotomy was higher in the lymphadenectomy at 12.4% compared to 6.5% in the no lymphadenectomy group (p = 0.01). **Conclusions:** Pelvic and para-aortic lymphadenectomy in surgically treated advanced ovarian cancer was not associated with longer overall survival and increased risk of complications.

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H Hematology

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Acronyms

Ab	antibody
AFib	atrial fibrillation
AFLP	acute fatty liver of pregnancy
aHUS	atypical hemolytic uremic syndrome
AIHA	autoimmune hemolytic anemia
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APC	activated protein C
APL	acute promyelocytic leukemia
APLA	antiphospholipid antibodies
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ATIII	antithrombin III
ATRA	all-trans retinoic acid
BM	bone marrow
CALR	calreticulin
CAR	chimeric antigen receptor
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CRP	C-reactive protein
DAT	direct antiglobulin test
DDAVP®	desmopressin
DIC	disseminated intravascular coagulation
DLBCL	diffuse large B-cell lymphoma
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EDTA	ethylenediaminetetraacetic acid
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESR	erythrocyte sedimentation rate
ET	essential thrombocythemia
FDP	fibrin degradation products
FNA	fine needle aspiration
FP	frozen plasma
G-CSF	granulocyte-colony stimulating factor
GSH	reduced glutathione
GU	genitourinary
GVHD	graft versus host disease
HA	hemolytic anemia
Hb	hemoglobin
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIT	heparin-induced thrombocytopenia
HL	Hodgkin lymphoma
HMWK	high molecular weight kininogen
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
IMF	idiopathic myelofibrosis
IMID	immunomodulatory drugs
INR	international normalized ratio
IPC	intermittent pneumatic compression
IPSS	international prognostic scoring system
ITP	immune thrombocytopenia
JAK2	Janus kinase 2
LAD	lymphadenopathy
LMWH	low molecular weight heparin
MAHA/TMA	microangiopathic hemolytic anemia/thrombotic microangiopathy
MCH	mean corpuscular Hb
MCHC	mean corpuscular Hb concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MF	myelofibrosis
MGUS	monoclonal gammopathy of unknown significance
MM	multiple myeloma
MPN	myeloproliferative neoplasm
MPV	mean platelet volume
MUGA	multi-gated acquisition
NHL	non-Hodgkin lymphoma
OCP	oral contraceptive pill
PCC	prothrombin complex concentrates
PE	pulmonary embolism
PFS	progression-free survival
Ph	Philadelphia chromosome
PI	proteasome inhibitors
PK	prekallikrein
PMN	polymorphonuclear neutrophil
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PTT	partial thromboplastin time
PUD	peptic ulcer disease
PV	polycythemia vera
RCMD	refractory cytopenia with multilineage dysplasia
RCMD-RS	refractory cytopenia with multilineage dysplasia and ringed sideroblasts
RDW	RBC distribution width
SCD	sickle cell disease
SCT	stem cell transplantation
SPEP	serum protein electrophoresis
sTfR	soluble transferrin receptor
TCL	T-cell lymphoma
TIBC	total iron binding capacity
TKI	tyrosine kinase inhibitor
T-LGL	T-cell large granular lymphocyte
TLS	tumour lysis syndrome
tPA	tissue plasminogen activator
TPO	thrombopoietin
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
UFH	unfractionated heparin
UPEP	urine protein electrophoresis
VTE	venous thromboembolism
VWD	von Willebrand disease
VWF	von Willebrand factor
WHO	World Health Organization
XRT	radiation therapy

Basics of Hematology

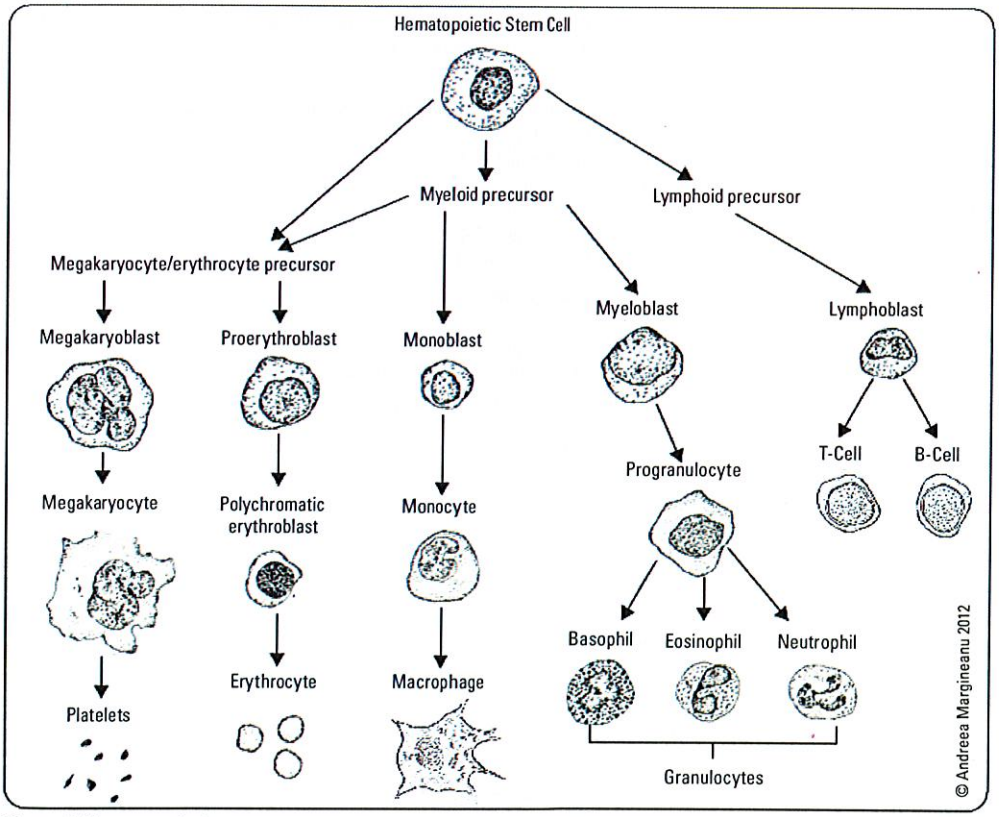


Figure 1. Hematopoiesis



Erythrocyte: carries oxygen from lungs to peripheral tissues
Reticulocyte: immature erythrocyte
Hb: protein contained in erythrocytes which binds oxygen
Neutrophil: granulocyte integral in innate immunity; main cell in acute inflammation
Eosinophil: granulocyte involved in response to parasites (especially helminths) and allergic response
Basophil: granulocyte mainly involved in allergy and parasitic infection
Lymphocyte: integral cell in adaptive immunity
Monocyte: involved in innate immunity; can differentiate into macrophage or dendritic cell
Platelet: mediator of primary hemostasis
Plasma: acellular, fluid component of blood containing water and proteins (including coagulation factors and immunoglobulins)
Serum: equivalent to plasma minus coagulation factors

- over 10^{11} blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies, and cranium
- lifespan of mature cells in blood
  - erythrocytes (90-120 d), neutrophils (~1 d), platelets (7-10 d), lymphocytes (varies – memory cells persist for years)

- role of lymphoid organs
  - spleen - part of reticuloendothelial system: sequesters aged RBCs, removes opsonized cells, and site of Ab production
  - thymus - involutes with age: site of T-cell maturation
  - lymph nodes: sites of B- and T-cell activation (adaptive immune response)

Complete Blood Count

Table 1. Common Terms Found in the CBC

Test	Definition	Normal Values*
RBC Count	Number of RBCs per volume of blood	3.5-5.0 x 10^{12}/L (female) 4.0-5.5 x 10^{12}/L (male)
Hb	Amount of Hb in the blood	115-155 g/L (female) 125-170 g/L (male)
Hct	Percentage of a given volume of whole blood occupied by packed RBCs	38-50%
MCV	Average RBC size	80-100 fL
MCH	Average amount of Hb per RBCs	25-34 pg (female) 27-34 pg (male)
MCHC	Average concentration of Hb inside RBCs	315-355 g/L
RDW	Percentage of variance in RBC size	11.5-15.5%
Reticulocyte Count	Number of reticulocytes per volume of blood	23-90 x 10^9/L (0.5-1.5%)
ESR	Rate at which RBCs separate from the serum, becoming sediment in the bottom of the test tube	<20 mm/h (female) <10 mm/h (male)
WBC Count	Number of WBCs per volume of blood	3.5-10.5 x 10^9/L
WBC Differential	Segmented neutrophils Band neutrophils Basophils Eosinophils Lymphocytes Monocytes	2-7 x 10v/L <0.7 x 10^9/L <0.10 x 10^9/L <0.5 x 10^9/L 0.8-3.3 x 10^9/L (female) 0.8-3.5 x 10^9/L (male)L 0.1-1.0 x 10^9/L
Platelet Count	Number of platelets per volume of blood	130-380 x 10^9/L
Mean Platelet Volume (MPV)	Measurement of platelet size	9.0-14.0 fL

*All values apply to adults. Reference standards do not apply to all ethnic groups.



To estimate Hb based on the Hct, multiply by 3

Approach to Interpreting a CBC

1. consider values in the context of an individual's baseline:
   - up to 5% of population without disease may have values outside "normal" range
   - an individual may display a clinically significant change from their baseline without violating "normal" reference range
2. is one cell line affected or are several?
   - if all lines are low: pancytopenia (see *Pancytopenia, H8*)
   - if RBCs and platelets are low: consider a MAHA/TMA (see *Microangiopathic Hemolytic Anemia/ Thrombotic Microangiopathy, H23*) or an autoimmune process (Evan's Syndrome)
   - if single cell line affected: see *Common Presenting Problems, H6*



Clinical Use of RDW
To distinguish the etiologies of microcytosis:
Iron deficiency: increased RDW (anisocytosis) as cells are of varying sizes in iron deficiency
β-thalassemia minor: normal RDW (also expect a high RBC count) as cells are of similar size because the red cell abnormality is not progressive

Blood Film Interpretation

RED BLOOD CELLS

Size

- microcytic (MCV <80 fL), normocytic (MCV = 80-100 fL), macrocytic (MCV >100 fL)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, HAs, MF, blood transfusion, and MDS

Colour

- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic disease, and sideroblastic anemia
- polychromasia: suggests increased reticulocytes (pinkish-blue cells)
  - increased RBC production by BM

Shape

- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, hemoglobinopathies, MF, severe B_{12} deficiency, MDS, and burns

Table 2. Common Erythrocyte Shapes

Shape	Definition	Associated Conditions
Discocyte 	Biconcave disc	Normal RBC
Spherocyte 	Spheroidal RBC (due to membrane defect or loss of membrane) Loss of central pallor	Hereditary spherocytosis, immune hemolytic anemia
Elliptocyte/Ovalocyte 	Oval-shaped, elongated RBCs • Elliptocytes: the RBC long axis is ≥2x the length of the short axis • Ovalocytes: the RBC long axis is <2x the length of the short axis	Hereditary elliptocytosis, megaloblastic anemia, MF, iron-deficiency anemia (pencil forms), and MDS
Schistocyte (helmet cell, fragment) 	Fragmented cells (due to traumatic disruption of membrane)	MAHA/TMA (HUS, aHUS, TTP, DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, burns, and prosthetic heart valves
Sickle Cell 	Sickle-shaped RBC (due to polymerization of HbS)	Sickle cell disorders: HbSC, HbSS
Codocyte (target cell) 	"Bull's eye" (due to a surface that is disproportionately large compared to their volume)	Liver disease, HbSC, thalassemia, iron deficiency anemia, and asplenia
Dacrocyte (teardrop cell) 	Single pointed end, looks like a teardrop	MF, MDS, β-thalassemia, megaloblastic anemia, and BM infiltration
Acanthocyte (spur cell) 	Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipid or protein composition)	Severe liver disease (spur cell anemia), starvation/anorexia, and post-splenectomy
Echinocyte (burr cell) 	RBC with numerous regularly spaced, small, spiny projections	Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, and storage artifact
Rouleaux Formation 	Aggregates of RBCs resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)	Pregnancy is most common cause (due to physiological increase in fibrinogen), inflammatory conditions (due to polyclonal immunoglobulins), plasma cell dyscrasias (due to monoclonal paraproteinemia, e.g. MM, macroglobulinemia), and storage artifact

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

Table 3. RBC Inclusions

Inclusions	Definition	Associated Conditions
Nucleus 	Present in erythroblasts (immature RBCs)	Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, and MPNs (MF)
Heinz Bodies 	Denatured and precipitated Hb	G6PD deficiency (post-exposure to oxidant), thalassemia, and unstable Hb
Howell-Jolly Bodies 	Small spherical nuclear remnant, typically in periphery and ordinarily removed by the spleen	Post-splenectomy, hyposplenism (SCD), neonates, and megaloblastic anemia
Basophilic Stippling 	Deep blue granulations indicating ribosome aggregation	Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, MDS, and hereditary (pyrimidine 5'-nucleotidase deficiency)
Sideroblasts 	Late erythrocytes in BM with Fe-containing granules in the cytoplasm	Hereditary, idiopathic, drugs, ethanol, hypothyroidism (see *Sideroblastic Anemia, H17*), MDS, and toxins (Pb)

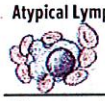
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

WHITE BLOOD CELLS

lymphocytes
- comprise 30-40% of WBCs; great variation in "normal" lymphocyte morphology
- the major classes of lymphocytes include: T cells, B cells, and natural killer (NK) cells
- nucleus occupies ~90% of cytoplasm

- neutrophils
  - normally, only mature neutrophils (with 3-4 lobed nuclei) and band neutrophils (immediate precursor with horseshoe-shaped nuclei) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B_{12} or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, MPNs (CML, MF), and G-CSF (growth factor that stimulates neutrophil production) use
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, and G-CSF use

Table 4. Abnormal WBC on Film

Appearance	Definition	Associated Conditions
Smudge Cell 	Lymphocytes damaged during blood film preparation indicating cell fragility	CLL and other lymphoproliferative disorders
Auer Rod 	Cytoplasmic inclusions that form long needles in the cytoplasm of myeloblasts	Pathognomonic for AML
Atypical Lymphocyte 	Pale blue cytoplasm with pink granules. Cytoplasm is indented by RBC edges	Viruses (particularly EBV) and T-LGL leukemia

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012 and Danielle Sayeau 2017

PLATELETS

- small, purple, anuclear cell fragments



Left Shift

Refers to an increase in granulocyte precursors in the peripheral blood film (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML)

The presence of predominantly blasts in the peripheral smear without further differentiated precursor cells or mature neutrophils, suggests clonal cell disorder (MDS, acute leukemias)

If >20% of the total WBC differential consists of blasts, this is acute leukemia and is a medical emergency

Bone Marrow Aspiration and Biopsy

- sites: posterior iliac crest/spine, sternum (aspiration only)
- analyses: most often done together
  - aspiration: takes a fluid marrow sample for cellular morphology (includes iron stain), flow cytometry, cytogenetics, molecular studies, and microbiology (C&S, acid-fast bacilli smear and culture, and PCR)
    - note: differential diagnosis for a "dry tap": MF, hairy cell leukemia, BM infiltration
  - biopsy: takes a sample of intact BM to assess histology (architecture) and immunohistochemistry
  - only aspirates, not biopsies, can be obtained from the sternal site

Indications

- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, and solid tumours
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores (gold standard, but rarely done)
- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of unknown origin, suspected mycobacterial, fungal, and parasitic infections, or granulomatous disease
- evaluate unexplained splenomegaly
- confirm normal BM in potential allogeneic hematopoietic cell donor

Important Considerations

- do not perform a BM biopsy if there is evidence of infection over the targeted skin site
- risk of procedure: 1/100 chance of bleeding, very rare infection risk

Common Presenting Problems

Anemia

Definition

- a decrease in RBC mass that can be detected by Hb concentration, Hct, and RBC count
  - adult males: Hb <130 g/L or Hct <38%
  - adult females: Hb <120 g/L or Hct <37% (changes with pregnancy and trimester)

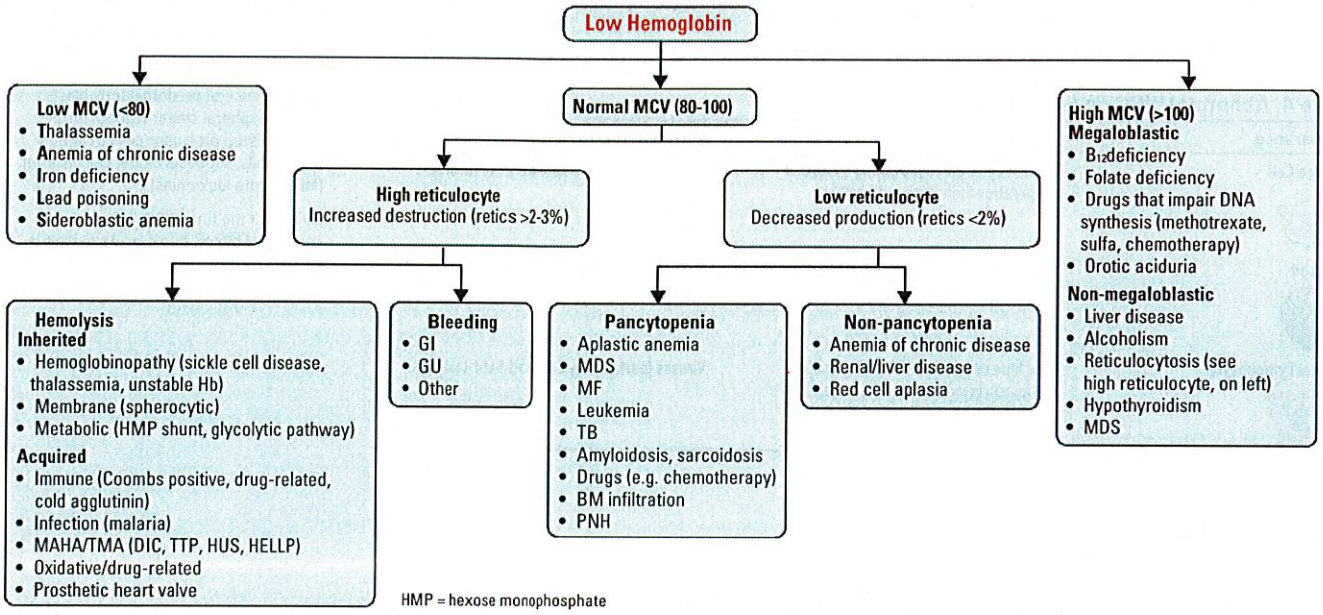


Figure 2. Approach to anemia – classification by MCV

Clinical Features

- history
  - symptoms of anemia: fatigue, headache, light-headedness, malaise, weakness, decreased exercise tolerance, dyspnea, palpitations, dizziness, tinnitus, and syncope
  - acute vs. chronic, bleeding, systemic illness, travel, medications, diet (Fe, B12 sources), alcohol, and family history
  - symptoms of hemolysis: jaundice, icterus
  - menstrual history: menorrhagia, menometrorrhagia
  - rule out pancytopenia (recurrent infection, mucosal bleeding, and easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes and conjunctiva at Hb <90 g/L, ocular bruits at Hb <55 g/L, angular cheilitis, and jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, and signs of CHF
  - dermatologic: ecchymosis, petechiae, pallor in palmar skin creases at Hb <75 g/L, jaundice (if due to hemolysis), nail changes (spooning), and glossitis
  - splenomegaly, lymphadenopathy

Reticulocytes

- Reticulocytes are immature erythrocytes and are markers of erythrocyte production (↑ colour, ↓ central pallor, ↑ size)
- The reticulocyte count should always be interpreted in the context of Hb concentration
- The reticulocyte count should normally increase in response to a decrease in RBC
- With blood loss, reticulocytes should increase 2-3x initially and then 5-7x over the next week
- A normal reticulocyte count in anemia should be interpreted as a sign of decreased production, and may result from BM infiltration, nutritional deficiency, or other causes
- Anemia with reticulocytosis suggests appropriate BM response

Investigations

- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential, reticulocyte count, and blood film
- rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see *Microcytic Anemia, H14, Normocytic Anemia, H17, Hemolytic Anemia, H18,* and *Macrocytic Anemia, H25*)
- N.B. may have a mixed picture with multiple concomitant nutritional deficiencies

Treatment

- treat underlying cause (see *Microcytic Anemia, H14, Normocytic Anemia, H17, Hemolytic Anemia, H18,* and *Macrocytic Anemia, H25*)

Erythrocytosis

Definition

- an increase in Hb and/or Hct: Hb >165 g/L or Hct >49% (males); Hb >160 g/L or Hct >48% (females)

Etiology

- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, and "stress" (Gaisböck's syndrome)
- absolute erythrocytosis

Table 5. Etiology of Erythrocytosis

Primary	Secondary	Inappropriate Production of Erythropoietin
PV (see *Polycythemia Vera, H43*)	Physiologic (poor tissue oxygenation/hypoxia)	Tumours
	Carbon monoxide poisoning	Hepatocellular carcinoma
	Heavy smoking	Renal cell carcinoma
	High altitude	Cerebellar hemangioblastoma
	Pulmonary Disease	Pheochromocytoma
	COPD	Uterine leiomyoma
	Sleep apnea	Ovarian tumour
	Pulmonary hypertension	Other
	Cardiovascular Disease	Polycystic kidney disease
	R to L shunt (Eisenmenger syndrome)	Renal artery stenosis
	Hemoglobinopathy	Post-kidney transplant
	High O_2 affinity Hb	Hydronephrosis
	Methemoglobinemia	Androgens
		Exogenous EPO
		SGLT2 inhibitors

Clinical Features

- secondary to high red cell mass and hyperviscosity
  - headache, dyspnea, dizziness, tinnitus, visual disturbances, hypertensive symptoms, and paresthesia
  - symptoms of angina, CHF, and aquagenic pruritus (only in MPNs)
- thrombosis (venous or arterial) or bleeding (seen with acquired VWD or acquired platelet dysfunction in MPNs)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

Investigations

- serum EPO: differentiates primary (low/normal) from other etiologies (elevated)
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis; if iron deficient with reticulocytosis, suggestive of PV)

Treatment

- if primary: see *Polycythemia Vera, H43*
- if secondary: treat underlying cause
  - O_2 for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours, counselling and education (e.g. smoking cessation, work environment), use the lowest dose possible if on androgen therapy
  - often cardiologists will be hesitant to treat high Hct in cyanotic patients

Thrombocytopenia

Definition

- platelet count <150 x 10^9/L

Clinical Features

- history: mucocutaneous bleeding (easy bruising, gingival bleeding), epistaxis, perioperative bleeding (including dental procedures), heavy menstrual bleeding, peripartum bleeding, and GI bleeding
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura, and wet purpura
- see *Disorders of Primary Hemostasis, H28* for complications

Investigations

- CBC and differential
- blood film
  - rule out pseudothrombocytopenia (platelet clumping or platelet satellitism)
  - decreased production: other cell line abnormalities, blasts (suggesting myeloid malignancy), hypersegmented PMNs (suggesting megaloblastic anemia), and leukoerythroblastic changes (suggesting BM infiltration or fibrosis)
  - increased destruction: large platelets (often seen in ITP), schistocytes (seen in MAHA/TMA)
- workup for nutritional deficiencies: B_{12}, RBC, folate
- PT/INR, aPTT, and fibrinogen if DIC suspected
- LFTs if findings of liver disease are present
- *H. pylori*, HIV, and HCV serology
- abdominal U/S to look for splenomegaly



Rule-of-thumb: a deficit in all cell lines suggests decreased production, sequestration, or hemodilution. A deficit in platelets and RBCs suggests non-immune destruction or Evan's syndrome. An isolated thrombocytopenia suggests an immune-mediated process. In hospitalized patients, drugs and infection account for the majority of cases of thrombocytopenia

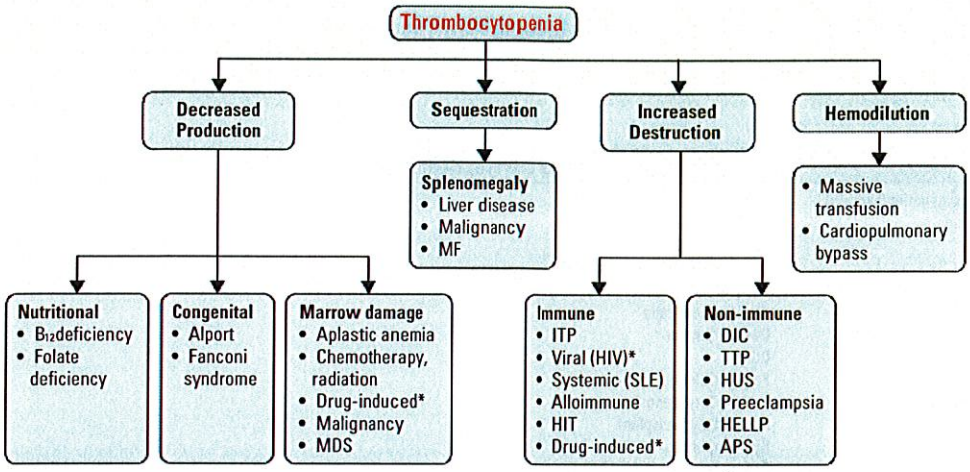


Rule out pseudothrombocytopenia: platelet clumping secondary to EDTA Abs present in serum. This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA)



Wet vs. Dry Purpura
Wet purpura: hemorrhage of mucous membranes
Dry purpura: bruising or petechiae on skin surface

Treatments
- life-threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see *Immune Thrombocytopenia, H28*



*In hospitalized patients most common causes of thrombocytopenia are drugs and infection

Figure 3. Approach to thrombocytopenia
Adapted from: Cecil Essentials of Medicine

References
APS: see *Hematology, H36*
Aplastic Anemia: see *Hematology, H17*
B12/Folate Deficiency: see *Hematology, H25, H26*
DIC: see *Hematology, H34*
HIT: see *Hematology, H30*
HIV: see Infectious Diseases, ID27
ITP: see *Hematology, H28*
Myelodysplasia: see *Hematology, H41*
Preeclampsia: see Obstetrics, OB26
SLE: see Rheumatology, RH11

Thrombocytosis

Definition
- platelet count >450 x 10^9/L
- primary thrombocytosis (uncommon): due to MPNs (e.g. CML, PV, primary MF, and ET; rarely associated with MDS)
- reactive/secondary thrombocytosis (common): acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasm, ischemic injury, and hyposplenia/asplenia)

Clinical Features
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, and constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, and aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly is a common finding among patients with MPNs

Investigations
- CBC and differential, peripheral blood film, serum ferritin
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, BM biopsy may be required to rule out MPN/MDS

Treatment
- primary: Aspirin™ ± cytoreductive agents (e.g. hydroxyurea, anagrelide, interferon-α)
- secondary: treat underlying cause

Pancytopenia

Definition
- a decrease in all hematopoietic cell lines below normal reference ranges

Clinical Features
- anemia: fatigue (see *Anemia, H6*)
- leukopenia: recurrent infections (see *Neutropenia, H9*)
- thrombocytopenia: mucocutaneous bleeding (see *Thrombocytopenia, H7*)

Investigations
- CBC and differential, peripheral blood film, serum ferritin, reticulocyte count, PT, PTT, blood type and screen, complete metabolic panel, B12, folate
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- workup as per *Figure 4, H9* and presenting symptoms/physical exam
- if reactive process has been ruled out, BM biopsy may be required

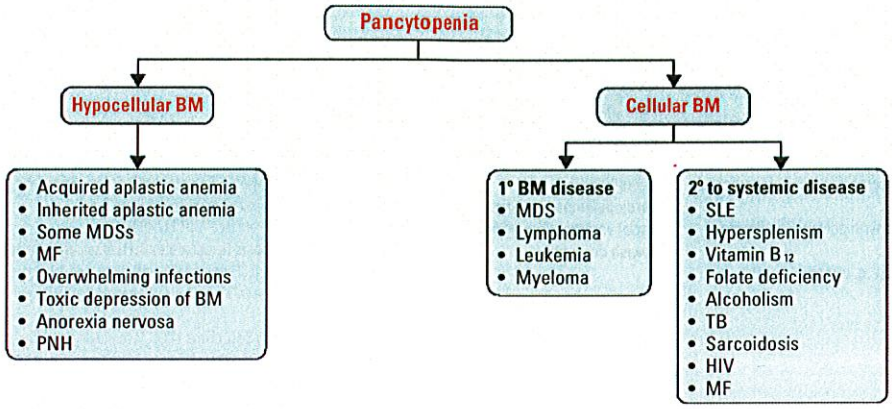


Figure 4. Approach to pancytopenia

Neutrophilia

Definition
- variable definition, but generally an ANC >7.7 x 10^9/L (WHO definition)

Etiology
- primary neutrophilia
  - CML, chronic neutrophilic leukemia
  - other MPNs: PV, ET, MF
  - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients
  - leukocyte adhesion deficiency
- secondary neutrophilia
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - obesity
  - infection
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, and burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - medications: glucocorticoids, β-agonists, lithium, G-CSF

Clinical Features
- signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  - including LAD and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

Investigations
- CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
- blood film: left shifted WBCs, Döhle bodies (intracytoplasmic structures composed of agglutinated ribosomes), toxic granulation, and cytoplasmic vacuoles in infection
- may require BM biopsy if MPN suspected

Treatment
- directed at underlying cause

Neutropenia

Definition
- mild: ANC 1.0-1.5 x 10^9/L
- moderate: ANC 0.5-1.0 x 10^9/L (risk of infection starts to increase)
- severe: ANC <0.5 x 10^9/L
- profound: ANC <0.1 x 10^9/L for >7 d

ANC Calculation
ANC = WBC count x (%PMNs + %bands)
Beware of fever + ANC <0.5 x 10^9/L = FEBRILE NEUTROPENIA

Etiology

Table 6. Etiology of Neutropenia

Decreased Production	Peripheral Destruction/Sequestration	Excessive Margination (Transient Neutropenia)
Infection Viral hepatitis, EBV, HIV, TB, typhoid, malaria **Hematological Diseases** Idiopathic, aplastic anemia, MF, BM infiltration, cyclic, PNH, MDS, large granular lymphocyte leukemia, hairy cell leukemia, immune-mediated **Drug-Induced** Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, antithyroid drugs **Toxins/Chemicals** High dose radiation, benzene, dichloro diphenyl trichloroethane (DDT) **Nutritional Deficiency** B_{12}, folate **Idiopathic** Constitutional neutropenia, benign cyclic neutropenia	Anti-neutrophil Abs Spleen or lung trapping Autoimmune disorders: RA (Felty syndrome), SLE Granulomatosis with polyangiitis (formerly Wegener's) Drugs: haptens (e.g. α-methyldopa)	Idiopathic (most common) Overwhelming bacterial infection Hemodialysis Cardiopulmonary bypass Racial variation (e.g. African or Ashkenazi Jewish descent)

Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection
Ann Intern Med 2007;147:400-411
Purpose: To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or SCT.
Study Selection: 148 RCTs comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.
Results: There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.9% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).
Conclusions: Prophylactic CSFs decrease infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but have no effect on mortality.

Clinical Features
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. *S. aureus*, Gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs and differential with peripheral smears to BM aspiration and biopsy

Treatment
- manage specific underlying causes and medications that contribute to neutropenia
- regular dental care: chronic gingivitis and recurrent stomatitis are major sources of morbidity
- treatment of febrile neutropenia
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, and methotrexate)

G-CSF = Neupogen® = filgrastim

Lymphocytosis

Definition
- absolute lymphocyte count >4.0 x 10^9/L

Etiology
- infection (reactive lymphocytosis)
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
- smoking
- physiologic response to stress (e.g. trauma, status epilepticus)
- hypersensitivity (e.g. drugs, serum sickness)
- autoimmune (e.g. RA)
- neoplasm (e.g. CLL, thymoma, B-cell lymphocytosis of undetermined significance)
- asplenia (e.g. post-splenectomy)

Presence of atypical lymphocytes suggests viral infection

Presence of smudge cells suggests a lymphoproliferative disorder if persistently elevated above 5.0 x 10^9/L for >3 mo; consider flow cytometry of peripheral blood

Investigations
- CBC and differential, peripheral smear assessing lymphocyte morphology, and in select cases, flow cytometry for assessing lineage and clonality

Treatment
- treat underlying cause

Lymphopenia

Definition
- absolute lymphocyte count <1.0 x 10^9/L

Etiology
- older age
- idiopathic CD4+ lymphopenia
- iatrogenic (radiation, chemotherapy, immunosuppressive agents)
- HIV/AIDS, HBV, HCV
- malignancy
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

Clinical Features
- opportunistic infections (see Infectious Diseases, ID29)

Investigations
- CBC and differential, lymphocyte subpopulations, immunoglobulin levels

Treatment
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID29)

Eosinophilia

Definition
- absolute eosinophil count >0.5 x 10^9/L

Etiology
- primary: due to clonal BM disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome (HES)
    - hypereosinophilia (absolute eosinophil count >1.5 x 10^9/L in the peripheral blood on 2 exams separated by ≥1 mo), with end-organ damage and no other identifiable cause
    - can involve heart, BM, and CNS
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes:
    - collagen vascular diseases (e.g. RA, polyarteritis nodosa, see Rheumatology, RH8)
    - respiratory causes (asthma, eosinophilic pneumonia, and eosinophilic granulomatosis with polyangiitis (EGPA))
    - cholesterol emboli
    - hematologic malignancy (myeloid and lymphoid variants), see *Chronic Myeloid Leukemia, H42* and *Hodgkin Lymphoma, H47*
    - adrenocortical insufficiency, see Endocrinology, E39
    - medications (penicillins)
    - atopic dermatitis



Basophilia and/or Eosinophilia
Can be an indicator of CML or other MPNs, associated with pruritus due to excessive histamine production

Investigations
- CBC and differential, peripheral smear assessing eosinophil morphology
- end organ involvement: electrolytes, renal function tests, LFTs, creatine kinase (CK), troponin, ECG, ECHO, pulmonary function tests (PFTs), CXR, chest and abdominal CT, consider BM biopsy

Treatment
- treat underlying cause
- before initiating steroids, ensure strongyloides serology is collected to rule out infection for patients at risk

Agranulocytosis

Definition
- ANC is <100/μL

Etiology
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced Abs or direct toxic effects upon marrow granulocytic precursors

Clinical Features
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

Prognosis
- high fatality without vigorous treatment

Investigations/Treatment
- discontinue offending drug
- if patient is febrile, pan-culture and screen for infection (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider BM aspirate and biopsy if cause unclear
- consider G-CSF

Leukemoid Reaction

Definition
- leukocytosis >50 x 10^9/L

Etiology
- infection
- drugs
- asplenia
- intoxication
- malignancy
- hemorrhage
- acute hemolysis

Investigations/Treatment
- marked left shift (myelocytes, metamyelocytes, and bands in peripheral blood smear)
- rule out CML and chronic neutrophilic leukemia
- detect and treat underlying cause

Approach to Lymphadenopathy

History
- constitutional/B-symptoms (seen in TB, lymphoma, other malignancies)
- growth pattern: acute vs. chronic
- exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), and high-risk behaviours (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

Constitutional/B-Symptoms

Unexplained temperature >38°C

Unexplained weight loss (>10% of body weight in 6 mo)

Night sweats

Lymphadenopathy-Causing Drugs
- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Cephalosporins
- Gold
- Hydralazine
- Penicillin
- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Sulfonamides
- Sulindac

Clinical Features
- determine if lymphadenopathy is localized or generalized
- generalized: typically features of systemic diseases (HIV, TB, EBV, SLE, medications, sarcoidosis, lymphoma)
- localized: typically reactive or neoplastic
  - cervical (bacterial/mycobacterial infections, ENT malignancies, and metastatic cancer)
  - supraclavicular (highest malignancy risk)
    - right (mediastinal, bronchogenic, esophageal cancer)
    - left (gastric, gallbladder, pancreas, renal, and testicular/ovarian cancer)
  - axillary (cat scratch fever, breast cancer, and metastatic cancer)
  - epitrochlear (infections, sarcoidosis, and lymphoma)
- check for splenomegaly, constitutional symptoms

Investigations
- CBC and differential, blood film
- if generalized, consider tuberculin test, HIV RNA, VDRL, Monospot®/EBV serology, antinuclear antibodies (ANA), and imaging
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → excisional biopsy to preserve lymph node architecture)
- in areas difficult to access (retroperitoneal, mediastinal/hilar), multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (excisional biopsy is the gold standard)
  - FNA is helpful for recurrence of solid tumour malignancy

Table 7. Inflammatory vs. Neoplastic Lymph Nodes

Feature	Inflammatory	Neoplastic
Consistency	Fluctuant/soft	Firm/hard
Mobility	Mobile	Matted/immobile
Tenderness	Tender	Non-tender
Size	<1 cm*	>1 cm*

Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender
*Note: inguinal lymph nodes can be up to 2 cm in size and non-pathologic

Table 8. Differential Diagnosis of Generalized Lymphadenopathy

Reactive	Inflammatory	Neoplastic
Bacterial (TB, Lyme, brucellosis, cat scratch disease, and syphilis)	Collagen disease (RA, dermatomyositis, SLE, vasculitis, and Sjögren's)	Lymphoproliferative disorder
Viral (EBV, CMV, HIV)	Drug hypersensitivity	Metastatic cancer
Parasitic (toxoplasmosis)	Sarcoidosis, amyloidosis	Histiocytosis X
Fungal (histoplasmosis)	Serum sickness	

Approach to Splenomegaly

Table 9. Differential Diagnosis of Splenomegaly

Increased Demand for Splenic Function			Congestive	Infiltrative
Hematological	**Infectious**	**Inflammatory**	**Cirrhosis**	**Non-Malignant**
Nutritional anemias	Viral e.g. EBV, HIV/ AIDS, CMV	SLE	Portal HTN	Benign metaplasia
Hemoglobinopathies	Bacterial e.g. bacterial endocarditis, TB	Sarcoidosis	Portal vein obstruction (including right heart failure)	Cysts
Hemolysis	Parasitic e.g. malaria, histoplasmosis, leishmaniasis	Felty syndrome	Splenic vein thrombosis	Amyloidosis
Spherocytosis	Fungal	Still's disease		Sarcoidosis
Sequestration crisis				Hamartomas
Elliptocytosis				Vascular abnormalities
				Lysosomal storage diseases (Gaucher's, Niemann-Pick)
				Glycogen storage diseases
				Malignant
				Leukemia (CML, CLL)
				Lymphoproliferative disease (CLL, NHL/HL)
				MPNs (CML, MF)
				Metastatic tumour

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis)

Causes of Splenomegaly

CHINA
Cirrhosis/Congestion (portal HTN)
Hematological
Infectious
Neoplasm
Autoimmune

History

- constitutional/B symptoms, feeling of fullness in LUQ, and early satiety
- signs or symptoms of infection (e.g. mononucleosis) or malignancy
- history of liver disease, hemolytic anemia, or high-risk exposures

Clinical Features

- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube's space, and Nixon's method) and palpation
- associated LAD or hepatomegaly
- signs of CHF

Investigations

- CBC and differential, blood film
- as indicated: liver enzymes (AST, ALT, ALP, and GGT) and/or LFTs (platelet, INR, albumin, and bilirubin), reticulocyte count, Monospot®/EBV, haptoglobin, LDH, infectious and autoimmune workup, and BM biopsy/aspirate when malignancy suspected
- imaging
  - ultrasound of abdomen/liver to assess for cirrhosis and portal vein thrombosis (if positive, refer to hepatology)
  - echo for cardiac function
  - CT to rule out lymphoma and assess splenic lesions

Microcytic Anemia

- MCV <80 fL
- see *Figure 2, H6*

Table 10. Iron Indices and Blood Film in Microcytic Anemia

	Lab Tests					Blood Film
	Ferritin	Serum Iron	TIBC	% saturation	RDW	
Iron Deficiency Anemia	↓↓	↓	↑	↓	↑ (>15)	Hypochromic, microcytic
Anemia of Chronic Disease	N/↑	↓	↓	N	N	Normocytic/microcytic
Sideroblastic Anemia	N/↑	↑	N	N/↑	↑	Dual population Basophilic stippling
Thalassemia	N/↑	N/↑	N	N/↑	N/↑	Hypochromic, microcytic Basophilic stippling Poikilocytosis

Causes of Microcytic Anemia

TAILS
Thalassemia
Anemia of chronic disease/ inflammation
Iron deficiency
Lead poisoning
Sideroblastic anemia

Iron Metabolism

Iron Intake (Dietary)

- average North American adult diet = 10-20 mg iron daily
- steady state absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid and ascorbic acid (vitamin C); reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males more likely to have positive iron balance; up to 20% of menstruating females have negative iron balance

Iron Absorption and Transport

- dietary iron is absorbed in the duodenum (absorption impaired in IBD and celiac disease)
- in circulation, the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the BM

Iron Levels

- hepcidin is a hormone produced by hepatocytes that regulates systemic iron levels
  - binds to iron exporter ferroportin (on duodenal enterocytes and reticuloendothelial cells) and induces its degradation, thereby inhibiting iron export into circulation (iron trapping in reticuloendothelial system cells and diminished absorption of iron)
  - hepcidin production is
    - increased in states of iron overload (inhibiting additional iron absorption) and inflammation (mediating anemia of chronic disease through iron trapping)
    - decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

Iron Storage

- ferritin
  - ferric iron (Fe^{3+}) complexed to a protein called apoferritin (liver, spleen, and BM are main ferritin storage sites)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated to some extent despite low iron stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is the main source of hemosiderin storage

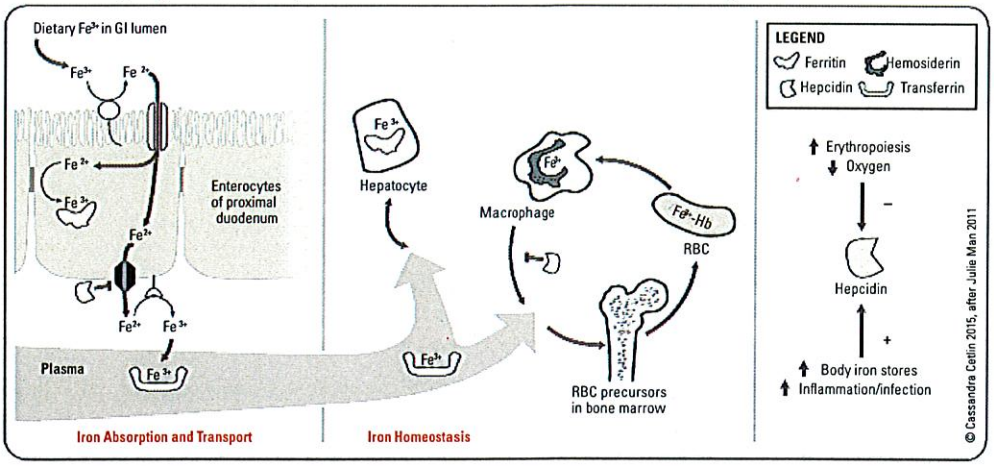


Figure 5. Iron metabolism

Iron Indices
- BM aspirate: gold standard test for assessment of iron stores (rarely done for this indication)
- serum ferritin: most important blood test for measuring iron stores
  - decreased in iron deficiency anemia
  - elevated in infection, inflammation, malignancy, liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
- TIBC: indirect measure of total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - increased TIBC has high specificity for decreased iron, low sensitivity
- transferrin saturation
  - serum iron divided by TIBC, expressed as a proportion or a percentage
- sTfR
  - reflects functional availability of iron at the tissue level
  - transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some are cleaved off and are present in circulation as sTfR
  - in iron deficient states, more transferrin receptors are expressed on erythroblasts leading to an increase in sTfR
  - sTfR also increased during extramedullary hematopoiesis (i.e. thalassemia syndromes)
  - low in reduced erythropoiesis and iron overload
  - useful in identifying iron deficiency in the setting of chronic inflammatory disorders (where ferritin levels can be elevated though iron stores are low; see *Iron Deficiency Anemia, H15*)

Iron Deficiency Anemia

- see Pediatrics, P51
- most common cause of anemia in North America

Etiology
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology in the developed world)
  - cow's milk (infant diet), "tea and toast" diet (elderly), absorption imbalances, post-gastrectomy, malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis, and *H. pylori* infection)
- increased losses
  - hemorrhage
    - obvious causes: abnormal uterine bleeding, GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - chronic intravascular hemolysis (e.g. PNH, cardiac valve RBC fragmentation)

Clinical Features
- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see *Anemia, H6*
- brittle hair, nail changes (brittle, koilonychia)
- pica (appetite for non-food substances, e.g. ice, paint, and dirt)
- restless leg syndrome

Investigations
- CBC, reticulocyte count, blood film, ferritin
  - low ferritin (<30 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup - complete iron indices, consider sTfR (if available)
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms (oval-shaped RBCs)
  - anisocytosis (RBCs with irregular sharp projections)
  - target cells (RBCs with thicker cell membranes)
- BM aspirate (gold standard, but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation





Plummer-Vinson Syndrome
- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia
- Stomatitis



Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.)
In males and in post-menopausal women, a GI workup is always warranted (gastroscopy, colonoscopy)

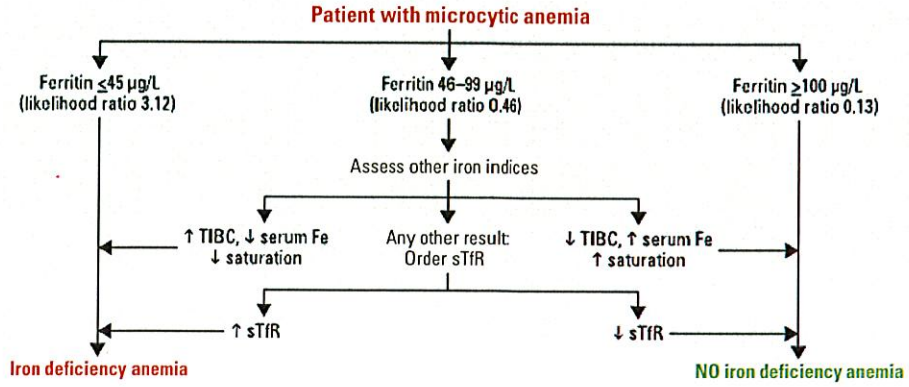


Figure 6. Approach to interpreting iron indices
Adapted from: Am Fam Physician 2007;75:671-678

Treatment
- treat underlying cause
- iron supplementation
  - oral (capsules, syrup)
    - ferrous sulphate 325 mg once daily (65 mg elemental iron), ferrous gluconate 300 mg once daily (35 mg elemental iron), or ferrous fumarate 300 mg once daily (100 mg elemental iron), polysaccharide iron complex (150 mg elemental iron), heme iron polypeptide (11 mg elemental iron)
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - recent studies demonstrate alternate day dosing may be non-inferior to daily or more frequent dosing, due to improved absorption, though this is still an area of investigation
    - there is no role for dosing oral iron more than once-daily; this results in hepcidin up-regulation and decreased absorption (and more side effects without clinical benefit)
  - IV iron can be considered if patient cannot tolerate or absorb oral iron, and/or if there is a need for quick recovery (e.g. chronic bleeding not manageable with oral iron)
- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb increases by 10 g/L per wk (if no blood loss)

Anemia of Chronic Disease

(Also known as anemia of inflammation)

Etiology
- infection, malignancy, inflammatory, and rheumatologic disease
- chronic renal and liver disease
- endocrine disorders (e.g. diabetes mellitus, hypothyroidism, hypogonadism, and hypopituitarism)

Pathophysiology
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - hepatic hepcidin production is increased in inflammatory processes, trapping iron in enterocytes and macrophages (via ferroportin inhibition), see *Figure 5, H14*
  - reduced plasma iron levels make iron relatively unavailable for new Hb synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present i.e. RBC survival is modestly decreased

Investigations
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen, and platelets)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- "classic" serum iron indices: see *Table 10, H14*
- BM
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

Treatment
- treat underlying disease; only treat in patients who would benefit from a higher Hb
- IV iron if no benefit from PO iron (overcomes sequestration in enterocytes) or with use of ESAs in CKD
- EPO indicated in chronic renal failure; ensure Hb target <110 g/L (increased risk of vascular events/ischemic stroke with higher Hb targets)

Sideroblastic Anemia

- uncommon compared to iron deficiency anemia or anemia of chronic disease

Sideroblasts
- erythrocytes with small coarse or fine blue iron-containing (basophilic) granules in the cytoplasm
- "normal": granules are small and randomly spread in the cytoplasm
- "ring": iron deposits in mitochondria, forming large, abnormal granules that surround the nucleus
  - hallmark of sideroblastic anemia

Etiology
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - refractory anemia with ringed sideroblasts: a subtype of MDS (see *Myelodysplastic Syndromes, H41*)
  - may be a preleukemic phenomenon (1-2% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, and hypothyroidism

Clinical Features
- anemia symptoms (see *Anemia, H6*)
- hepatosplenomegaly

Investigations
- serum iron indices: see *Table 10, H14*
- CBC and blood film
  - ring sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikilocytosis (abnormally shaped RBCs), basophilic stippling
- BM biopsy

Treatment
- depends on etiology
  - X-linked: high dose pyridoxine (vitamin B_6) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia
- monitor for iron overload driven by ineffective erythropoiesis and/or transfusion

Lead Poisoning

Definition/Etiology
- blood lead levels >80 μg/dL, may be symptomatic at 50 μg/dL
- identify source: consider occupational history, exposures history, and utensil history

Clinical Features
- pallor, abdominal pain, constipation, irritability, and difficulty concentrating

Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Consider lead poisoning in any child with microcytic anemia who lives in a house built before 1977

Features of Lead Poisoning

LEAD
Lead lines on gingivae and epiphyses of long bones on x-ray
Encephalopathy and Erythrocyte basophilic stippling
Abdominal colic and microcytic Anemia (sideroblastic)
Drops (wrist and foot drop)

Normocytic Anemia

- MCV 80-100 fL
- see *Figure 2, H6*

Aplastic Anemia

Definition
- destruction of hematopoietic cells of the BM leading to pancytopenia and hypocellular BM

Causes of Normocytic Anemia

ABCD
Acute blood loss
BM failure
Chronic disease
Destruction (hemolysis)

Etiology

Table 11. Etiology of Aplastic Anemia

Congenital	Acquired	
Fanconi syndrome Shwachman-Diamond syndrome Telomeropathies (dyskeratosis congenita)	**Idiopathic** Often T-cell mediated **Drugs** Dose-related (i.e. chemotherapeutics) Idiosyncratic (chloramphenicol, antimalarials, and phenylbutazone) **Toxins** Benzene/organic solvents, DDT, insecticides	**Ionizing Radiation** **Post-Viral Infection** Parvovirus B19, EBV, HDV, HEV, HBV, HHV6, HIV **Autoimmune (rare)** SLE, Graft-versus-host disease Others PNH, pregnancy, anorexia nervosa, and thymoma

Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see *Anemia, H6*), thrombocytopenia (see *Thrombocytopenia, H7*), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)

Investigations
- exclude other causes of pancytopenia (see *Figure 4, H9*), including PNH (50% of aplastic anemia patients have PNH+ stem cell clones)
- CBC
  - anemia, neutropenia, or thrombocytopenia (any combination including pancytopenia)
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- BM aspirate and biopsy
  - aplasia or hypoplasia of cells with adipose tissue replacement
  - no evidence of infiltration with malignant cells or fibrosis

Treatment
- remove offending agents
- supportive care (RBC and platelet transfusions, antibiotics)
  - judicious use of blood products to decrease the risk of immune sensitization
  - iron chelation therapy for iron overload (accumulation of iron after multiple >20-unit RBC transfusions)
- immunosuppressive therapy (for idiopathic aplastic anemia)
  - horse or rabbit anti-thymocyte globulin: 40-50% of patients respond
  - cyclosporine (for improved response and survival)
- allogeneic BM transplant
- eltrombopag (TPO receptor agonist) shown to be effective; G-CSF and EPO not effective

Hemolytic Anemia

Definition
- anemia due to destruction and consequently shortened survival of circulating RBCs, usually defined as <100 d
- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

Classification
- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal Hb synthesis (hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold AIHA, see *Table 14, Classification of AIHA, H23*
    - alloimmune: hemolytic disease of the fetus/newborn and post-transfusion
  - non-immune
    - TMA (includes MAHA): thrombus in blood vessel causes RBCs to be sheared – associated with DIC, HUS, aHUS, TTP, preeclampsia/HELLP, vasculitis, and malignant hypertension
    - other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, and mechanical heart valves
- also classified as intravascular or extravascular
  - intravascular: TMA and PNH (complement mediated)
  - extravascular: RBCs are coated with Abs (AIHA) or have an abnormal membrane structure/shape or inclusions
  - infections can cause intravascular (*Clostridium*), extravascular, or both (malaria)

On blood film, schistocytes reflect an intravascular hemolysis while spherocytes usually reflect an extravascular hemolysis

Disruption of the heme biosynthetic pathway causes **porphyria**

Porphyria
Inherited or acquired disorders of defective heme synthesis leading to accumulation of porphyrin precursors. Typically presents with non-specific clinical findings (abdominal pain, peripheral neuropathy, neuropsychiatric changes, and/or cutaneous photosensitivity)

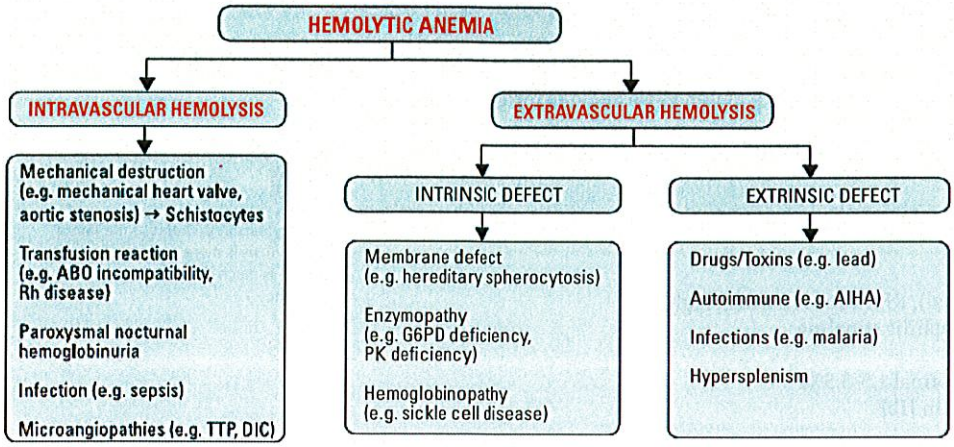


Figure 7. Hemolytic anemia

Heme Breakdown

Heme
↓ Heme oxygenase
Biliverdin
↓ Biliverdin reductase
Bilirubin

Haptoglobin is a circulating protein that mops up free Hb, allowing its clearance in the spleen; when free Hb is abundant, haptoglobin levels decrease

Clinical Features

- jaundice
- dark urine (hemoglobinuria, bilirubinuria)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

Table 12. Investigations for Hemolytic Anemia

Screening Tests	Tests Specific For Intravascular Hemolysis
Increased LDH	Schistocytes on blood film (MAHA)
Decreased haptoglobin	Free Hb in serum
Increased unconjugated bilirubin	Methaemalbuminaemia (heme + albumin)
Increased urobilinogen	Hemoglobinuria (immediate)
Reticulocytosis	Hemosiderinuria (delayed) – most sensitive
Tests Specific for Extravascular Hemolysis	
Direct Antiglobulin Test (direct Coombs) Detects IgG or complement on the surface of RBC Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction	
Indirect Antiglobulin Test (indirect Coombs) Detects Abs in serum that can recognize antigens on RBCs Mix patient's serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA	

Thalassemia

Definition

- defects in production of the α or β chains of Hb
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depend on specific gene and number of alleles affected
- common features
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film
  - CBC: low MCV, low Hb, high RBC count, ± high reticulocyte count

Thalas"SEA"mia

β-thalassemia → more prevalent in Mediterranean
α-thalassemia → more prevalent in South East Asia (SEA) and Africa
(α = Asia, Africa)

Pathophysiology

- defect may be in any of the Hb genes
  - normally 4 α genes in total; 2 on each copy of chromosome 16
  - normally 2 β genes in total; 1 on each copy of chromosome 11
  - fetal Hb, HbF ($\alpha_2\gamma_2$), switches to adult forms HbA ($\alpha_2\beta_2$) and HbA2 ($\alpha_2\delta_2$) at age 3-6 mo
  - HbA constitutes 97% of adult Hb
  - HbA2 constitutes 3% of adult Hb

β-Thalassemia Minor (Thalassemia Trait)

Definition
- defect in single allele of β gene (heterozygous for one normal β globin allele and one β globin thalassemia allele)
- common in people of Mediterranean and South Asian descent

Clinical Features
- usually asymptomatic; a palpable spleen is very rare

Investigations
- Hb (100-140 g/L), MCV (<70 fL), Fe (normal), RBC count (normal/high)
- peripheral blood film – microcytosis, basophilic stippling
- Hb electrophoresis
  - specific: HbA2 increased to 3.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

Treatment
- no treatment required
- genetic counselling for patient and family



Microcytosis in β-Thalassemia Minor
Microcytosis is more profound and the anemia is much milder than that of iron deficiency

β-Thalassemia Major

Definition
- defect in both alleles of β gene (homozygous, autosomal recessive)

Pathophysiology
- ineffective chain synthesis leading to decreased erythropoiesis, hemolysis of RBCs, and increase in HbF

Clinical Features
- initial presentation at age 6-12 mo when HbA (α_2/β_2) normally replaces HbF (α_2/γ_2)
  - severe anemia, jaundice
- iron overload due to compensatory gastrointestinal iron uptake progressing to hemochromatosis
  - secondary to repeated transfusions and ineffective erythropoiesis (through an erythroferrone-mediated mechanism)
  - results in iron-induced organ damage
- stunted growth and development (due to hypogonadism)
- gross hepatosplenomegaly (due to extramedullary hematopoiesis)
- radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
  - skull x-ray has "hair-on-end" appearance
  - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
- death can result from:
  - untreated anemia (should transfuse)
  - infection (should identify and treat early)
  - iron overload (common, late complication)



Hemochromatosis Clinical Features

ABCDH
Arthralgia
Bronze skin
Cardiomyopathy, Cirrhosis of liver
Diabetes (pancreatic damage)
Hypogonadism (anterior pituitary damage)

Investigations
- CBC and iron studies
- severe microcytic anemia (Hb <60 g/L)
- peripheral blood film: teardrop, target, hypochromic, microcytic
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA2 >2.5%
  - HbF: 90-100%

Treatment
- life-long regular RBC transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, and deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogeneic BM transplantation (potentially curative) or cord blood transplant
- gene therapy (to encode adult Hb A) or CRISPR-Cas 9 gene editing (to allow for increased HbF production) under study
- splenectomy (now performed less frequently)

β-Thalassemia Intermedia

Definition
- clinical diagnosis in patients whose clinical manifestations are too mild to be classified as β-thalassemia major, but too severe to be classified as β-thalassemia minor

Clinical Features
- wide variety of clinical phenotypes
- in most cases of β-thalassemia intermedia, both β-globin genes are affected
- three main mechanisms account for the milder phenotype compared to β-thalassemia major: (1) subnormal (vs. absent) β-chain synthesis, (2) increased number of γ chains, and (3) coinheritance of α-thalassemia (in some cases)
- complications more commonly seen in β-thalassemia intermedia than β-thalassemia major include extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, pulmonary hypertension, and growth retardation

Treatment
- most patients only require periodic transfusions, although regular transfusions may eventually be necessary in adulthood (third to fourth decade of life)
- folic acid supplementation if not transfused
- iron chelation therapy may be needed to mitigate iron overload from ineffective erythropoiesis and subsequent hepcidin downregulation via erythroferrone; can assess liver iron concentration (LIC) with an MRI, chelation should be considered if LIC >5 mg/g

α-Thalassemia

Definition
- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Southeast Asians and Africans

Clinical Features
- 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
- 2 defective α genes (cis: aa/-- or trans: a-/a-): normal Hb, decreased MCV
  - N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in Africa – this leads to increased risk of fetal hydrops in offspring of patients from Southeast Asia vs. Africa
- 3 defective α genes (a-/--): HbH (β4) disease; presents in adults, decreased Hb, decreased MCV, and splenomegaly
- 4 defective α genes (--/--): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

Investigations
- CBC and iron studies (for iron overload)
- peripheral blood film – screen for HbH inclusion bodies with supravital stain
- Hb electrophoresis can be used to identify HbH disease, but may miss 1- or 2-gene deletions; definitive diagnosis with DNA genotyping

Treatment
- referral for genetic/prenatal counselling
- depends on degree of anemia
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - Hb Barts: no definitive treatment
    - majority of pregnancies terminated (fetal/maternal mortality risk)
    - intrauterine transfusion, stem cell transplants

Sickle Cell Disease

Definition
- autosomal recessive sickling disorders are most commonly caused by a Glu → Val substitution at position 6 of the β-globin chain (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
  - increased incidence of HbS allele in patients with Sub-Saharan African, Indian, Middle Eastern, or Mediterranean heritage (thought to be protective against malaria)
- SCD occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

Pathophysiology
- at low pO_2, deoxyHbS polymerizes leading to rigid crystal-like rods that distort membranes → 'sickles'
- the pO_2 level at which sickling occurs is related to the percentage of HbS present
- sickling is aggravated by acidemia, increased CO_2, increased 2,3-DPG, fever, and increased osmolality
- fragile sickle cells then cause injury in two main ways
  1. fragile sickle cells hemolyze (nitric oxide depletion)
  2. occlusion of small vessels (hypoxia, ischemia-reperfusion injury)

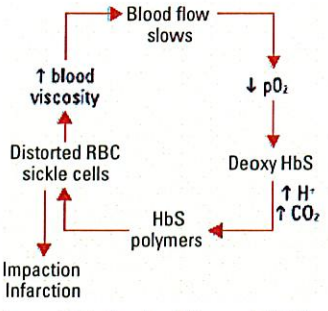


Figure 8. Pathophysiology of sickling

Functional Asplenism: increased susceptibility to infection by encapsulated organisms
- *S. pneumoniae*
- *N. meningitidis*
- *H. influenzae*
- *Salmonella (osteomyelitis)*

Clinical Features

- sickle cell trait (HbAS): asymptomatic except during extreme hypoxia or infection
  - increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SS often presents with acute pain episode
  1. aplastic crises
     - toxins and infections (especially parvovirus B19) transiently suppress BM
  2. splenic sequestration crises
     - usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
     - uncommon in adults due to asplenia from repeated infarction
  3. vaso-occlusive crises (microcirculation infarction)
     - may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis
     - can cause a stroke or a silent MI
     - precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol
  4. acute chest syndrome
     - acute illness characterized by fever and/or respiratory symptoms
     - new pulmonary infiltrate on chest x-ray
     - precipitated by pulmonary infection, fat emboli, and pulmonary infarction
- SCD-SC (HbSC): most common compound heterozygote
  - 1 in 833 live births in African-Americans, common in West Africa
  - milder anemia than HbSS
  - similar complications as HbSS but typically milder and less frequent (exception is proliferative sickle cell retinopathy, glomerulonephritis, and avascular necrosis)
  - spleen not always atrophic in adults

Organs Affected by Vaso-Occlusive Crisis

Organ	Problem
Brain	Ischemic or hemorrhagic stroke, vasculopathy
Eye	Hemorrhage, blindness
Liver	Infarcts, RUQ syndrome
Lung	Acute chest syndrome, long-term pulmonary hypertension
Gallbladder	Stones
Heart	Hyperdynamic flow murmurs
Spleen	Enlarged (child); atrophic (adult)
Kidney	Hematuria, loss of renal concentrating ability, proteinuria
Intestines	Acute abdomen
Placenta	Stillbirths
Penis	Priapism
Digits	Dactylitis
Bone	Infarction, infection, avascular necrosis (femoral and humeral head)
Skin	Leg ulcers (ankle)

Investigations

- sickle cell prep (detects sickling of RBCs under the microscope in response to O_2 lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants
- all newborns in developed countries typically screened for SCD

Table 13. Investigations for Sickle Cell Disease

	HbAS	HbSS
CBC	Normal	Increased reticulocytes, decreased Hb, and decreased Hct
Peripheral Blood	Normal; possibly a few target cells	Sickled cells
Hb Electrophoresis	HbA fraction of 0.65 (65%) HbS fraction of 0.35 (35%)	No HbA, only HbS and HbF (proportions change with age); normal amount of HbA2

Treatment

- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
  1. folic acid to prevent folate deficiency
  2. hydroxyurea (HU) to enhance production of HbF
     - mechanism of action = stops repression of fetal Hb-γ gene thereby increasing production of stem cells expressing HbF (HbF decreases polymerization and precipitation of HbS in sickle cell RBCs)
     - short-term harms (within 6 mo): dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count; decreased sperm production, mucositis, skin ulcers
     - long-term harms: potentially birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug
  3. treatment of vaso-occlusive crisis
     - supportive care: oxygen, hydration (reduces viscosity), correct acidosis, analgesics/opiates
     - indication for exchange transfusion: SCD complications (acute chest syndrome, aplastic crises, hepatic or splenic sequestration, and stroke), prevention of complications, preoperative
     - less routinely: antimicrobials for suspected infection
  4. prevention of crises
     - establish diagnosis
     - avoid conditions that promote sickling (hypoxia, acidosis, dehydration, and fever)
     - vaccination in childhood (*S. pneumoniae, N. meningitidis*, and *H. influenzae* type b)
     - prophylactic penicillin (age 3 mo-5 yr)
     - good hygiene, nutrition, and social support

Hydroxyurea (Hydroxycarbamide) for Sickle Cell Disease
Cochrane DB Syst Rev 2017;4:CD002202
Purpose: To assess the effects of hydroxyurea therapy in patients of any age and genotype with sickle cell disease (SCD).
Study Selection: Randomised and quasi-randomised controlled trials ≥1 month comparing hydroxyurea with placebo, standard therapy or other interventions.
Results: 8 RCTs were included, 899 total patients (both adults and children with SCD). When compared to placebo, hydroxyurea was associated with statistically significant improvements in pain alteration (pain crisis frequency, duration, intensity, hospital admissions and opioid use), measures of HbF and neutrophil counts, and fewer occurrences of acute chest syndrome and blood transfusions. Differences in quality of life and adverse events (including serious or life-threatening events) were not statistically significant.
Conclusion: Evidence suggests that hydroxyurea can effectively decrease the frequency of pain episodes and other acute complications in patients with SCD. However, data on the long-term benefits and risks of hydroxyurea is still insufficient.

5. screen for complications
   - regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, and creatinine)
   - urinalysis annually (proteinuria and glomerulopathy)
   - transcranial doppler annually until 16 yr (stroke prevention)
   - retinal examinations annually from 8 yr (screen for retinopathy)
   - echocardiography once in late childhood/early adulthood (screen for pulmonary hypertension)
6. newer therapies
   - gene therapy
   - voxelotor
   - crizanlizumab

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)
Blood 2012;119:3925-32
Purpose: To compare standard treatment (transfusions/chelation) to alternative treatment (hydroxyurea/phlebotomy) for children with sickle cell anemia (SCA), stroke, and iron overload.
Methods: 133 pediatric patients were randomized to (1) continuation of monthly erythrocyte transfusions with oral deferasirox (28.2 ± 6.0 mg/kg/d) or (2) initiation on hydroxyurea (20 mg/kg/d escalated to maximum tolerated dose (MTD)=26.2 ± 4.9 mg/kg/d) with discontinuation of transfusions at MTD, and monthly phlebotomy (5-10 mL/kg/mo) for iron overload.
Primary Outcome: Secondary stroke recurrence rate and quantitative liver iron content.
Results: Stroke recurrence rate was significantly lower in patients on transfusions/deferasirox as compared to those initiated on hydroxyurea/phlebotomy (0% vs. 10%, P<0.05). Differences in liver iron content between the two treatment arms were not statistically different (16.6 mg/g dry weight liver in transfusions/deferasirox vs. 15.7 mg/g in hydroxyurea/phlebotomy).
Conclusion: Transfusions and chelation remain the preferred management strategies for pediatric patients with SCA, stroke, and iron overload.

Autoimmune Hemolytic Anemia

Table 14. Classification of AIHA

	Warm (75-90% cases)	Cold
Ab Allotype	IgG	IgM
Agglutination Temperature	37°C	4-37°C
Direct Coombs Test (direct antiglobulin test)	Positive for IgG ± complement	Positive for complement
Etiology	Idiopathic Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin lymphoma) Secondary to autoimmune disease (e.g. SLE) Pregnancy Drug-induced (e.g. penicillin, quinine, methyldopa)	Idiopathic Secondary to infection (e.g. mycoplasma pneumonia, EBV, HCV, syphilis) Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL)
Blood Film	Spherocytes	Agglutination
Management	Treat underlying cause Folic acid Corticosteroids (1st-line) Folic acid Rituximab (2nd-line to steroids) Immunosuppression Splenectomy	Treat underlying cause Folic acid Warm patient/avoid cold Rituximab regimen (1st-line) Plasma exchange (2nd-line for high IgM levels) Low dose alkylating agents (chlorambucil, cyclophosphamide) or interferon may be useful but less effective

Microangiopathic Hemolytic Anemia (MAHA)/Thrombotic Microangiopathy (TMA)

Definition
- hemolytic anemia due to intravascular fragmentation of RBCs

Etiology
- see *Thrombotic Thrombocytopenic Purpura (TTP), H31*
- *see Hemolytic Uremic Syndrome, H31*
- see *Disseminated Intravascular Coagulation, H34*
- eclampsia, HELLP syndrome, AFLP
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic APS

Investigations
- blood film: schistocytes
- hemolytic workup (CBC, reticulocyte count, LDH, haptoglobin, indirect bilirubin)
- Coombs test: negative
- urine: hemosiderinuria, hemoglobinuria

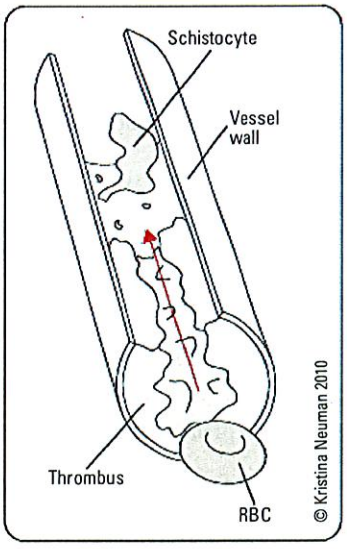


Figure 9. Schistocytosis

Hereditary Spherocytosis

Definition/Etiology
- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
- autosomal dominant (variable penetrance), can also be autosomal recessive or de novo
- presents with hemolytic anemia, jaundice, splenomegaly

Investigations
- CBC and differential blood film (shows spherocytes)
- RBC dehydration and membrane loss result in elevated MCHC
- osmotic fragility (increased)
- molecular analysis for spectrin gene
- U/S (splenomegaly and gallstones (pigment))

Treatment
- genetic counselling
- in severe cases, splenectomy (avoid splenectomy in early childhood); vaccination against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b pre-splenectomy

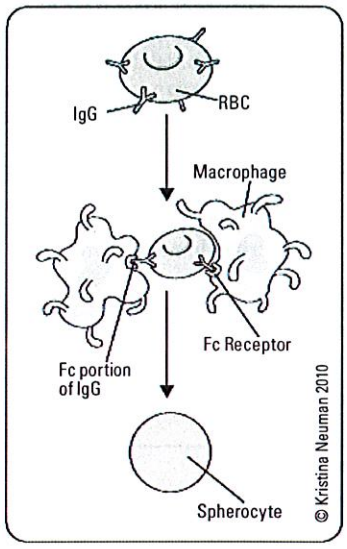


Figure 10. Spherocytosis secondary to AIHA

Hereditary Elliptocytosis

Definition/Etiology
- abnormal interactions between spectrin and other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

Treatment
- genetic counselling
- if severe hemolysis: folate supplementation, immunization, splenectomy

Glucose-6-Phosphate Dehydrogenase Deficiency

Definition/Etiology
- deficiency in G6PD leading to a lack of reduced glutathione and increased RBC sensitivity to oxidative stress
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

Clinical Features
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, and nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

Investigations
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (clumps of denatured Hb attached to RBC membrane)
  - bite cells (indicative of oxidative hemolysis; generated by passage through spleen)

Treatment
- genetic and prenatal counselling
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases

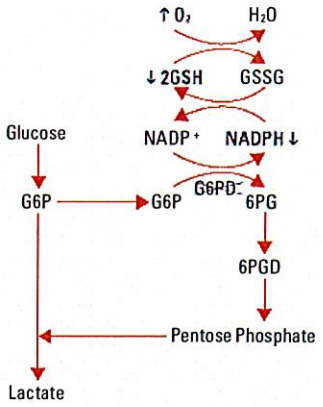


Figure 11. G6PD deficiency

Macrocytic Anemia

- MCV >100 fL
- see *Figure 2, H6*

Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

	Megaloblastic	Non-Megaloblastic
Morphology	Large, oval, nucleated RBC precursor Hypersegmented neutrophils	Large round RBC Normal neutrophils
Pathophysiology	Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm	Reflects membrane abnormality with abnormal cholesterol metabolism

Note: MDS is a non-megaloblastic macrocytic anemia that commonly presents with oval macrocytosis

Causes of Macrocytic Anemia

ABCDEF
Alcoholism (liver disease)
B_{12} deficiency
Compensatory reticulocytosis
Drugs (cytotoxic, azidothymidine)/
Dysplasia
Endocrine (hypothyroidism)
Folate deficiency/Fetus (pregnancy)

Characteristics of Megaloblastic Macrocytic Anemia
Pancytopenia
Hypersegmented neutrophils
Megaloblastic BM

Vitamin B_{12} Deficiency

- B_{12} (cobalamin)
- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

Etiology

Table 16. Etiology of Vitamin B_{12} Deficiency

Diet	Gastric	Intestinal Absorption	Genetic
Strict vegan More likely to present in pediatric population Vegetarian in pregnancy Malnutrition	**Mucosal atrophy** Gastritis, autoimmune **Pernicious anemia (see below)** **Post-gastrectomy**	**Malabsorption** Crohn's, celiac disease, pancreatic insufficiency, *H. pylori* **Stagnant bowel** Blind loop, stricture **Fish tapeworm** **Resection of ileum** **Drugs** Neomycin, biguanides, proton pump inhibitors, N_2O anesthesia, metformin	**Transcobalamin II deficiency** **IF receptor defect**

Pathophysiology of Pernicious Anemia

- auto-Abs produced against gastric parietal cells leading to achlorhydria and lack of IF secretion
- IF is required to stabilize B_{12} as it passes through the bowel
- decreased IF leads to decreased ileal absorption of B_{12}
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- most common in Northern European White populations, usually >30 yr (median age of 60 yr)

Clinical Features

- neurological (severity of anemia and neurological sequelae depends on deficiency)
  - peripheral neuropathy (variable reversibility)
    - usually symmetrical, affecting lower limbs more than upper limbs
  - spinal cord (irreversible damage)
    - subacute combined degeneration
    - posterior columns: decreased vibration sense, proprioception, 2-point discrimination, and paresthesia
    - pyramidal tracts: spastic weakness, ataxia
  - cerebral (common, reversible with B_{12} therapy)
    - confusion, delirium, and dementia
  - cranial nerves (rare)
    - optic atrophy

Investigations

- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fL
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum B_{12} and RBC folate
  - caution: lower serum B_{12} leads to low RBC folate; absence of B_{12} results in folate polyglutamate synthesis failure
  - alternatively, can measure elevated urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils

- BM
  - hypercellularity due to abnormal proliferation and maturation of multiple myeloid cell lines
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- celiac disease testing
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- pernicious anemia investigations: anti-parietal cell Ab (more sensitive), anti-intrinsic factor Ab (more specific), gastrin level (elevated), upper endoscopy (for biopsy - atrophic gastritis, also to screen for gastric malignancy)

Treatment
- treatment dose = vitamin B12 1000-1200 µg PO once daily if intestinal absorption intact or 1000 µg IM weekly; route and duration depends on cause
- maintenance dose (once replete) = vitamin B12 1000 µg PO once daily or 1000 µg IM monthly
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation (enriched in flour)
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables, and fortified cereals
- maternal folate deficiency is associated with fetal neural tube defects

Etiology

Table 17. Etiology of Folate Deficiency

Diet/Deficiency	Malabsorption	Drugs	Increased Demand
Alcohol use disorder	Celiac disease	Anti-folates (methotrexate)	Pregnancy
Substance misuse	IBD	Anticonvulsants (phenytoin)	Hemolysis
Elderly/infants	Short bowel syndrome	Alcohol	Prematurity
Poor intake		Oral contraceptive	Exfoliative dermatitis/psoriasis
			Hemodialysis

Clinical Features
- anemia, mild jaundice, glossitis, diarrhea, confusion, pallor
- consider social history, alcohol use disorder/substance misuse, very poor diet (e.g. elderly, depressed)

Investigations
- similar to B12 deficiency (CBC, reticulocytes, blood film, RBC folate, and serum B12)
- if decreased RBC folate, rule out B12 deficiency as cause

Management
- folic acid 1-5 mg PO once daily x 1-4 mo; then 1 mg PO once daily maintenance if cause is not reversible

Never give folate alone to an individual with megaloblastic anemia because it will mask B12 deficiency and neurological degeneration will continue

Hemostasis

Stages of Hemostasis

1. Primary Hemostasis
- mediated by platelets and VWF
- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (*Figure 12a, H27*)
  - adhesion: platelets adhere to subendothelium via VWF
  - activation: platelets are activated resulting in morphology change, and granule release
  - aggregation: activated GPIIbIIIa on platelets binds soluble ligands, which results in aggregation and the formation of a localized platelet plug

2. Secondary Hemostasis
- platelet plug is reinforced by production of a fibrin clot (*Figure 12b, H27*)
- extrinsic (initiation) pathway: initiation of secondary hemostasis
- intrinsic (amplification) pathway: amplification once secondary hemostasis has started via positive feedback
- both the intrinsic and extrinsic pathways converge onto the common pathway, which results in thrombin generation and fibrin formation

3. Fibrin Stabilization
- conversion from a soluble to an insoluble, cross-linked clot

4. Fibrinolysis
- once healing is initiated, clot dissolution is mediated by the fibrinolytic system

Phases of Hemostasis
Primary Hemostasis
Vascular response and platelet plug formation via VWF
Secondary Hemostasis
Fibrin clot formation
Fibrin Stabilization
Fibrinolysis

Check out this educational module created by St. Michael's Hospital residents and hematology faculty: www.coagtesting.com

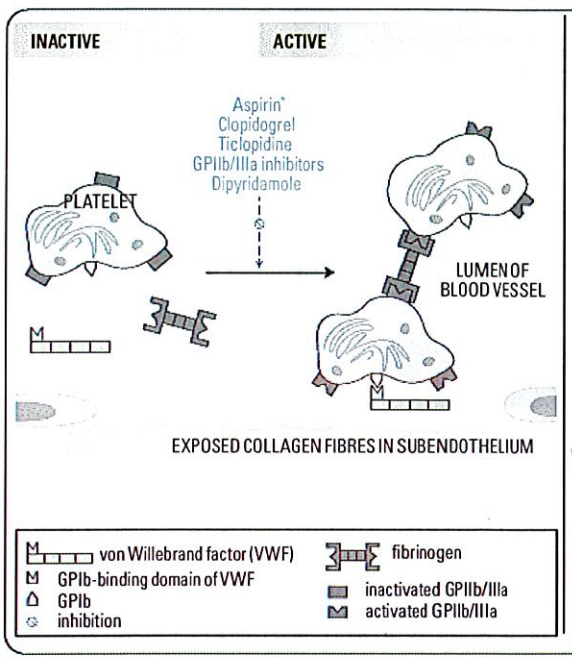


Figure 12a. Platelet activation

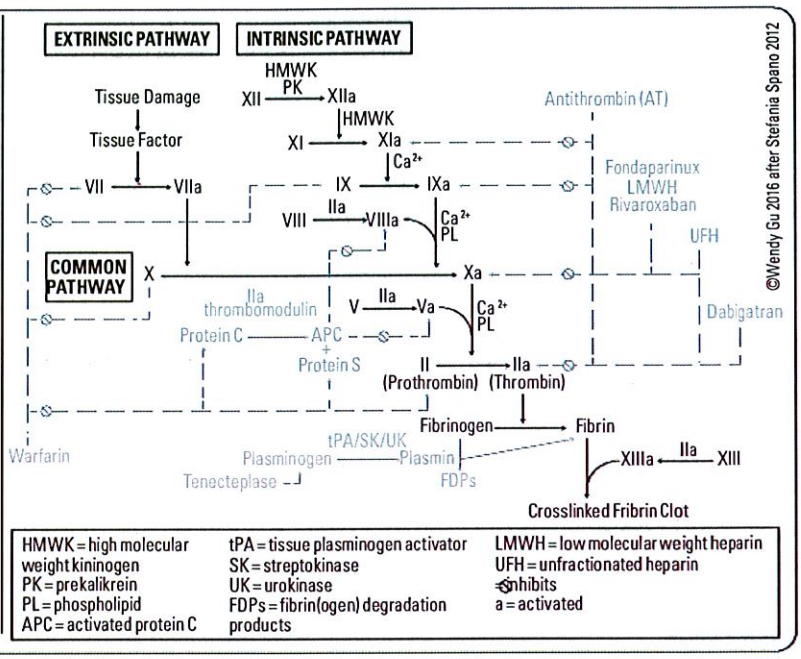


Figure 12b. Coagulation cascade

Table 18. Commonly Used Tests of Hemostasis

Type of Hemostasis	Test	Typical Reference Range (lab dependent)	Purpose	Examples of Associated Diagnoses
Primary	Platelet count	150-400 x 10^9/L	To quantitate platelet number	Low in ITP, HUS/TTP, DIC, HIT
Secondary	PTT	28-38 s	Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway Used to monitor heparin and argatroban therapy	Prolonged in hemophilia A and B (if factor deficiency is below reagent threshold of detection) N.B. Prolonged if lupus anticoagulant present (inhibits pathway *in vitro*)
	PT	10-13 s	Measures extrinsic pathway (factor VII) and common pathway	Prolonged in vitamin K deficiency, vitamin K antagonist therapy (warfarin), factor VII deficiency
	INR	0.9-1.2	Used to monitor warfarin therapy and for assessment of hepatic function	
	Mixing studies		May differentiate inhibitors of coagulation factor(s) from a deficiency in coagulation factors Mix patient's plasma with normal plasma in 1:1 ratio and repeat abnormal test	Normalization of coagulation time if deficiency of single coagulation factor (normalization may not occur if multiple coagulation factors are deficient) Lack of normalization if inhibitor present
Fibrinolysis	Euglobulin lysis time	N >90 min	Looks for accelerated fibrinolysis	May be shortened (increased fibrinolysis) in DIC or factor XIII deficiency
Other	Fibrinogen D-dimer Specific factor assays (e.g. factor VIII) Lupus anticoagulant von Willebrand tests (VWF antigen, Ristocetin cofactor activity (VWF activity), factor VIII)			

Note: INR is mathematically derived from PT

Table 19. General Rules of Thumb: Signs and Symptoms of Disorders of Hemostasis

	Primary (Platelet, VWF)	Secondary (Coagulation)
Surface Cuts	Excessive, prolonged bleeding	Normal/slightly prolonged bleeding
Onset After Injury	Immediate	Delayed
Site of Bleeding	Superficial i.e. mucosal (nasal, gingival, GI tract, vaginal), skin	Deep i.e. joints, muscles (excessive, post-traumatic)
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas

Tests of Secondary Hemostasis

PT/INR: Tennis is played outside (Extrinsic pathway)
PTT: Table Tennis is played inside (Intrinsic pathway)

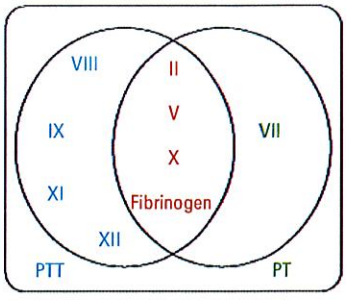


Figure 13. Coagulation factors involved in PT and PTT

Causes of a Prolonged PTT without Bleeding include:
1. Early contact factor (Factor XII, HMWK, PK) deficiency
2. Lupus anticoagulant
3. Inappropriate blood draw
4. Laboratory error

Consider PTT
IV heparin, argatroban monitoring
Factor VIII deficiency (Hemophilia A), Factor IX deficiency (Hemophilia B), factor XI deficiency, severe VWD

Table 20. Lab Values in Disorders of Hemostasis

	PT	PTT	Platelet Count	Hb
Hemophilia A/B	N	↑	N	N*
VWD	N	±	N/↓	N*
DIC	↑	↑	↓	N/↓
Liver Failure	↑	N/↑	N/↓	N
ITP	N	N	↓	N*
TTP	N	N	↓	↓

* = anemia may develop from progressive iron deficiency and/or active bleeding

Consider PT/INR
Warfarin
Liver disease
Risk factor for vitamin K deficiency (e.g. malabsorption, cholestasis, malnutrition)

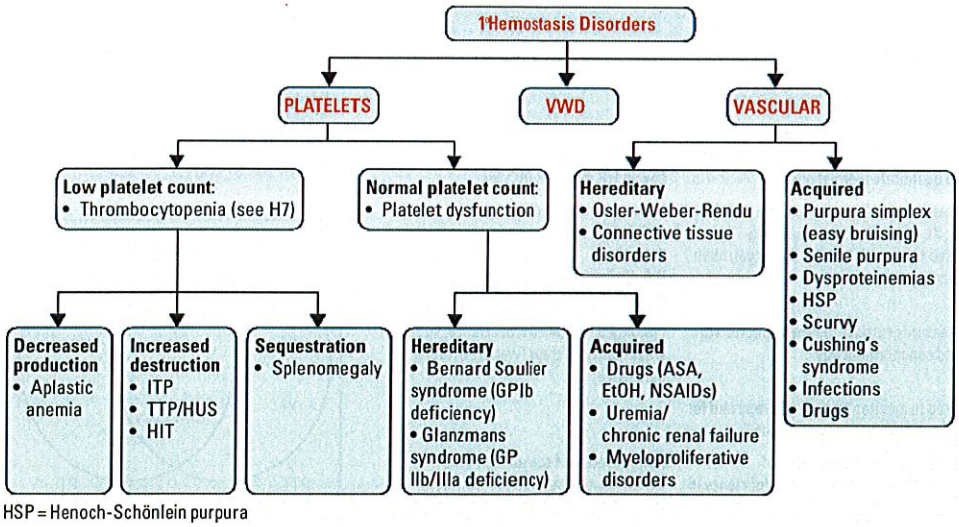
Consider both PTT and PT/INR
Suspected DIC
Trauma patient, or requiring massive transfusion protocol
Bleeding patient
Patient receiving thrombolytic therapy

Disorders of Primary Hemostasis

Definition

- inability to form an adequate platelet plug due to:
  - disorders of blood vessels
  - disorders of platelets: abnormal function/numbers
  - disorders of VWF
- characterized as immediate bleeding, mucocutaneous bleeding, and manifesting as petechiae/ ecchymosis/ epistaxis/ gum bleeding/ menorrhagia

Classification



HSP = Henoch-Schönlein purpura

Figure 14. Approach to disorders of primary hemostasis

Drugs Commonly Associated with Thrombocytopenia

Trimethoprim/ sulfamethoxazole	Heparin	NSAIDs
Vancomycin	Digoxin	Acetaminophen
Rifampin	Amiodarone	Ethanol
Ethambutol	Quinidine	H2-antagonists
Amphotericin B	Quinine (common)	Chemotherapy

Immune Thrombocytopenia

Table 21. Features for Childhood vs. Adult Immune Thrombocytopenia

Features	Childhood ITP (see Pediatrics, P53)	Adult ITP
Peak Age	2-6 yr	20-40 yr
Gender	F=M	F>M
History of Recent Infection	Common	Rare
Duration	Usually wk	Mo to yr
Spontaneous Remissions	80% or more	Uncommon

Definition

- a disease of low platelet count (see *Thrombocytopenia, H7*) secondary to aberrant immune responses

Terminology of ITP

- primary: ITP (platelet count <100 x 10^9/L) with no other cause of thrombocytopenia
- secondary: ITP associated with another condition (e.g. HIV, HCV, SLE, or CLL)
- drug-induced: platelet destruction caused by anti-platelet Abs secondary to drug exposure

Classification of Primary ITP

- acute: 3 mo from diagnosis
- persistent: 3-12 mo from diagnosis

- chronic: >12 mo from diagnosis
- refractory: post-splenectomy

Pathophysiology
- primary or secondary ITP
- an acquired immune-mediated disorder
  - increased platelet destruction induced by medications, viral infections, autoimmune diseases, and pregnancy
    - anti-platelet Abs bind to platelet surface → increased splenic clearance
    - helper T-cell and cytotoxic T-cell activation
- impaired platelet production
  - myelosuppression mediated by cytotoxic chemotherapy
  - drug induced megakaryocyte suppression

Clinical Features
- variable presentation: asymptomatic, fatigue, minimal bruising, mucocutaneous bleed (e.g. purpura, ecchymoses, petechiae, continuous epistaxis, menorrhagia) most common but bleeding can occur anywhere including intracranial hemorrhage
- assess for symptoms/signs suggesting a secondary cause

Investigations
- CBC: platelet count <100 x 10^9/L
- PT and PTT: normal
- peripheral blood film: decreased platelets ± large platelets (rule out platelet clumping)
- HIV, HCV
- depending on clinical suspicion: *H. pylori* testing (urea breath test, stool antigen, or endoscopy) vitamin B_{12}, ANA, C3, C4, APLA, quantitative immunoglobulins (to rule out underlying immunodeficiency) depending on clinical symptoms
- blood group RhD typing
- BM aspirate and biopsy: increased number of megakaryocytes
  - BM aspirate and biopsy should be considered pre-splenectomy to confirm diagnosis or if there is suspicion of diminished BM function (systemic symptoms, refractory ITP and/or abnormal blood film)

Treatment
- rarely indicated if platelets >30 x 10^9/L unless active bleeding, trauma, or surgery
- emergency treatment (active bleeding (CNS, GI, or GU) or in need of emergency surgery)
  - general measures: stop antiplatelet medications, control blood pressure, minimize trauma
  - corticosteroids: prednisone (0.5-2 mg/kg/d) or dexamethasone (40 mg PO once daily x 4 d)
  - if corticosteroids contraindicated: IVIg 1 g/kg x 1 dose, to be repeated if necessary (raises platelet count faster than corticosteroids)
  - IVIg can be used with corticosteroids when a more rapid increase in platelet count is required
  - antifibrinolytic: tranexamic acid (1 g PO TID or 1 g IV q8 h) if mucosal bleeding
  - platelet transfusion: for refractory, major bleeding, or need for urgent surgery (expect that platelet recovery will be diminished)
  - management of life threatening bleeding (i.e.intracranial bleeding): IV steroids, IVIg, platelet transfusion, may also consider emergency splenectomy -vaccinations prior if possible (*S. pneumoniae, N. meningitidis*, and *H. influenzae* type b)
  - management of intracranial bleeding: IV steroids, IVIg, platelet transfusion
- non-urgent treatment (platelet count <20-30 x 10^9/L and no bleeding)
  - 1st-line
    - corticosteroids (dexamethasone 40 mg PO once daily x 4 d x 1-4 cycles (not wk) or prednisone (0.5-2 mg/kg/d) x 2-3 wk then slow taper over 6 wk)
    - IVIg 1 g/kg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause transient hemolysis (avoid if low Hb at baseline or if DAT is positive)
  - 2nd-line
    - splenectomy (need vaccinations prior to splenectomy: *S. pneumoniae, N. meningitidis*, and *H. influenzae* type b) – not preferred if within 12 mo from diagnosis
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag) – may not be accessible as second line due to funding considerations
    - rituximab
  - 3rd-line
    - immunomodulating therapy (azathioprine, cyclophosphamide, danazol, and vincristine)
      - may be considered as defacto second line due to funding considerations and access limitations to other treatments
    - Syk inhibitors (Fostamatinib) - blocks platelet clearance

Definitions of Response to Treatment
- complete response: platelet count >100 x 10^9/L
- partial response: platelet count 30-100 x 10^9/L
- no response: platelet count <30 x 10^9/L

Prognosis

- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- life expectancy similar to general population (however, risk of mortality from bleeding/infection increases with advancing age)
- major concern is spontaneous intracranial hemorrhage, more common in the elderly

Table 22. Heparin-Induced Thrombocytopenia (HIT)

Pathophysiology	Immune mediated Ab recognizes a complex of heparin and platelet factor 4 leading to platelet activation via platelet Fc receptor and activation of coagulation system
Diagnosis	Suspected with intermediate or high probability HIT score Screen with immunoassays (e.g. HIT ELISA) and confirm with functional testing (Serotonin Release Assay)
Onset of Decreased Platelets	5-14 d (if previously exposed to heparin within 100 d, HIT can develop in hours due to an anamnestic response)
Risk of Thrombosis	30-50% (25% of events are arterial) if untreated
Clinical Features	Bleeding complications uncommon Venous thrombosis: DVT, PE, limb gangrene, cerebral venous sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (with LMWH) Non-necrotizing erythematous skin lesions Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.)
Specific Tests	Pre-test clinical scoring models can help rule-out HIT: 4Ts and the HIT Expert Probability (HEP) score 14C serotonin release assay (tests the functional ability of patient's plasma to activate platelets) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay, faster turnaround time, high negative predictive value) Ultrasound of lower limb veins and upper extremity with central venous catheter for DVT
Management	Clinical suspicion of HIT should prompt discontinuation of UFH and LMWH including flushes (specific tests take several days) Initiate anticoagulation with a non-heparin anticoagulant: e.g. argatroban, danaparoid, fondaparinux, bivalirudin unless there is a strong contraindication (duration depends on presence or absence of thrombosis) warfarin should be started when platelet count >150 x 10^9/L DOACs can be started before platelet count recovery Allergy band and alert in patient records

Table 23. The 4T Pre-Test Clinical Scoring Model for HIT

Category	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall >50% AND platelet nadir ≥20 x 10^9/L	Platelet count fall 30-50% OR platelet nadir 10-19 x 10^9/L	Platelet count fall <30% OR platelet nadir <10 x 10^9/L
Timing of Platelet Count Fall	Clear onset between 5-10 d of heparin exposure OR platelet count fall at ≤1 d if prior heparin exposure within last 30 d	Consistent with fall in platelet count at 5-10 d but unclear (e.g. missing platelet counts) OR onset after 10 d OR fall ≤1 d with prior heparin exposure within 30-100 d	Platelet count fall after ≤4 d of heparin exposure, and no recent heparin
Thrombosis or Other Sequelae	Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus, adrenal hemorrhage	Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven	None
Other Causes for Thrombocytopenia	None apparent	Possible	Definite

6-8 points = high probability of HIT; 4-5 points = intermediate probability of HIT; 0-3 points = low probability of HIT
Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360-3392

Heparin-induced thrombocytopenia (previously known as HIT type II): immune-mediated reaction following treatment with heparin leading to platelet activation and subsequent coagulation activation
Heparin-associated thrombocytopenia (previously known as HIT type I): transient thrombocytopenia following administration of heparin

Heparin-Associated Thrombocytopenia (previously known as HIT type I)

- Direct heparin mediated platelet aggregation (non-immune)
- Platelets >100 X 10^9/L
- Self-limited (no thrombotic risk)
- May continue with heparin therapy
- Onset 24-72 h

LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.6% in UFH vs. 0.2% in LMWH)

American Society of Hematology Choosing Wisely Recommendation
Don't test or treat for HIT in patients with low pre-test probability of HIT (4T's score of 0-3) as HIT can be excluded
Do not discontinue heparin or start a non-heparin anticoagulant in these low-risk patients because of increased risk of bleeding and increased cost of alternatives

Thrombotic Microangiopathies (TMAs)

Definition

- thrombotic disorder characterized by thrombi formation in small blood vessels
- TTP, HUS, and aHUS are examples of TMAs

Table 24. TTP and HUS

	TTP	HUS (see Pediatrics, P82)
Epidemiology	Immune form presents predominantly in adults Congenital form presents predominantly in children	Predominantly children and elderly
Etiology	Deficiency of ADAMTS13: metalloproteinase that breaks down ultra-large VWF multimers Congenital (genetic absence of ADAMTS13) Acquired (drugs, malignancy, transplant, HIV-associated, and idiopathic)	Shiga toxin (*E. coli* serotype 0157:H7) in 90% Other bacteria, viruses, genetic causes, and drugs
Clinical Features	1. Thrombocytopenia 2. MAHA/TMA 3. Neurological symptoms: headache, confusion, focal defects, and seizures 4. Symptoms can be mild and non-specific	1. Severe thrombocytopenia 2. MAHA/TMA 3. Acute kidney injury 4. Bloody diarrhea 5. GI prodrome
Investigations (both TTP, HUS)	CBC and blood film: decreased platelets and increased schistocytes PT, PTT, fibrinogen: normal Markers of hemolysis: increased unconjugated bilirubin, increased LDH, and decreased haptoglobin Negative Coombs test/DAT Creatinine and urea to follow renal function (kidney injury is uncommon in TTP vs. HUS induces severe injury that is sudden in onset) ADAMTS13 gene, activity or inhibitor testing (TTP)	
Management	Medical emergency: TTP mortality ~90% if untreated Plasma exchange ± steroids Platelet transfusion avoided unless life-threatening bleed (associated with microvascular thrombosis) Plasma infusion if plasmapheresis is not immediately available Caplacizumab in certain cases of acquired TTP	Supportive therapy (fluids, RBC transfusion, nutrition, etc.) Some evidence for plasma exchange Possible role of eculizumab (C5 Ab blocks complement activation) for neurologic symptoms

Note: aHUS is a complex disease with different etiology, treatment depends on genetic abnormalities



Pathophysiology of TTP

- Normally, large VWF multimers secreted by endothelial cells are rapidly cleaved by ADAMTS13 protease
- Congenital TTP is due to a genetic deficiency in ADAMTS13
- Acquired TTP (the more common form) is due to Abs against ADAMTS13
- Without ADAMTS13, uncleaved VWF continues to promote platelet adhesion, causing excess platelet aggregation in small blood vessels



Differential Diagnosis of TTP

DIC
HUS
aHUS
HELLP
Catastrophic APS
Evans syndrome (AIHA + ITP)

von Willebrand Disease

Definition

- bleeding disorder characterized by impaired clot formation due to qualitative or quantitative deficiencies in VWF

Pathophysiology

- most common inherited bleeding disorder (prevalence of 1%)
- usually autosomal dominant (types 2N and 3 are autosomal recessive)
- women more commonly diagnosed (heavy menstrual bleeding, peripartum bleeding)
- qualitative defect or quantitative deficiency of VWF depending on type
  - VWF mediates platelet adhesion/aggregation and acts as a chaperone for Factor VIII (extending its half-life in circulation); abnormal VWF can affect both primary and secondary hemostasis
  - VWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion/aggregation
    - both large and small multimers complex with Factor VIII
    - VWF levels vary according to blood group (lowest in group O patients) and other factors (higher with pregnancy, hormonal medication, acute inflammation)

Classification

- type 1: mild quantitative deficiency (decreased amount of VWF and proportional decrease in VWF activity) – 80% of cases
- type 2: qualitative defect (VWF activity disproportionally lower than quantity) – 20% of cases
  - type 2A: reduced VWF-dependent platelet adhesion due to high and intermediate molecular weight VWF multimer deficiency
  - type 2B: increased affinity for platelet GPIb and subsequent loss of high and intermediate molecular weight VWF multimers
  - type 2M: reduced VWF-dependent platelet adhesion with normal VWF multimer levels
  - type 2N: decreased affinity for Factor VIII
- type 3: severe total quantitative defect (virtually no VWF produced) – 1 in 1000000

Clinical Features

- bleeding history is the single most important predictor of an underlying bleeding disorder
- validated, standardized bleeding assessment tools (e.g. ISTH-BAT) to facilitate exploration of the bleeding history
- mucocutaneous bleeding (easy bruising, epistaxis (>10 min), heavy menstrual bleeding, peripartum bleeding, post-dental extraction bleeding, excessive postoperative bleeding, and unexplained gastrointestinal bleeding)

  - type 3 VWD patients can experience musculoskeletal bleeding due to significant deficiency in Factor VIII (lack of Factor VIII chaperoning as VWF is absent)
- family history of a bleeding disorder (a negative family history cannot be used to exclude the diagnosis)

Investigations
- CBC, platelet, VWF antigen (determine how much VWF is present), VWF ristocetin cofactor activity (determine how well VWF binds to platelet), Factor VIII (determine how well VWF chaperones Factor VIII), and PTT
- tests to further categorize type/subtype of VWD: multimer analysis, ristocetin induced platelet agglutination, and genetic studies

Table 25. Investigations in VWD

Test	Expected Result
PTT	N/↑
Plt Count	N/↓ (can be low in type 2B)
Blood group	Affects antigen quantification (↓ in group O)
Ferritin	Rule out secondary iron deficiency due to bleeding
von Willebrand antigen	↓
Ristocetin activity	↓ (cofactor for VWF-Plt binding)
Factor VIII	N/↓
VWF multimer analysis	Multimer variants



Consider VWD in all women with heavy menstrual bleeding



VWD is the most common heritable bleeding disorder

Treatment
- DDAVP® is effective treatment for 85-90% of patients with type 1 VWD and for some subtypes of type 2 VWD
  - causes release of VWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs after 4 consecutive doses
  - need to document responsiveness with "DDAVP® challenge"
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- VWF:Factor VIII concentrate (Humate P®, Wilate®) if DDAVP® unresponsive/clinically ineffective or for severe bleeding episode
  - need to monitor VWF and factor VIII levels (very high factor VIII level can be prothrombotic)
- gynecologic focused care for heavy menstrual bleeding (N.B. estrogens have the added benefit of increasing VWF levels)

Prognosis
- patients with mild type 1 VWD usually have auto-correction of VWF deficiency in pregnancy
- most cases are mild-moderate, and only ~10% of cases require long-term prophylactic therapy

Disorders of Secondary Hemostasis/Fibrinolysis

Definition
- inability to form an adequate fibrin clot
  - disorders of coagulation factors or cofactors
  - disorders of proteins associated with fibrinolysis
- patients can experience bleeding anywhere in the body but delayed bleeding, deep muscular bleeding, and spontaneous hemarthroses are highly suggestive of disorders of secondary hemostasis/fibrinolysis

Table 26. Classification of Secondary Hemostasis Disorders

Hereditary	Acquired
Factor VIII deficiency: Hemophilia A, VWD	Liver disease
Factor IX deficiency: Hemophilia B (Christmas Disease)	DIC
Factor XI deficiency: Hemophilia C	Vitamin K deficiency
Other factor deficiencies are rare	Acquired inhibitors (Factor VIII most common)

Hemophilia A (Factor VIII Deficiency)

Pathophysiology
- X-linked recessive disorder where factor VIII is absent or deficient, 1 in 5000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features
see *Table 19, H27* under secondary coagulation
- patients may have also acquired HIV or HCV from contaminated blood products (no cases observed from transfusions in Canada since 1985)

Investigations
- CBC
- prolonged PTT, normal INR (PT)
- decreased factor VIII (<40% of normal)
- VWF antigen and ristocetin activity testing to rule out VWD

Treatment
- DDAVP® in mild hemophilia A
- factor VIII concentrate for:
  - prophylaxis (recommended for patients with severe hemophilia A)
  - on-demand (i.e. to treat a bleed)
- antifibrinolytic agents (e.g. tranexamic acid), especially for mucosal bleeds

Hemophilia B (Factor IX Deficiency)

- X-linked recessive, 1 in 30000 males; approximately half have severe disease (factor IX activity <1% of normal)
- clinical and laboratory features identical to hemophilia A (except deficiency in factor IX instead of factor VIII)
- treatment: factor IX concentrate (prophylaxis or on-demand), antifibrinolytic agents

Factor XI Deficiency

- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild (severe spontaneous bleeding is rare), often diagnosed in adulthood following bleeding challenge (e.g. surgery)
- factor XI level does not correlate proportionally with bleeding risk – risk of bleeding correlates with a previous history or family history of bleeding
- treatment: antifibrinolytic agents, FP, Factor XI concentrate, DDAVP®

Liver Disease

- see Gastroenterology, G32

Pathophysiology
- thrombocytopenia secondary to: hypersplenism, nutritional deficiency, direct BM toxicity related to alcohol, diminished production from chronic viral infections (e.g. HCV), and decreased production of TPO
- deficiency in synthesis of all factors except VIII (also made in endothelium)
- aberrant or diminished synthesis of fibrinogen (factor I)
- diminished synthesis of natural anticoagulants and altered regulation of fibrinolysis

Investigations
- CBC, peripheral blood film: thrombocytopenia, target cells
- primary hemostasis affected
  - thrombocytopenia
- secondary hemostasis affected
  - elevated INR (PT), PTT, TT
  - low fibrinogen in end-stage liver disease



Investigations in Liver Disease
Factor V, VII, VIII. Expect decreased V and VII because they have the shortest half-life. Factor VIII will be normal or increased because it is produced in the endothelium

Treatment
- supportive, treat liver disease, blood products if active bleeding (FP, platelets, cryoprecipitate)

Vitamin K Deficiency

Etiology
- drugs
  - vitamin K antagonist (e.g. warfarin) – diminished production of functional Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet: e.g. prolonged fasting or starvation (especially due to chronic alcohol consumption)
- biliary obstruction
- chronic liver disease (decreased stores)
- fat malabsorption (e.g. celiac disease, disorders of bile or pancreatic secretion, intestinal disease, and cystic fibrosis)



Vitamin K Dependent Factors
Vitamin K antagonists (e.g. warfarin) affect function of these factors:
"1972 Canada vs. **S**oviets"
X, IX, VII, II, proteins **C** and **S**



PT should improve within 24 h of adequately dosed vitamin K repletion (onset is in 6-12 h); if not, search for other causes

Investigations
- INR (PT) is elevated out of proportion to elevation of the PTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

Treatment
- hold anticoagulant if vitamin K antagonist on board
- vitamin K PO if no active bleeding
- if bleeding, give vitamin K 10 mg IV (reversal may take up to 12 h)
- if life-threatening bleeding and vitamin K antagonist used, give PCC or FP if PCC contraindicated
  - PCCs are relatively contraindicated in liver disease or if there is a previous history of HIT (PCC product contains heparin)

American Society of Hematology Choosing Wisely Recommendation
Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (e.g. outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery)

Disseminated Intravascular Coagulation

Definition
- excessive, dysregulated release of plasmin and thrombin leading to intravascular coagulation and fibrinolysis
- depletion of platelets, coagulation factors, and fibrinogen
- risk of life-threatening hemorrhage and/or thrombosis

Etiology
- occurs as a complication of many other severe medical, surgical, or obstetrical conditions
- widespread endothelial damage and extensive inflammatory cytokine release

DIC is a spectrum which may include thrombosis, bleeding, or both

Clinical Features
- presence of both hemorrhage and clotting

Table 27. Clinical Features of DIC

Signs of Microvascular Thrombosis	Signs of Hemorrhagic Diathesis
Neurological: multifocal infarcts, delirium, coma, seizures **Skin:** focal ischemia, superficial gangrene, purpura fulminans **Renal:** oliguria, azotemia, cortical necrosis **Pulmonary:** ARDS **GI:** acute ulceration, liver dysfunction **Adrenal failure:** adrenal hemorrhage or infarction **RBC:** microangiopathic hemolysis (schistocytes)	**General:** Bleeding from any site in the body (secondary to decreased platelets and coagulation factors) **Neurologic:** intracranial bleeding **Skin:** petechiae, ecchymosis, oozing from puncture sites **Renal:** hematuria **Mucosal:** gingival oozing, epistaxis, massive bleeding

Factor Levels in Acquired Coagulopathies

Factor	Liver Disease	Vitamin K Def	DIC
V	↓	N	↓
VII	↓	↓	↓
VIII	N/↑	N	↓

Investigations
- peripheral blood smear: schistocytes
- primary hemostasis: CBC, decreased platelets
- secondary hemostasis: prolonged INR (PT), PTT, TT, decreased fibrinogen and other factors
- accelerated fibrinolysis: increased FDPs or D-dimers and short euglobulin lysis time

Important Etiologies of DIC

OMITS
Obstetric complications
Malignancy
Infection
Trauma
Shock

Treatment
- individualize supportive therapy according to underlying condition: recognize early and treat underlying disorder – supportive measures: hemodynamic and/or ventilator support, aggressive hydration, and RBC transfusion if severe bleed
- in bleeding phase (recommendations from ISTH Guidance Statement 2013):
  - treat the underlying condition
  - transfuse platelets in patients with active bleeding if platelet count $<50 \times 10^9$/L or in those with a high-risk of bleeding and a platelet count of $<20 \times 10^9$/L
  - FP may be useful in patients with active bleeding with either prolonged PT/aPTT (>1.5 times normal). FP should be considered in DIC patients requiring an invasive procedure with similar laboratory abnormalities
  - fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with persisting severe hypofibrinogenemia (<1.5 g/L)
  - PCC may be considered in actively bleeding patients if FP transfusion is not possible
- in thrombotic phase:
  - LMWH preferred over UFH in critically ill, non-bleeding patients

Clinical Prediction of DIC - International Society of Thrombosis and Hemostasis (ISTH) Calculator
Presence of an underlying, predisposing condition is a requirement

DIC diagnosis is defined as ≥5 points

Points	0	1	2	3
Platelet count x 10^9/L	>100	50-100	<50	
Level of Fibrin markers (D-dimer or FDP)	No increase		Moderate increase <5 x ULN	Strong increase ≥5 x ULN
Prolonged PT (s)	<3	≥3-6	≥6	
Fibrinogen (g/L)	>1.0	≤1.0		

Table 28. Differential Diagnosis for Abnormal Coagulation Testing

Increased PT/INR Only	Increased PTT Only	Both Increased
Warfarin Vitamin K deficiency Factor VII deficiency Liver disease Factor VII inhibitors	Intrinsic factor deficiency: Factor VIII (Hemophilia A), Factor IX (Hemophilia B), Factor XI, Factor XII Heparin, DOACs Antiphospholipid Ab Intrinsic factor inhibitors (e.g. Factor VIII)	Deficiency of common pathway factors: Prothrombin (Factor II), fibrinogen, Factor V, Factor X Severe liver disease Factor V, Factor X, prothrombin, and fibrinogen inhibitors Excessive anticoagulation Severe vitamin K deficiency

Hypercoagulable Disorders

Hypercoagulability Workup – Venous Thrombosis

- workup for hypercoagulable state should be considered *ONLY* if it will alter treatment decisions
- includes inherited or acquired thrombophilia
  - hypercoagulability workup may be considered in patients with:
    - multiple recurrent thromboses
    - warfarin-induced skin necrosis or neonatal purpura fulminans (protein C or S deficiency)
    - thrombosis at an unusual venous site
    - abnormal blood work, constitutional symptoms, or physical exam findings suggestive of cancer
  - arterial thrombotic events due to a hypercoagulable state are typically associated with APS, HIT, JAK2+ MPNs, and PNH, not hereditary thrombophilias
- workup (if indicated)
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function tests, urinalysis, and hemolysis markers (if anemic)
    - malignancy history, age appropriate cancer screening
    - serology: APLA (lupus anticoagulant will be affected by anticoagulation)
    - depending on CBC, consider JAK2
  - post-treatment (or ≥6 wk, as protein levels are depleted/consumed by clot and can be affected by anticoagulation)
    - antithrombin activity
    - proteins C, S activity
- note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state
- decision to pursue hypercoagulability workup should be made in consultation with a hematologist

SELECTED CAUSES OF HYPERCOAGULABILITY

Factor V Leiden (Activated Protein C Resistance)

- most common cause of hereditary thrombophilia
- 3-7% of European White population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Prothrombin Gene Mutation (PT) G20210A

- 1-3% of European White population are heterozygotes
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency

- protein C inactivates Factors Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous or compound heterozygous: neonatal purpura fulminans
  - heterozygous
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin, and certain chemotherapeutic agents
  - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, and warfarin

Antithrombin Deficiency

- antithrombin slowly inactivates thrombin, a process accelerated by heparin
- causes/etiology: autosomal dominant inheritance, urinary losses in nephrotic syndrome, or reduced synthesis in liver disease
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to UFH (LMWH may be considered, with monitoring of anti-Xa levels)
  - heparin resistance: suspect if >35000 IU of UFH required during 24 h use

Elevated Factor VIII Levels

- an independent marker of increased incident and recurrent thrombotic risk, but levels can also be increased in numerous states as an acute phase reactant, therefore its clinical use is controversial



Differential Diagnosis of Elevated D-Dimer

- Arterial thromboembolic disease (e.g. MI, cerebrovascular accident, acute limb ischemia, AFib, intracardiac thrombus)
- Venous thromboembolic disease (e.g. DVT, PE)
- Abnormal fibrinolysis (e.g. use of thrombolytic agents)
- Surgery/trauma (e.g. tissue ischemia, necrosis)
- Vaso-occlusive episode of SCD
- Renal disease (nephrotic syndrome, acute/chronic renal failure)
- Pregnancy-related (e.g. normal pregnancy, preeclampsia, eclampsia)
- Cardiovascular-related (e.g. cardiovascular disease, CHF)
- Severe infection/sepsis/inflammation, systemic inflammatory response syndrome
- DIC
- Malignancy
- Severe liver disease
- Venous malformation



Isolated prolonged INR is most commonly due to Factor VII deficiency in the extrinsic pathway since it has the shortest half-life
Isolated elevated PTT is usually due to factor deficiency or inhibitors in the intrinsic pathway



American Society of Hematology Choosing Wisely Recommendations

1. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (i.e. surgery, trauma, or prolonged immobility)
2. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism



Common Causes of Hypercoagulability

CALM APES
Protein **C** deficiency
APS
Factor **V** Leiden
Malignancy
Antithrombin deficiency
Prothrombin G20210A
Increased Factor **VIII** (Eight)
Protein **S** deficiency



Causes of Both Venous and Arterial Thrombosis include:
APS
MPN
HIT
Distal venous clot with patent foramen ovale
PNH



Protein C, protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, they must be tested outside of this time period

Congenital Dysfibrinogenemia
- may predispose to thromboembolic disease, bleeding, or both

Disorders of Fibrinolysis
- includes congenital plasminogen deficiency, and tPA deficiency, but association with VTE risk is not clear

Antiphospholipid Antibody Syndrome
- definition: ≥1 clinical and ≥1 laboratory criteria
  - clinical: arterial or venous thrombosis, recurrent (>3) early pregnancy losses <10 wk, one late fetal loss ≥10 wk (morphologically normal), or premature birth before 34 wk due to (pre)eclampsia or placental insufficiency
  - laboratory (must be confirmed on two occasions, tested ≥12 wk apart): anticardiolipin IgG and IgM, anti-β2 glycoprotein-I Ab, or lupus anticoagulant
- mechanism: not well understood, Abs interact with platelet membrane phospholipids causing increased activation; can also interfere with thrombin regulation, fibrinolysis, and inhibit the protein C pathway
- see Rheumatology, RH13

Venous Thromboembolism

Definition
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- includes superficial vein thrombosis , DVT, and PE
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- DVT is more common in lower extremity than upper extremity (upper extremity DVT are increasing due to more central venous access lines)
- incidence ~1% if age >60 yr
- most important sequelae of DVT are PE (~50% chance with proximal DVT) and post thrombotic syndrome (chronic venous insufficiency)
- acutely, PE can result in cardiorespiratory failure and death (rare in treated patients). Most severe chronic sequela of PE is chronic thromboembolic pulmonary hypertension (CTEPH)

Etiology (Virchow's Triad)
- endothelial damage
  - exposure of procoagulant proteins on dysfunctional endothelium promotes thrombosis
  - decreased inhibition of coagulation and local fibrinolysis
  - changes to vessel wall integrity may result in turbulent blood flow
- venous stasis
  - immobilization (e.g. post-MI, CHF, stroke, and postoperative) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see *Hypercoagulable Disorders, H35*)
  - acquired
  - age (risk increases with age)
  - surgery (especially orthopedic, thoracic, GI, and GU)
  - trauma (especially fractures of spine, pelvis, femur, or tibia, and spinal cord injury)
  - neoplasms (especially pancreas, stomach, lung, lymphoma, bladder, testicular, colorectal, and gynecologic - based on the Khorana score)
  - blood dyscrasias (MPNs, especially PV, ET), PNH, hyperviscosity (multiple myeloma, polycythemia, leukemia, and SCD), hemolytic anemias
  - prolonged immobilization (e.g. CHF, stroke, MI, and leg injury)
  - hormone related (combined OCP, hormone replacement therapy, and selective estrogen receptor modulators)
  - pregnancy
  - APS
  - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
    - New York Heart Association (NYHA) Class III and IV
- idiopathic (10-20% are later found to have cancer)

Clinical Features of DVT
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness; purple-blue colour may indicate severe limb-threatening thrombus
- palpable cord (i.e. thrombosed vein)
- phlegmasia alba dolens (white appearance) and phlegmasia cerula dolens (acute pain and edema) with massive thrombosis
- Homan's sign (pain or resistance with foot dorsiflexion) is unreliable

Differential Diagnosis of DVT
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, and arterial occlusive disease



Malignancy is a Common Cause of Acquired Hypercoagulability

Workup should include:
Complete history and physical
Age appropriate screening:
Mammogram, Pap, PSA, colonoscopy
Additional imaging/laboratory testing based on clinical suspicion
Close follow-up



Screening for Occult Cancer in Unprovoked VTE (SOME)

NEJM 2015;373:697-704

Purpose: To assess the efficacy of a screening program for occult cancer that employs CT of the abdomen and pelvis in patients experiencing their first unprovoked episode of VTE.

Methods: Patients (n=854) were randomly assigned to limited occult-cancer screening or limited occult-cancer screening plus CT.

Results: 3.2% of patients in the limited-screening group and 4.5% of patients in the limited-screening plus CT group received a new diagnosis of occult cancer between the randomization point and 1-year followup (P=0.28). Four occult cancers were missed by the limited screening strategy, while five occult cancers were missed by the limited screening plus CT strategy (P=1.0).

Conclusion: Routine screening with CT in patients who had a first unprovoked VTE did not provide a clinically significant benefit.



Although lupus anticoagulant prolongs PTT, this is a misnomer, as its main clinical feature is thrombosis



Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy

Risk Factor	RR (95% CI)	P-value
Age >75 yr	1.79 (1.18-2.71)	0.007
Cancer	1.58 (1.01-2.51)	
Previous VTE	1.67 (1.01-2.77)	0.08
Obesity	0.94 (0.59-1.51)	0.91
Hormone therapy	0.51 (0.08-3.38)	0.70
Heart failure	1.08 (0.72-1.62)	0.82
NYHA III	0.89 (0.55-1.43)	0.72
NYHA IV	1.48 (0.84-2.6)	0.27
Acute infectious disease	1.50 (1.00-2.26)	0.06
Acute rheumatic disease	1.45 (0.84-2.50)	0.27

Source: JAMA 2004;164:963-968



Virchow's Triad
Endothelial damage
Blood stasis
Hypercoagulability

Investigations for DVT

- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease (Modified Wells' Pre-test Probability ≤1) and no other acute medical issues; positive result may be non-specific
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- venography is the gold standard, but is expensive, invasive, and higher risk
- CT pulmonary angiogram or V/Q scan if PE suspected

Post-Thrombotic Syndrome

- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, and venous ulcers
- clinical severity can be assessed using the Villalta score
- large impact on quality of life following a DVT
- treatment: extremity elevation, exercise, compression stockings, and skin/ulcer care
- for clinical features and treatment of PE, see Respirology, R20

Approach to Treatment of Venous Thromboembolism

Purpose

- prevent further clot extension (minimum 3 mo duration)
- prevent acute PE (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications (e.g. post-thrombotic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary HTN)

Initial Treatment

- consider empiric treatment in patient with moderate/high suspicion of DVT and low-risk of bleeding, if diagnostic imaging will be delayed (definitive imaging should be obtained at first opportunity)
- DOACs
  - apixaban or rivaroxaban alone (with loading dose)
  - dabigatran or edoxaban require 5-10 d of parenteral anticoagulation (usually LMWH) prior to initiation
  - contraindications: during conception/pregnancy, and in breastfeeding women
  - there remains limited evidence in severe renal deficiency and some clinicians do not use DOACs in this population
- LMWH
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule, lab monitoring not required, <1% HIT, safe and effective outpatient therapy (including pregnant and cancer patients)
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renally cleared – may require dose adjustment in patients with renal dysfunction
- UFH
  - in patients with high-risk of bleed, or requiring rapid interruption for surgical procedures; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT or heparin levels with adjustment of dose to reach therapeutic level (~2x normal value); higher risk for development of HIT

Long-Term Oral Treatment

- anticoagulation therapy
  - warfarin
    - should be initiated with heparin overlap: dual therapy for at least 48 h with INR >2, due to initial prothrombotic state (secondary to warfarin's inhibition of natural anticoagulants protein C/S), half-life of vitamin K factors and risk of warfarin-induced skin necrosis
    - dosed to maintain INR at 2-3, monitor twice weekly for 1-2 wk
    - discontinue heparin after INR >2.0 for 2 consecutive days
  - DOACs
    - apixaban or rivaroxaban: INR not used, patients with CrCl >15 mL/min
    - dabigatran (factor IIa inhibitor) or edoxaban: LMWH or IV heparin for at least 5 d before initiating dabigatran, INR not used, patients with CrCl >15 mL/min (Edoxaban) and >30 mL/min (Dabigatran)
    - important drug interactions to consider for DOACs: inducers or inhibitors of CYP3A4 or P-gp
    - cancer patients: LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients; DOACs are as effective as LMWH (more bleeding observed for patients with GI cancer taking rivaroxaban or edoxaban)

Wells' Score for Predicting DVT

- Paralysis, paresis, or recent orthopedic casting of lower extremity (1)
- Recently bedridden (>3 d) or major surgery within past 4 wk (1)
- Localized tenderness in deep vein system (1)
- Swelling of entire leg (1)
- Calf swelling >3 cm compared to the other leg (measured 10 cm below the tibial tuberosity) (1)
- Pitting edema greater in the symptomatic leg (1)
- Collateral non-varicose superficial veins (1)
- Active cancer or cancer treated within 6 mo (1)
- Alternative diagnosis more likely than DVT (e.g. Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis) (-2)

Total Score Interpretation
3-8: High probability, 1-2: Moderate probability, -2-0: Low probability

Modified Wells' Score
Same as above except with 1 additional point for a history of DVT or major surgery within past 12 wk, and the score interpretation is DVT likely for ≥2 points and DVT unlikely for ≤1 point. D-dimer is ordered for DVT unlikely patients to fully rule out DVT which can help reduce unnecessary ultrasounds

See Landmark Hematology Trials for more information on the CLOT trial. It details the efficacy of low-molecular-weight heparin vs. oral anticoagulant agents in preventing recurrent thrombosis in patients with cancer.

Duration of Treatment with Vitamin K Antagonists (VKA) in Symptomatic Venous Thromboembolism
Cochrane DB Syst Rev 2014;CD001367
Purpose: To evaluate the efficacy and safety of various durations of therapy with VKA in patients with symptomatic VTE.
Study Selection: RCTs comparing various durations of therapy with VKA in patients with symptomatic VTE.
Results: 11 studies (total 3716 participants) were included. A significant reduction in the risk of recurrent VTE was observed during prolonged VKA treatment (RR 0.20, 95% CI, 0.11 to 0.38) independent of the time elapsed since the index thrombotic event. Patients receiving prolonged treatment were at increased risk of bleeding complications (RR 2.60, 95% CI 1.51 to 4.49).
Conclusion: Treatment with VKA strongly reduces the risk of recurrent VTE for as long as they are used. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time).

Common Medications that Interact with Warfarin
Acetaminophen (interference with vitamin K metabolism)
Allopurinol
NSAIDs (GI injury)
Fluconazole
Metronidazole
Sulfamethoxazole
Tamoxifen

  - LMWH
    - typically reserved as long term therapy for patients unable to tolerate oral anticoagulants (e.g. unable to absorb oral medications, high risk bleeding patients with intraluminal GI malignancy)
- duration of anticoagulant treatment
  - provoked VTE with transient risk factor: 3 mo
  - provoked VTE with ongoing risk factor: consider indefinite therapy with annual reassessment
  - first unprovoked proximal DVT or PE: ≥3 mo, consider indefinite therapy with annual reassessment
  - second unprovoked VTE: consider indefinite therapy if not already on
  - cancer-associated DVT: consider indefinite therapy for as long as patient has active malignancy (in patients who have cancer in remission, anticoagulation is usually extended for 3-6 mo post last treatment)
  - inferior vena cava filters
  - temporary filter indicated only if acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding) or if anticoagulation must be interrupted (i.e. for urgent surgery)
  - must be retrieved once safe to do so as filter is pro-thrombotic in the long-term and associated with other complications (migration of filter, etc.)
- special considerations
  - pregnancy: treat with LMWH during pregnancy, then LMWH or warfarin for 6 wk post-partum (minimum total anticoagulation time of 3-6 mo, but must include 6 wk post-partum, as this is a high-risk period)
  - avoid warfarin in pregnancy due to teratogenicity outside of select patient populations (e.g. may be used by some thrombosis experts during the second and third trimesters in women with mechanical heart valves)
  - avoid DOAC in conception and pregnancy (due to lack of data) and if breastfeeding in postpartum period
  - surgery: avoid elective surgery in the first 3 mo after a venous thromboembolic event
    - preoperatively: IV heparin may be used up to 4-6 h preoperatively
    - warfarin or DOACs discontinued for at least 2-5 d preoperatively (consider mechanism of drug clearance)
    - postoperatively: IV heparin, LMWH, DOAC can be used for anticoagulation (consult with surgeon prior to re-initiation)
    - for patients at high-risk for thromboembolism (VTE <12 wk, recurrent VTE, APS, AFib with prior stroke, and mechanical heart valve), IV heparin or LMWH (bridging) may be considered before and after the procedure while the INR is below 2.0. Bridging not required for DOACs

In Hospital Prophylaxis

- consider for those with a moderate to high-risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), and intermittent pneumatic compression (IPC)
- LMWH as per hospital protocol (e.g. enoxaparin 40 mg SC once daily, dalteparin 5000 U SC once daily), or rarely UFH 5000 IU SC BID, UFH 5000 IU SC TID
- DOACs for orthopedic surgery thromboprophylaxis

Table 29. Contraindications of Anticoagulant Therapy

Absolute Contraindications to Treatment	Relative Contraindications to Treatment
Active bleeding Severe bleeding diathesis or platelet count <20 x 10^9/L (<20000/mm^3)	Mild-moderate bleeding diathesis or thrombocytopenia Recent major trauma Recent stroke Major abdominal surgery within past 2 d GI/GU bleeding within 1-4 d Endocarditis Neurosurgery or ocular surgery within 10 d

Treatment of Pulmonary Embolism

- see Respirology, R20



Effect of Treatment Delay on the Effectiveness and Safety of Antifibrinolytics in Acute Severe Hemorrhage: a Meta-analysis of Individual Patient-level Data from 40138 Bleeding Patients
Lancet 2018;391:125-132
Purpose: To examine if the effectiveness of antifibrinolytics in reducing death from acute severe hemorrhage is influenced by treatment delay.
Methods: Meta-analysis of individual patient-level data from 2 RCTs with 40138 total patients that investigated the use of tranexamic acid in acute severe bleeding. Treatment benefit was measured by absence of death from bleeding and logistic regression was used to assess the effect of treatment delay.
Results: Overall survival from bleeding was significantly increased by tranexamic acid (OR 1.2; 95% CI 1.08-1.33; P=0.001). Survival was improved by >70% with immediate treatment (OR 1.72, 95% CI 1.42–2.10; P<0.0001). In contrast, treatment benefit was significantly reduced by treatment delay (P<0.0001). Specifically, survival was reduced by 10% for every 15 min delay of treatment until 3 h, at which point no benefit was demonstrated.
Conclusion: Patients with severe acute bleeding should be treated immediately, as even a short delay in treatment reduces the survival benefit of tranexamic acid.



ASCO Clinical Practice Guidelines for VTE Prophylaxis and Treatment in Patients with Cancer
J Clin Oncol 2020;38:496-520
Clinicians can offer thromboprophylaxis (apixaban, rivaroxaban, or LMWH) for:
- High-risk outpatients with cancer
- As options for VTE treatment
- For long-term anticoagulation (min. 6 mo; better efficacy profiles than vitamin K antagonists)
- Throughout hospitalization (patients with cancer and an acute medical condition)
- Major cancer surgery (prophylaxis starting prior and continuing for min. 7-10 d)



Initiation of Warfarin Therapy Requires Bridging with Heparin Therapy for 4-5 Days
10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
Warfarin decreases Factor VII levels in first 48 h, INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~4 d)



Low-Risk Surgical Patients
<40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal, or thoracic surgery

Moderate-Risk Surgical Patients
>40 yr, >1 risk factor for VTE, GA >30 min

High-Risk Surgical Patients
>40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency, or other risk factors

High-Risk Medical Patients
Heart failure, severe respiratory disease, ischemic stroke or lower limb paralysis, confined to bed, and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD)

Hematologic Malignancies and Related Disorders

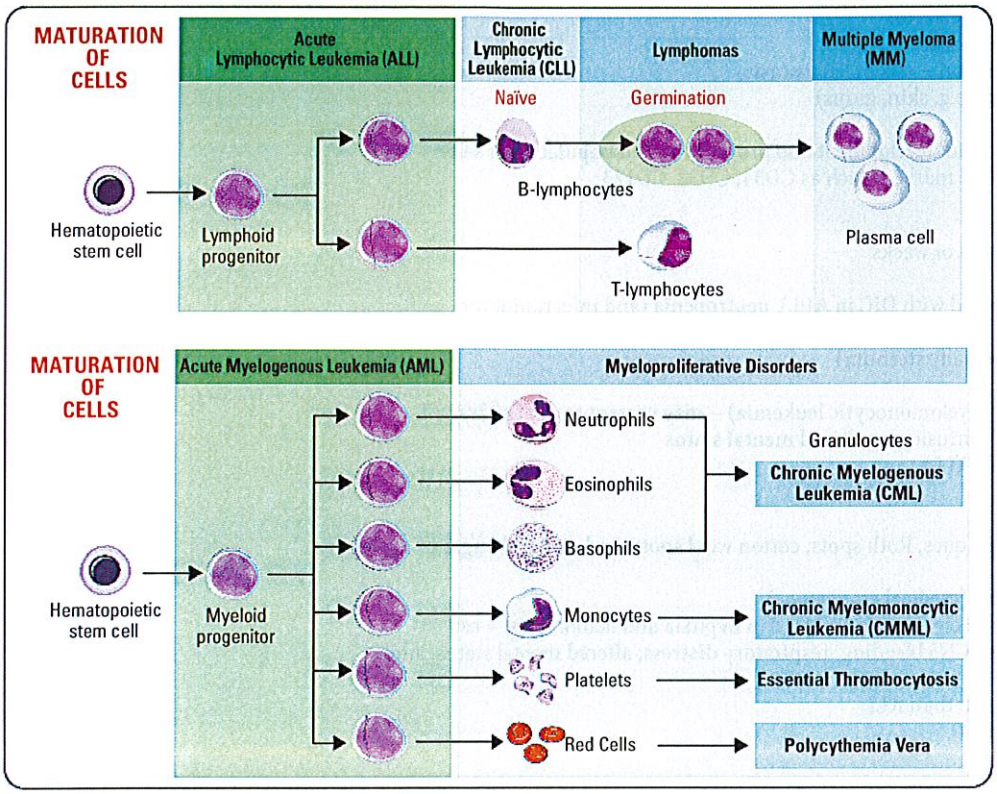


Figure 15. Hematopoietic derivation of hematologic disorders

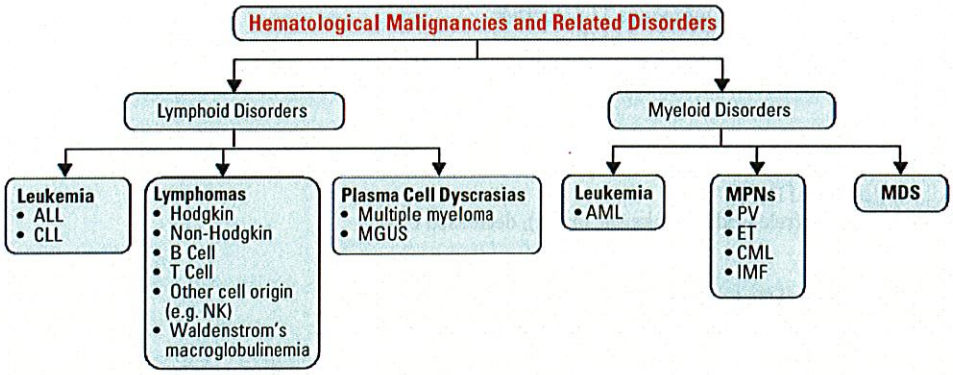


Figure 16. Overview of hematologic malignancies and related disorders

Leukemia: malignant cells arise in BM that may spread elsewhere (including blood, lymph nodes, and lymphoid tissue)
Lymphoma: malignant cells arise in lymph nodes and lymphoid tissues that may spread elsewhere (including blood and BM)
BUT the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes)

Acute Leukemia
Definition (WHO): presence of 20% blast cells or greater in the peripheral blood or BM at presentation
Classification: divided into myeloid (AML) and lymphoid (ALL) depending on whether blasts are myeloblasts or lymphoblasts, respectively

Typical Age of Presentation of Leukemias
ALL: Children and older adults
CML: 40-60 yr
AML, CLL: >60 yr

Auer rods are pathognomonic for AML

Basic Initial Workup for all Hematologic Malignancies:
1. ALL WOMEN OF CHILDBEARING AGE must have a b-HCG before initiation of treatment of any cancer diagnosis
2. ALL PATIENTS MUST HAVE Hepatitis B surface antibody (HBsAb), Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb) collected irrespective of cancer diagnosis and must be treated to avoid reactivation
3. All aggressive lymphoma patients must be screened for HIV
4. All patients must be screened for TB risk factors

Cure: survival that parallels age-matched population
Complete Remission: tumour load below threshold of detectable disease (normal peripheral blood film, normal BM with <5% blasts, normal clinical state)

Myeloid Malignancies

Acute Myeloid Leukemia

Definition
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

Epidemiology
- incidence increases with age; median age of onset is 65 yr; accounts for 80% of acute adult leukemias
- accounts for 10-15% of childhood leukemias

Risk Factors
- male, older age, smoking, obesity, MDS, benzene, radiation, Down syndrome, alkylating agents, and radiation therapy as treatment for previous malignancy

Pathophysiology

- etiology subdivided into:
  - primary: *de novo*
  - secondary: prior hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood – risk of leukostasis
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; TLS
- cancer stem cells thought to play key role in development and progression, subpopulation of self-renewing cancer cells with unique surface markers such as CD34, CD38, CD123

Clinical Features

- signs and symptoms develop over a period of weeks
- manifestations of BM failure
  - anemia, thrombocytopenia (associated with DIC in APL), neutropenia (and infection/fever)
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - CNS extramedullary involvement: confusion or altered mental status
  - hepatosplenomegaly (also present in ALL)
  - lymphadenopathy
  - skin: leukemia cutis
  - eyes: hemorrhages and/or whitish plaques, Roth spots, cotton wool spots, and vision changes (uncommon)
- leukostasis/hyperleukocytosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, and priapism
  - more commonly associated with AML than ALL
- metabolic effects (aggravated by treatment)
  - TLS
    - increased uric acid → nephropathy, gout
    - release of phosphate → decreased Ca^{2+}, decreased Mg^{2+}
    - release of procoagulants → DIC (higher risk in APL)
  - hyperkalemia pre-treatment from blastic proliferation and spontaneous TLS, further hyperkalemia after treatment (from lysed cells). Note – some forms of AML can present with hypokalemia due to secreted muramidase that causes K+ wasting from renal tubules

Investigations

- blood work
  - CBC: anemia, thrombocytopenia, variable WBC (most often cytopenias + blasts)
  - INR up, aPTT up, FDP up, fibrinogen down (in case of DIC)
  - increased LDH, increased uric acid, increased PO_4^{3-} (released by leukemic blasts), decreased Ca^{2+}, increased/decreased K^+
  - baseline renal and liver function tests
  - if considering treatment: screen for HBV, HCV, HIV, CMV serology
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- BM aspirate for definitive diagnosis
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytogenetic, and/or immunophenotypic features are used to establish lineage and maturation
- CXR to rule out pneumonia; ECG, MUGA scan prior to chemotherapy (cardiotoxic)

Treatment

- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
- patients who are not eligible for intensive chemotherapy can be treated with low-dose cytarabine and hypomethylating agents in combination with venetoclax (BCL-2 inhibitor)
- all AML subtypes are treated similarly, except APL with t(15:17) translocation
  1. **induction**: chemotherapy to induce complete remission of AML
     - several possible regimens
     - patients with poor response to initial induction therapy – worse prognosis
     - supportive care - management of TLS and DIC, febrile neutropenia/infections, transfusion support (including platelet transfusions if $<10 \times 10^9$/L)
  2. **consolidation**: to prevent recurrence
     - intensive consolidation chemotherapy

    - stem cell transplantation – allogeneic (younger patients with better performance status and/or adverse cytogenetics)
- supportive care
  - fever: pan-cultures, CXR, and start broad-spectrum antibiotics
  - platelet and RBC transfusions
  - prevention and treatment of metabolic abnormalities
    - allopurinol, rasburicase for prevention/management of hyperuricemia
  - leukostasis
    - needs immediate cytoreductive therapy (i.e. hydroxyurea)
  - treatment strategy for APL
    - APL is an emergency as DIC is often present at diagnosis
    - ATRA added to induce differentiation (should be started ASAP if APL is in the differential); arsenic trioxide and ATRA combination therapy for APL is superior to traditional chemotherapy

Prognosis
- achievement of first remission
  - 70-80% if ≤60 y/o, 50% if >60 y/o
  - median survival 12-24 mo
  - prognosis depends on cytogenetics, age, performance status, prior cytotoxic agents, or radiation therapy

Myelodysplastic Syndromes

Definition
- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias and a variable risk of transformation to acute leukemias
- syndromes defined according to WHO classifications

Pathophysiology
- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in BM (usually hypercellular); formed elements sometimes exhibit morphological and functional defects
- intramedullary apoptosis: programmed cell death within BM
- both processes lead to reduced mature cells in periphery
- <30% develop AML

Risk Factors
- elderly, post-chemotherapy, exposures (benzene, tobacco, radiation), inherited genetic abnormalities
- incidence: 50 persons per million per year, rises to 200-400 per million per year for age 70 or older

Clinical Features
- highly variable, commonly presents with symptoms of anemia (fatigue and dyspnea), thrombocytopenia (bruising, bleeding, or petechiae), and neutropenia (recurrent infections) over months-years

Investigations
- diagnosed by:
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bi-lobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size, and cytoplasm (e.g. giant hypogranular platelets)
- BM aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - BM: dysplastic and often normocellular/hypercellular
  - cytogenetics: high-risk (partial or total loss of chromosome 7) and complex (>3 abnormalities)

Treatment
- low-risk of transformation to acute leukemia (Revised International Prognostic Scoring System (IPSS-R) Very Low or Low)
  - EPO stimulating agents weekly is first line in reducing transfusion requirements (EPO level must be <500 IU/L)
  - if 5q deletion based on cytogenetics: lenalidomide PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high-risk of transformation to acute leukemia (IPSS-R Intermediate, High, or Very High)
  - supportive care (transfusion support)
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacitidine)
  - consider stem cell transplantation according to patient factors (age, frailty, overall health)

Prognosis
- IPSS-R uses 5 factors to estimate mean survival:
  - cytology, % BM blasts, Hb, platelets, and ANC
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High", or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively

Myeloproliferative Neoplasms

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (erythrocytes, platelets, and other cells of myeloid lineage)

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 30. Chronic Myeloproliferative Disorders

	CML	PV	IMF	ET
Hct	↓/N	↑↑	↓	N
WBC	↑↑	↑	↑/↓	N
Plt	↑/↓	↑	↑/↓	↑↑↑
Marrow Fibrosis	±	±	+++	±
Splenomegaly	+++	+	+++	+
Hepatomegaly	+	+	++	–
Genetic Association	BCR-ABL mut.	JAK2 mut. (96%)	JAK2 mut. (~50%) CALR mut. (~30%)	JAK2 mut. (~50%) CALR mut. (~30%)

Use of Epoetin and Darbepoetin in Patients with Cancer
Blood 2008;111:25-41
Clinical practice guideline update by American Societies of Hematology and Clinical Oncology (2010).
Initial Recommendations
1. Initiate an ESA when Hb is 100 g/L (10 g/dL) in patients with palliative chemotherapy-associated anemia to decrease the need for transfusions
2. Discontinue ESAs when patient not responding to treatment beyond 6-8 wk
3. Monitor iron stores and supplement iron intake for ESA-treated patients when necessary
4. Use ESAs cautiously with chemotherapy or in patients with an elevated risk for thromboembolic complications
5. It is not recommended that ESA be used for therapy in patients with cancer who are not receiving chemotherapy as it increases thromboembolic risks and lowers survival rate. Patients with low-risk myelodysplasia are an exception

MDS ineffective maturation
MPN overproduction of mature cells

Basophilia is uncommon in other medical conditions

Chronic Myeloid Leukemia

Definition
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Epidemiology
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

Pathophysiology
- Ph chromosome
  - translocation between chromosomes 9 and 22 is necessary and sufficient to result in CML
  - the c-Abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (BCR) of chromosome 22 to produce BCR-ABL fusion gene, a constitutively active tyrosine kinase

Clinical Features
- 3 clinical phases
  - chronic phase: 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase: impaired neutrophil differentiation
    - circulating blasts (10-20%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia <100 x 10^9/L or thrombocytosis
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - blast crisis: more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or BM; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical features
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever

Chronic Myeloproliferative Neoplasms: 11-Year Follow-Up of Patients Receiving Imatinib for the First-Line Treatment of CML
NEJM 2017;376:917-927
Study: Long-term outcomes of imatinib treatment for chronic myeloid leukemia.
Methods: 1106 patients with Ph-positive CML in the chronic phase were randomized 1:1 to imatinib or interferon alpha plus cytarabine. Crossover to imatinib was allowed if no response by 6 mo or major cytogenetic response by 12 mo.
Results: Assessing the imatinib arm after a median of 11 years of follow-up, the complete cytogenetic response rate was 83%. Among patients who attained a major molecular response after 18 mo of imatinib therapy, the overall survival at 10 years was 93% and freedom from CML-related deaths was 100%.
Conclusion: This 11-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

- secondary to splenic involvement
  - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
  - splenomegaly (most common physical finding)
- anemia
- bleeding: secondary to platelet dysfunction
- pruritus, PUD: secondary to increased blood histamine
- leukostasis, priapism, encephalopathy: secondary to very elevated WBC (rare)

Investigations
- CBC with differential
  - elevated WBCs, decreased/normal RBCs, increased/decreased platelets, increased basophils
  - WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- BM biopsy
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of BM or peripheral blood for Ph chromosome (or BCR-ABL transcripts)
- abdominal imaging for spleen size

Treatment
- **prophylactic**: allopurinol
- **chronic phase**
  - imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for BCR-ABL. 2nd/3rd generation can be used as first line therapy
    - if loss of response or intolerance (~40%), trial of 2nd or 3rd generation TKIs: dasatinib, nilotinib, or bosutinib. Note: ponatinib only provided for the T315I mutation
  - interferon-α: may improve response to TKIs; typically now only used for pregnant patients
  - hydroxyurea in palliative setting to reduce WBCs
- **accelerated phase or blast phase**
  - for imatinib-naive patients, use imatinib
  - refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard induction for acute leukemia
- stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones
- treatment success is monitored based on therapeutic milestones
  - hematologic: improved WBC and platelet counts, reduced basophils
  - cytogenetic: undetectable Ph chromosome in the BM
  - molecular: reduction/absence of BCR-ABL transcripts in periphery and marrow

Prognosis
- survival dependent on response
  - those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  - those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
- acute phase (blast crisis – usually within 3-5 yr of presentation if untreated CML)
  - 2/3 acute phase CML have cellular features similar to AML
    - unresponsive to remission induction
  - 1/3 acute phase CML have cellular features similar to ALL
    - remission induction (return to chronic phase) achievable

Polycythemia Vera

Definition
- stem cell disorder characterized by elevated RBC count (erythrocytosis) ± increased white cell and platelet production
- diagnosis (WHO 2016) requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion
  - Major Criteria
    1. Hb >165 g/L in men, >160 g/L in women, OR Hct >49% in men, >48% in women, OR increased red cell mass (>25% above mean normal predicted value)
    2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
    3. presence of JAK2 V617F or JAK2 exon 12 mutation
  - Minor Criterion
    1. serum EPO level below reference range for normal (must have the first two major criteria if using EPO level)



Erythromelalgia is a pathognomonic microvascular thrombotic complication in PV and ET



Cardiovascular Events and Intensity of Treatment in Polycythemia Vera
NEJM 2013;368:22-33
Study: Prospective, RCT, mean follow-up of 28.9 mo. Blinding not described.
Population: 365 patients with JAK2-positive polycythemia vera being treated with phlebotomy, hydroxyurea, or both.
Intervention: Patients were randomized to a target hematocrit <45% (low-hematocrit group) or 45-50% (high-hematocrit group).
Outcome: Composite of time until death from cardiovascular causes of major thrombotic events.
Results: The hazard ratio (HR) for the primary outcome was 3.91 (95% CI 1.45-10.53, P=0.007), while the HR for the primary outcome plus superficial venous thrombosis was 2.69 (95% CI 1.19-6.12, P=0.02) for the high-hematocrit vs. low-hematocrit group.
Conclusions: The hematocrit target of <45% was associated with a lower incidence of CV death, major thrombotic events, and superficial venous thrombosis in patients with polycythemia vera.

Clinical Features
- symptoms are secondary to high red cell mass and hyperviscosity (see *Erythrocytosis, H7*)
- thrombotic complications: DVT, PE, Budd-Chiari (hepatic vein thrombosis), portal vein thrombosis, thrombophlebitis, increased incidence of stroke/TIA, and MI
  - due to increased blood viscosity, increased platelet number, and/or activity
  - bleeding complications: epistaxis, gingival bleeding, ecchymoses, and GI bleeding
  - if high platelet counts: associated with acquired VWD (although seen more with ET)
- erythromelalgia (burning pain in hands and feet and erythema of the skin)
  - associated with platelets >400 x 10^9/L
  - pathognomonic microvascular thrombotic complication in PV and ET
- pruritus, especially after warm bath or shower (40%) due to cutaneous mast cell degranulation and histamine release
- epigastric distress, PUD
  - due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
- gout (hyperuricemia), due to increased cell turnover
- characteristic physical findings
  - plethora (ruddy complexion) of face (70%), palms
  - splenomegaly (70%), hepatomegaly (40%)

Investigations *(see Erythrocytosis, H7)*
- must rule out secondary polycythemia if high EPO level

Treatment
- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- ruxolitinib for those with insufficient response or intolerance to hydroxyurea
- low-dose ASA (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

Prognosis
- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Idiopathic Myelofibrosis

Definition
- excessive BM fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood, and hepatosplenomegaly

Epidemiology
- rare, median age at presentation is 65 yr

Pathophysiology
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (see below)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

Clinical Features
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety and severe left upper quadrant pain
- hepatomegaly (70%) → may develop portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Investigations
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B12 (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- molecular test: JAK2 (70%) and CALR(25%) mutations
- BM aspirate: "dry tap" in as many as 50% of patients (no marrow spicules aspirated)
- BM biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)



Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera
NEJM 2004;350:114-124
Study: Double-blind, placebo-controlled, RCT.
Participants: 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.
Intervention: Patients received either low-dose ASA 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 yr.
Primary Outcome: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus PE and major venous thrombosis.
Results: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; P=0.09 and RR 0.4; P=0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.
Conclusion: Low-dose ASA can safely prevent thrombotic complications in patients with PV.



Ruxolitinib Versus Standard Therapy for the Treatment of Polycythemia Vera
NEJM 2015;372:426-35
Purpose: To evaluate the efficacy and safety of ruxolitinib vs. standard therapy in patients with PV who had insufficient responses or intolerable side effects with hydroxyurea.
Methods: 222 phlebotomy-dependent patients with splenomegaly were randomly assigned to receive ruxolitinib or standard therapy.
Primary Outcome: Hematocrit control through week 32 and spleen volume reduced ≥35% at week 32.
Results: 21% of patients on ruxolitinib vs. 1% of those on standard-therapy achieved the primary outcome (P<0.001). 60% of patients on ruxolitinib and 20% on standard therapy achieved hematocrit control. ≥35% reduction in spleen volume was seen in 38% and 1% of patients in the two groups, respectively. Compared to standard-therapy, ruxolitinib was associated with a significantly greater rate of complete hematologic remission (24% vs. 9%; P=0.003).
Conclusion: Ruxolitinib was superior to standard therapy in controlling hematocrit, reducing the spleen volume, and improving symptoms associated with PV in patients who had insufficient responses or intolerable side effects with hydroxyurea.



Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET



A "leukoerythroblastic" blood film (RBC and granulocyte precursors) implies BM infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF)



IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells)

Treatment
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors (ruxolitinib, fedratinib, or hydroxyurea)
- symptomatic treatment
  - transfusion for anemia
  - EPO: 30-50% of patients respond
  - androgens for anemia (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, and systemic symptoms
    - interferon-α (as second line therapy)
    - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis and symptomatic splenomegaly

Prognosis
- Dynamic International Prognostic Scoring System (DIPSS) Plus for IMF uses 5 risk factors along with karyotype, platelet count, and transfusion status to predict survival
  - presence of constitutional symptoms; age >65; Hb <100 g/L; leukocyte count >25000/mm ^{3}; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as "low", "intermediate 1", "intermediate 2", or "high" with a mean survival of 185, 78, 35, and 16 mo, respectively
  - eligible patients with intermediate 2 or high risk DIPSS are considered for allogeneic stem cell transplant
- risk of transformation to AML (8-10%)



A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis
NEJM 2012;366:799-807
Study: Double-blinded RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo.
Outcome: Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.
Results: A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 0.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (45% vs. 5.3%) and less mortality (13 vs. 24). There was no difference in rate of discontinuation due to adverse events (11.0% vs. 10.6%) but anemia and thrombocytopenia were more common with ruxolitinib.
Conclusions: Ruxolitinib reduced spleen size, and improved symptoms and survival, compared with placebo.

Essential Thrombocythemia

Definition
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia

Epidemiology
- increases with age; F:M=2:1, → F=M at older

Diagnosis (2008 WHO Criteria Revised in 2016) requires meeting all four criteria
1. sustained platelet count >450 x 10^9/L
2. BM biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. not meeting WHO criteria for PV, primary myelofibrosis, BCR-ABL CML, or MDS or other myeloid neoplasms
4. most patients have a mutation in JAK2 V617F, CALR, or MPL. A minority (~10%) have a mutation in some other gene, which causes proliferation (hence "clonal marker")

Clinical Features
- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets >1000 x 10^9/L)
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies or VWD studies
- JAK2 (and other) mutational assays
- BM hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased K^+, increased PO_4^{3-} (2° to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment
- low dose ASA
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st-line therapy), anagrelide, interferon-α, or 32P (age >80 or lifespan <10 yr)



Etiology of Secondary Thrombocythemia
Infection
Inflammation (IBD, arthritis)
Malignancy
Hemorrhage
Iron deficiency
Hemolytic anemia
Post-splenectomy
Post-chemotherapy
Drugs (vinca alkaloids)



There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count; treatment includes observation, ASA, sulfinpyrazone, or dipyridamole

Lymphoid Malignancies

Acute Lymphoblastic Leukemia

75% of ALL occurs in children <6 yr; second peak at age 40

Definition
- malignant disease of the BM in which early lymphoid precursors proliferate and replace normal hematopoietic cells
- WHO subdivides ALL into two types depending on cell of origin
  - 1. B-cell: precursor B lymphoblastic leukemia
  - 2. T-cell: precursor T lymphoblastic leukemia
- the French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged as morphology is not prognostic

Clinical Features
- see *Acute Myeloid Leukemia, H39* for full list of symptoms
- distinguish ALL from AML based on *Table 32*
- clinical symptoms usually secondary to:
  - BM failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), and thrombocytopenia
  - organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations
- >20% BM or peripheral blood lymphoblasts, with samples collected for flow cytometry, cytogenetics, and molecular studies
- Ph chromosome in ~25% of adult ALL cases
- CBC: increased leukocytes >100 x 10^9/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- screen for TLS: increased uric acid, K^+, PO_4^{3-}, low Ca^{2+}, high LDH
- screen for DIC: PT, aPTT, fibrinogen
- CXR: patients with ALL may have a mediastinal mass
- CT C/A/P and testicular ultrasound to screen for extranodal disease
- mandatory lumbar puncture to assess for CNS involvement (ensure adequate platelet count and PT/PTT and delay until blasts have cleared from peripheral blood) at the time treatment is initiated
- HIV, HBV, HCV serologies, CMV Ab testing

Treatment
- eliminate abnormal clonal cells
  1. induction chemotherapy: to induce complete remission, <5% blasts (restore normal hematopoiesis)
  2. consolidation and/or intensification of chemotherapy
     - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
     - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. maintenance chemotherapy: low dose intermittent chemotherapy over prolonged period (1 yr) to prevent relapse
  4. prophylaxis: CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation (for certain indications): potentially curative (due to pre-transplant myeloablative chemoradiation and post-transplant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high
  - if BCR-ABL positive, tyrosine kinase inhibitors started up front and given continuously
  - in relapse setting, CAR T-cell therapy, inotuzumab, or blinatumomab
- CAR T-cell therapy
  - extraction of patient's own T-cells, genetic modification of T-cells to produce Chimeric Antigen Receptors (CARs) that recognize antigens presented selectively on cancer cell surface (often CD19 in ALL)
  - most effective in treating diffuse large B-cell lymphoma and CD19-positive ALL
  - first approved in Canada in 2018, currently of limited utility in treating other types of hematologic malignancies and solid tumours

Treatment of ALL vs. AML
No proven benefit of maintenance chemotherapy in AML
No routine CNS prophylaxis in AML

Prognosis
- depends on response to initial induction, minimal residual disease testing, or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x 10^9/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 75% long-term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of BCR-ABL fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5 yr survival

Table 31. Differentiating AML From ALL

AML	ALL
Big people (adults)	Small people (kids)
Big blasts	Small blasts
Big mortality rate	Small mortality rate (kids)
Lots of cytoplasm	Less cytoplasm
Lots of nucleoli (3-5)	Few nucleoli (1-3)
Lots of granules and Auer rods	No granules and no Auer rods
Myeloperoxidase, Sudan black stain	PAS (periodic acid-Schiff)
Maturation defect beyond myeloblast or promyelocyte	Maturation defect beyond lymphoblast



To Differentiate AML from ALL: Remember Big and SmALL

Lymphomas

Definition

- collection of lymphoid malignancies in which malignant lymphocytes accumulate in lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease, and constitutional symptoms



American Society of Hematology Choosing Wisely Recommendation
Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma

Table 32. Ann Arbor System for Staging Lymphomas

Stage	Description
I	Involvement of a single lymph node region or extralymphatic organ/site (Stage IE)
II	Involvement of ≥2 lymph node regions or an extralymphatic site and ≥1 lymph node regions on same side of diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Diffuse involvement of one or more extralymphatic organs including BM

- subtypes
  A = absence of B-symptoms (*see Approach to Lymphadenopathy, H12*)
  B = presence of B-symptoms



- Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma
- Prognostic scores are different for indolent vs. aggressive lymphomas
- Highly aggressive lymphomas act like acute leukemias

Table 33. Chromosome Translocations

Translocation	Gene Activation	Associated Neoplasm
t(2;5)	ALK1 mutation	Anaplastic large cell lymphoma
t(8;14)	c-Myc activation	Burkitt's lymphoma
t(14;18)	Bcl-2 activation	Follicular lymphoma
t(11;14)	Overexpression of cyclin D1 protein	Mantle cell lymphoma
t(11;18)	MALT1 activation	Mucosa-associated lymphoid tissue (MALT)

Hodgkin Lymphoma

Definition

- malignant proliferation of lymphoid cells with Reed-Sternberg cells



Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells

Epidemiology

- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases and causal role not determined

Clinical Features

- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with superior vena cava syndrome and pleural effusion
- systemic symptoms
  - B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C, or night sweats for ≥2 wk without evidence of infection), extreme fatigue especially in widespread disease, and pruritus
- non-specific/paraneoplastic
- starts at a single site in lymphatic system (node) and spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system



Hodgkin lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region

Investigations

- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, lymphopenia, platelets normal or increased in early disease, and decreased in advanced disease

- biochemistry
  - HIV, HBV, HCV serologies
  - liver enzymes and/or LFTs (liver involvement)
  - renal function tests (prior to initiating chemotherapy)
  - ALP, Ca^{2+}(bone involvement)
  - ESR (prognosis), LDH (staging, monitor disease progression)
- imaging
  - CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), and PET scan
  - cardiac function assessment (MUGA scan or echocardiography): for patients at high-risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, and previous radiation to lung)
- excisional lymph node or core biopsy confirms diagnosis
- BM biopsy to assess marrow infiltration (only necessary if B-symptoms, PET positive marrow on imaging, or cytopenia)

Treatment

- stage I-II: chemotherapy (ABVD (adriamycin, bleomycin, vinblastine, dacarbazine)) followed by involved field or involved site radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD, Brentuximab-AVD, or BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone)) ± XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy and autologous stem cell transplant, anti-CD30 Ab therapy
  - PET scan results essential in assessing disease response



Treatment of HL depends on stage; treatment of NHL depends on histologic subtype

Complications of Treatment

- cardiac disease: secondary to XRT, adriamycin cardiomyopathy (1% of patients)
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: <3% with ABVD (important to discuss sperm banking/egg retrieval prior to initiation of chemotherapy)
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumours of lung or breast (>8 yr after treatment)
  - non-Hodgkin lymphoma
- hypothyroidism: post XRT

Prognosis

- Hasenclever adverse prognostic factors:
  1. serum albumin <40 g/L
  2. Hb <105 g/L
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >15 x 10^9/L)
  7. lymphocytopenia (lymphocytes <0.06 x 10^9/L or <8% of WBC count or both)
- each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)



International Prognostic Factors Project 1998

Prognostic Factors	FFP
0	84%
1	77%
2	67%
3	60%
4	51%
5-7	42%

FFP = freedom from progression at 5 yr

Non-Hodgkin Lymphoma

Definition

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

Classification

- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, and mantle cell lymphoma
  - WHO/REAL classification system: 3 categories of NHLs based on natural history
    1. indolent (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, and mantle cell lymphoma
    2. aggressive (~50% of NHL): e.g. diffuse large B-cell lymphoma
    3. highly aggressive (~5% of NHL): e.g. Burkitt's lymphoma
  - T-cell NHL: e.g. mycosis fungoides (indolent TCL of the skin), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), and anaplastic large cell lymphoma

Clinical Features

- painless superficial lymphadenopathy, usually >1 lymph node region, rapid growth in aggressive lymphomas
- can have localized or widespread adenopathy (more common in indolent NHL)
- constitutional symptoms are less common in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when BM is involved
- abdominal signs ± hepatosplenomegaly, retroperitoneal, and mesenteric involvement

- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract, testes, bone, and kidney
- CNS involvement in 1% (often with HIV, testicular DLBCL, or >2 extranodal sites)

Investigations

- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia rare (more common in CLL)
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic blood film
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood only if lymphocytosis is present
- biochemistries, HIV, HBV, HCV serologies
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease and poor prognostic factor)
- SPEP and immunoglobulin quantitation (screen for high IgM monoclonal protein and hyperviscosity in indolent lymphomas, specifically lymphoplasmacytic lymphoma)
- staging: CT neck, chest, abdomen, pelvis, and BM biopsy
- PET imaging pre- and post-therapy to ensure post treatment remission
- diagnosed by:
  - lymph node biopsy: excisional biopsy is preferred, core biopsy (FNA is unreliable)
  - BM biopsy: sub-optimal mode of diagnosis as BM is involved in only 30% of high-grade lymphomas

Treatment

- indolent NHL, localized disease (e.g. stage I or II)
  - radiotherapy to primary site and adjacent nodal areas
  - splenectomy: splenic marginal zone lymphoma
- goal of treatment in stage III or IV indolent NHL is symptom management
  - watchful waiting
  - radiation therapy for localized symptomatic disease
  - bendamustine plus rituximab, an anti-CD20 Ab, is superior to CHOP and rituximab (CHOP-R) for advanced stage disease
  - obinutuzumab (novel anti-CD20 Ab) is superior to rituximab for advanced stage follicular lymphoma (GALLIUM Trial)
- aggressive lymphoma: goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (e.g. testes)
  - relapse, resistant to therapy: high dose chemotherapy, autologous SCT, CAR T-cell therapy in second relapse
- highly aggressive lymphoma
  - Burkitt lymphoma: short bursts of intensive chemotherapy; "CODOX-M" chemotherapy regimen also often used ± IVAC with rituximab
  - CNS prophylaxis and (TLS) prophylaxis



NHL: Associated Conditions
Immunodeficiency (e.g. HIV)
Autoimmune diseases (e.g. SLE)
Infections (e.g. EBV)



Common Chemotherapeutic Regimens
R-CHOP: cyclophosphamide, hydroxydoxorubicin (Adriamycin®), vincristine (Oncovin®), prednisone
ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone

Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- bowel perforation
- (TLS particularly in very aggressive lymphoma); see *Tumour Lysis Syndrome, H54*

Prognosis

- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used: age >60; >4 nodal areas; >6 cm nodal areas; elevated LDH; Lugano stage III-IV; Hb <120 g/L; high β-2 microglobulin; BM involvement
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrod 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - ~40% rate of cure

Table 34. Characteristics of Select Non-Hodgkin Lymphomas

	Follicular Lymphoma	DLBCL	Burkitt Lymphoma	Mantle Cell Lymphoma
Percentage of NHLs	22-30%	33%	<1% adult NHLs 30% childhood NHLs	6%
Genetic Mutation	Bcl-2 activation	Bcl-2, Bcl-6, Myc rearrangements	c-Myc activation	Overexpression of cyclin D1 (Bcl-1 activation)
Classification	Indolent	Aggressive (high-grade)	Very aggressive	Indolent
Risk Factors	Middle-age – elderly	Previous CLL (Richter's transformation: 5% CLL patients progress to DLBCL)	Endemic: African origin, EBV-associated Sporadic: no EBV HIV-related: AIDS-defining illness	Male (M:F=4:1)
Clinical Features	Widespread painless LAD* ± BM involvement Frequent transformation to aggressive lymphoma Very responsive to chemoradiation treatment	Rapidly progressive LAD and extranodal infiltration 50% present at stage I/II, 50% widely disseminated	Endemic form: massive jaw LAD "Starry-sky" histology High-risk of tumour lysis syndrome upon treatment	Often presents as stage IV with palpable LAD Involvement of GI tract (lymphomatous polyposis), Waldeyer's Ring 5 yr survival 25% B symptoms present in ⅓ of patients

Malignant Clonal Proliferations of Mature B-Cells

Table 35. Characteristics of B-Cell Malignant Proliferation

	CLL	Lymphoplasmacytic Lymphoma	Myeloma
Cell Type	Lymphocyte	Plasmacytoid	Plasma cell
Protein	IgM if present	IgM	IgG, A, light chain (rarely M, D, or E)
Lymph Nodes	Very common	Common	Rare
Hepatosplenomegaly	Common	Common	Rare
Bone Lesions	Rare	Rare	Common
Hypercalcemia	Rare	Rare	Common
Renal Failure	Rare	Rare	Common
Immunoglobulin Complications	Common	Rare	Rare



Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality)

Chronic Lymphocytic Leukemia



Definition
- indolent disease characterized by clonal malignancy of mature B-cells

Epidemiology
- most common leukemia in Western world
- mainly older patients; median age 70 yr
- M>F

Pathophysiology
- accumulation of neoplastic lymphocytes in blood, BM, lymph nodes, and spleen

Clinical Features
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C, or night sweats for ≥2 wk without evidence of infection), extreme fatigue
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (DAT positive), ITP, hypogammaglobulinemia ± neutropenia
- BM failure: late, secondary to marrow involvement by CLL cells

Investigations
- CBC: clonal population of B lymphocytes >5 x 10^9/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry characteristics of peripheral blood
  - CD5, CD20dim, CD23, light chain restriction
- cytogenetics: FISH (dictates response to therapy and prognosis) imaging must be done post-therapy to ensure post treatment remission

- BM aspirate
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis), or mixed (25%)

Natural History and Treatment

- natural history: indolent and incurable; most cases show slow progression
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- first line therapy is dictated by cytogenetic status and patient co-morbidities
  - observation if early, stable, asymptomatic
    - treatment options vary by region; commonly fludarabine + cyclophosphamide + rituximab (FCR) in fit patients age <65, with normal creatinine clearance and lack of 17p deletion/p53 disease
    - chlorambucil (or venetoclax + obinutuzumab in the elderly)
    - ibrutinib or acalabrutinib in patients with unmutated IgVH and/or 17p deletion/p53 positivity
  - autoimmune phenomena: corticosteroids, rituximab
  - radiotherapy for isolated bulky nodes
- molecular therapies
  - idelalisib – PI3K inhibitor
  - ibrutinib, acalabrutinib – BTK (Bruton's tyrosine kinase) inhibitor
  - venetoclax – Bcl-2 inhibitor



Smudge cells are artifacts of damaged lymphocytes from slide preparation

Prognosis

- 9 yr median survival, but varies greatly
- prognosis: Rai staging, Binet staging or Revised CLL International Prognostic Index (includes age >65, Rai/Binet stage, B2M, IGHV mutation status, 17p del or TP53 mutation positivity)

Complications

- BM failure
- immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia and impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see *Table 35, H50*)

Multiple Myeloma



Definition

- neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
- usually a single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory
- preceded by smoldering myeloma or MGUS



Multiple Myeloma

SLiM CRAB
Sixty percent plasma cells in BM specimen
Light chain ratio >100
MRI lytic lesion >0.5 cm
Calcium >2.80 mmol/L
Renal failure (Cr >176 mmol/L)
Anemia
Bony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)

Epidemiology

- incidence 3 in 100000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68 yr; M>F

Pathophysiology

- malignant plasma cells secrete monoclonal Ab
  - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    - IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    - 15-20% produce free light chains or light chains alone found in either:
      - serum has an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      - urine has Bence-Jones protein
  - <5% are non-secretors



Amyloid
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues
Found in a variety of clinical disorders and can cause systemic (e.g. MM (light chains)) or localized amyloidosis (e.g. Alzheimer disease (AB amyloid))

Clinical Features and Complications

- bone disease: pain (usually back), bony tenderness, pathologic fractures
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia: weakness, fatigue, pallor
  - secondary to BM suppression
- weight loss
- infections
  - usually *S. pneumoniae* and Gram-negatives
  - secondary to suppression of normal plasma cell function
- hypercalcemia: N/V, confusion, constipation, polyuria, and polydipsia
  - secondary to increased bone turnover

- renal disease/renal failure
  - most frequently causes cast nephropathy (see Nephrology, NP36)
- bleeding
  - secondary to thrombocytopenia, may see petechiae, purpura
  - can also be caused by acquired VWD
- extramedullary plasmacytoma
  - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity: may manifest as headaches, stroke, angina, and MI
  - rare in MM as secondary to increased viscosity caused by IgM protein (more common in WM/LPL)
- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease: muscle weakness, pain, and paresthesias
  - radiculopathy caused by vertebral fracture and extramedullary plasmacytoma
  - spinal cord compression (10-20% of patients) is a medical emergency

Investigations

- CBC
  - normocytic anemia, thrombocytopenia, and leukopenia
  - rouleaux formation on peripheral film
- biochemistry
  - increased Ca^{2+}, increased ESR, decreased anion gap, increased Cr, albumin, β2-microglobulin, and LDH (as part of staging), and proteinuria (24 h urine collection)
- monoclonal proteins
  - SPEP: demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - UPEP: demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- BM aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for fluorescence in situ hybridization (FISH) or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression, PET imaging to pick up lytic lesions in asymptomatic MM
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- elevated β2-microglobulin and LDH, and low albumin, are poor prognosticators
  - HBV surface and core Abs, and HBV surface antigen



Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis



Light Chain Disease

- 15% of MM produce only light chains
- Renal failure is a major problem
- Kappa > lambda light chain has better prognosis



Serum Free Light Chain Ratio is an Independent Risk Factor for Progression in MGUS
Blood 2005;106:812-817

Purpose: To determine whether the presence of monoclonal free kappa or lambda immunoglobulin light chains in MGUS increases the risk of progression to malignancy.

Methods: Retrospective study with median follow-up of 15 yr. Baseline serum samples obtained from 1383 MGUS patients seen at the Mayo clinic between 1960-1994. 1148 baseline samples were obtained within 30 d of diagnosis.

Results: Malignant progression had occurred in 87 (7.6%) patients. In 379 (33%) patients, an abnormal serum free light chain (FLC) ratio was detected. There was a significantly higher risk of progression in patients with an abnormal FLC ratio relative to patients with a normal ratio (hazard ratio, 3.5; 95% CI 2.3-5.5; P<0.001). This finding was independent of the size and type of the serum monoclonal (M) protein. In high-risk MGUS patients (abnormal serum FLC ratio, non-IgG MGUS, high serum M protein level [≥1.5 gm/dL]), the risk of progression at 20 yr was 58% compared to 37% in high-intermediate-risk MGUS (two risk factors), 21% low-intermediate risk (with one risk factor), and 5% low-risk (no risk factors).

Conclusions: The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. The low-risk subset of patients with MGUS accounts for 40% of all MGUS patients and have a small lifetime risk of progression, thus less follow-up can be justified.

Diagnosis

- International Myeloma Working Group Criteria ("SLiM CRAB"):
  - ≥60% clonal plasma cells on BM examination
  - light chain ratio (free, involved/uninvolved) of ≥100 in the blood (involved must be at least 100 mg/L)
  - MRI with more than one bone lesion (≥5 mm)
  - CRAB – presence of end-organ damage related to plasma cell dyscrasia, such as:
    - increased serum Ca^{2+}
    - renal failure
    - anemia
    - lytic bone lesions

Treatment

- non-curative
- treatment goals
  - improvement in quality of life (improve anemia, reverse renal failure, prevent fractures)
  - prevention of progression and complications
  - increase overall survival
- autologous transplant if ≤70 yr
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents (i.e. IMIDs or PIs)
- transplant ineligible if >70 yr or comorbidities
  - pending on patient comorbidities can include a combination of: melphalan, prednisone, cyclophosphamide, PI (i.e. bortezomib), IMIDs (revlimid), anti-CD38 agents (e.g. daratumumab)
- supportive management
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, EPO for anemia, and DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities, and preferences

Prognosis
- International Staging System (ISS) (β2-microglobulin and albumin) used to stage and estimate prognosis
- revised ISS for risk stratification: combination of original ISS, cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy), and LDH
- median survival based on stage, usually 5-10 yr

Monoclonal Gammopathy of Unknown Significance

Definition
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr
  - asymptomatic

Diagnosis
- presence of a serum monoclonal protein (M protein) at a concentration <30 g/L
- <10% plasma cells in BM
- absence of SLiM CRAB
- 0.3-1% of patients develop a hematologic malignancy each yr
  - patients with M protein peak ≥15 g/L, abnormal free light chain ratio, or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with history q6-12 mo, physical, CBC, Cr, calcium, albumin, LDH, and SPEP (considered pre-malignant)

Lymphoplasmacytic Lymphoma

Definition
- LPL/Waldenstrom's macroglobulinemia
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

Clinical Features
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, and cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, and retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) are large and confined mainly to intravascular space

Investigations and Diagnosis
- BM shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely shows hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, and high ESR if hyperviscosity not present
- HBV, HCV serologies (note: can be associated with HCV; HCV eradication can put LPL into remission)



Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome

Treatment
- chemotherapy + rituximab (most commonly bendamustine + rituximab)
- if HCV positive – treat HCV prior to a trial of chemotherapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

Definition
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum Igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

Clinical Features
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, and stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

Treatment
- plasmapheresis, chemotherapy

Tumour Lysis Syndrome

Definition
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, acute leukemia)

Clinical Features
- metabolic abnormalities
  - cells lyse, releasing K^+, uric acid, PO_4^{3-} (increased levels)
  - PO_4^{3-} binds Ca^{2+} (decreased Ca^{2+})
- complications
  - lethal cardiac arrhythmia (increased K^+)
  - acute kidney injury (formerly known as renal failure) see Nephrology, NP21

Treatment
- prevention
  - aggressive IV hydration
  - alkalinization not recommended due to risk of calcium phosphate or xanthine precipitation in renal tubules
  - allopurinol (prevents uric acid accumulation) or rasburicase (lowers existing uric acid)
  - correction of pre-existing metabolic abnormalities
- dialysis

Blood Products and Transfusions

Blood Products

- RBCs, platelets, and coagulation factors (FP, cryoprecipitate, fibrinogen concentrate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and plasma
  - plasma is further fractionated
    - need to pool multiple units of platelets and WBCs to obtain therapeutic amounts
    - FP (previously known as FFP) is plasma frozen within 24 h of collection
    - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures
  - single donor platelets and plasma can also be obtained by apheresis donations

Specialized Products
- irradiated blood products
  - prevent proliferation of donor T-cells in recipients at risk of GVHD
  - used for patients with severe T-cell immunodeficiency, on purine analogue chemotherapy, with Hodgkin lymphoma, candidates for BM transplant, or receiving directed transfusions from first-degree relatives, HLA-matched products, or intrauterine transfusions
- CMV-negative blood products
  - seronegative pregnant women
  - intrauterine transfusions

Blood Groups

Group	Antigen (on RBC)	Antibody (in serum)
O	H	Anti-A, anti-B
A	A	Anti-B
B	B	Anti-A
AB	A and B	Nil

In Canada, blood products are leukodepleted via filtration immediately after donation; therefore it is considered:
- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV safe (because CMV is found in leukocytes)

Red Blood Cells

Packed Red Blood Cells
- stored at 4°C
- shelf life is 42 d after collection
- infuse each unit over 2 h (max of 4 h)

1 unit of pRBC will increase Hb by approximately 10 g/L

Indications for Packed RBC Transfusion

- Hb <70 g/L; this may change as per patient's tolerance or symptoms
  - maintain Hb between 70 and 90 g/L during active bleeds
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding

American Society of Hematology Choosing Wisely Recommendation
Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe Hb range (70-80 g/L) in stable non-cardiac patients

Selection of Red Cells for Transfusion

- when anticipating an RBC transfusion, the following should be ordered:
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of auto- or alloantibodies against major/minor blood group antigens in the patient's plasma
  - cross-match: involves mixing the recipient's blood with potential donor blood and looking for agglutination (takes 30-45 min)
- when blood is required, several options are available
  - 1st-line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2nd-line: donor blood of the same group and Rh status as the recipient
  - 3rd-line: O- blood for females of reproductive age; O +blood for all others

Platelets

Table 36. Platelet Products

Product	Indication
Random Donor (Pooled)	Thrombocytopenia with bleeding
Single Donor Platelets	Potential BMT recipients. Refractory to pooled platelets
HLA Matched Platelets	Refractory to pooled or single donor platelets, presence of HLA Abs

See Landmark Hematology Trials for more information on the FOCUS trial. It details the efficacy of liberal or restrictive transfusion in high-risk patients after hip surgery

- stored at 20-24°C
- random donor platelets come in a pool of 4 units; while a unit of apheresis platelets comes from a single donor
- 1 platelet pool should increase the platelet count by ≥15 x 10^9/L
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies (Anti-HLA or Anti-HPA), consumption (bleeding, sepsis, DIC), or hypersplenism may be present

Table 37. Indications for Platelet Transfusion

Plt (x 10^9/L)	Indications
<10	Non-immune thrombocytopenia
<20	Procedures not associated with significant blood loss
<50	Procedures associated with blood loss or major surgery (>500 mL estimated blood loss)
<100	Pre-neurosurgery or head trauma
Any	Platelet dysfunction (or antiplatelet agents) and marked bleeding

Relative Contraindications of Platelet Transfusion

- TTP, HIT, post-transfusion purpura, and HELLP

Coagulation Factors

Table 38. Coagulation Factor Products

Product	Indication
FP	Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose when factor concentrates are not available
Cryoprecipitate (enriched fibrinogen, VWF, VIII, XIII)	Hemophilia A (Factor VIII deficiency) and von Willebrand disease – use in emergencies when specific factor concentrates are not available Hypofibrinogenemia
Fibrinogen Concentrate (FC)	Hypofibrinogenemia
Humate P or Wilate	von Willebrand disease and Hemophilia A
Factor VIII concentrate	Factor VIII deficiency (Hemophilia A)
Factor IX concentrate	Factor IX deficiency (Hemophilia B)
Recombinant factor VIIa	Factor VII deficiency with bleeding/surgery, Hemophilia A or B with inhibitors, Glanzmann's thrombasthenia
Prothrombin complex concentrate; PCC (Octaplex®, Beriplex®)	Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (<6 h) surgical procedure, urgent non-specific "reversal" of direct Xa inhibitors
Activated prothrombin complex concentrate; aPCC (FEIBA)	Hemophilia A or B with inhibitors

Group & Screen vs. Cross-Matching:
G&S: ABO group + Rh factor
Cross-Matching: match recipient's serum with donor's packed RBC or Abs

Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions
- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1/40000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - send new specimen to blood bank for repeat testing and draw hemolysis labs: CBC, bilirubin, LDH, reticulocytes, DAT
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions
- due to alloantibodies to WBC, platelets, or other donor plasma antigens, and release of cytokines from blood product cells
- occurs within 6 h of transfusion
- risk per unit of blood is 1/100 (minor), 1/10000 to 40000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia
- look for serious symptoms of shaking, chills/rigors, hypotension, tachycardia, anxiety, dyspnea, back/chest pain, N/V
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <39°C and no serious symptoms, continue with transfusion but decrease rate and give antipyretics
  - if temperature ≥39°C or presence of serious symptoms, stop transfusion, investigate the reaction, and start supportive measures

Allergic Nonhemolytic Transfusion Reactions
- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1/100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension (1/40000)
- can occur in some IgA deficient patients with anti-IgA
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenydramine, steroids, epinephrine, IV fluids, and bronchodilators

Transfusion-Related Acute Lung Injury
- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - profound hypoxemia (PaO_2/FiO_2 <300 mmHg)
  - bilateral pulmonary edema on imaging
  - no clinical evidence of left atrial hypertension or if present, judged not to be the main contributor
- pathogenesis uncertain; perhaps due to binding of donor Abs to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post-transfusion and resolves in 24-72 h
- risk per unit of blood is 1/10000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
- inform blood bank; patient and donor testing will be arranged

NONIMMUNE

Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessively rapid transfusion
- presentation: dyspnea, orthopnea, hypertension, tachycardia, crackles at base of lungs, and increased venous pressure
- incidence: 1/100
- risk factors: age >70 yr, heart failure, history of MI, renal failure, positive fluid balance
- treatment: stop transfusion, give diuretics, and oxygen. Transfuse at lower rate ± diuretics to prevent

DDx of Post-Transfusion Fever
Acute hemolytic transfusion reaction
Febrile non-hemolytic transfusion reaction (FNHTR)
Bacterial contamination
Allergy

DDx of Post-Transfusion Dyspnea
Transfusion-associated circulatory overload (TACO)
Transfusion-related acute lung injury (TRALI)
Allergy (bronchospasm/anaphylaxis)

Bacterial Infection
- Gram-positive: *S. aureus, S. epidermidis, Bacillus cereus*
- Gram-negative: *Klebsiella, Serratia, Pseudomonas, Yersinia*
- overall risk is 1/100000 for RBC and 1/10000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Hyperkalemia
- due to K^+ release from stored RBC
- risk increases with storage time and if blood is irradiated; decreases with fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP15

Citrate Toxicity
- occurs with massive transfusion and in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca^{2+} and causes signs and symptoms of hypocalcemia and exacerbates coagulopathy
- treatment: IV calcium gluconate 1 g

Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no coagulation factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FP, cryoprecipitate, and platelets

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of Ab at time of transfusion is too low to be detected and to cause hemolysis; Ab levels increase later due to secondary stimulus and causes extravascular hemolysis
- occurs 3-14 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion
- N.B. serologic transfusion reactions are the development of alloantibodies in the absence of frank hemolysis



Allogeneic SCT GVHD
To reduce risk of GVHD development after allogeneic SCT, administer inhibitors of T-cell activation, including cyclosporin A or tacrolimus

Transfusion-Associated Graft Versus Host Disease
- transfused T-lymphocytes recognize and react against "host" (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presentation: fever, diarrhea, liver function abnormalities, and pancytopenia
- can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if no longer requiring blood transfusion and not anemic

Viral Infection Risk
- HBV 1/7000000
- HCV 1/12000000
- HIV 1/20000000
- Human T-lymphotropic virus (HTLV) 1/600000000
- other infections include EBV, CMV, WNV (West Nile virus)

Common Medications

Antiplatelet Therapy

• see *Figure 12a, H27*

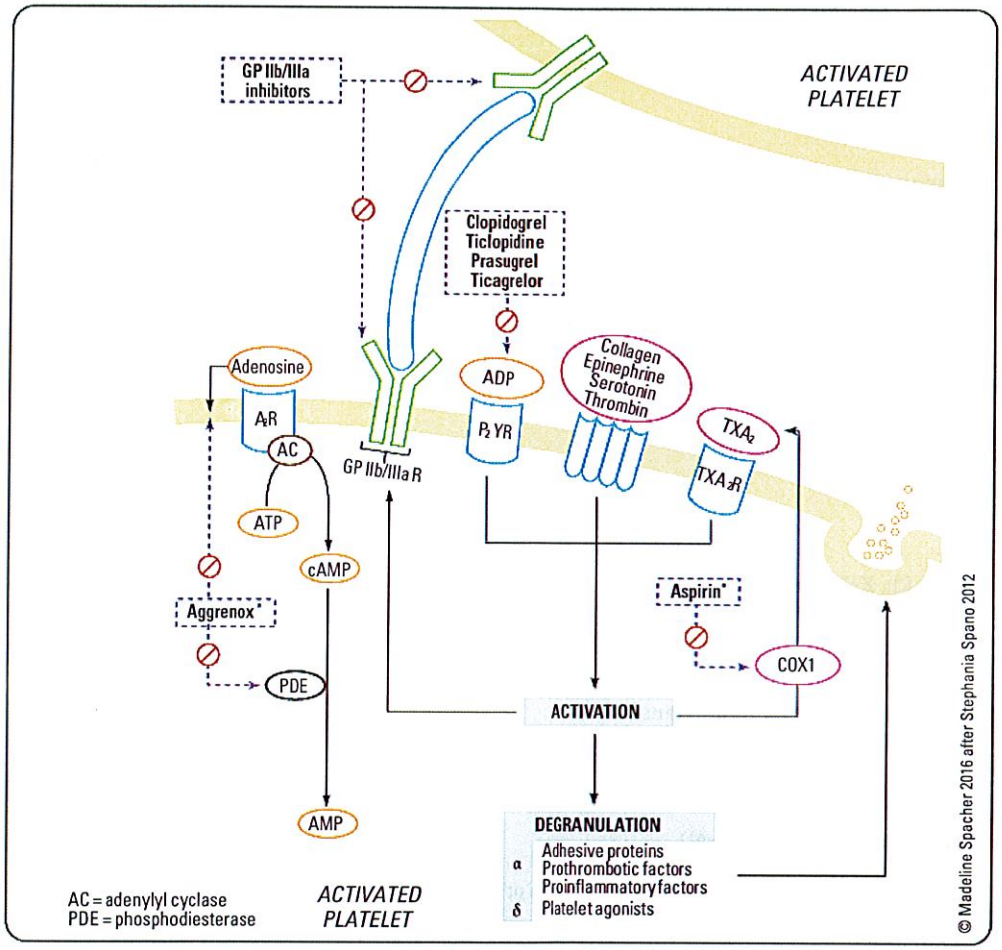


Figure 17. Mechanisms of action of antiplatelet therapy

Table 39. Antiplatelet Therapy

	Mechanism of Action	Typical Dose/ Route of Administration	Onset/Peak/ Duration	Specific Side Effects	Remarks
Aspirin® (ASA)	Irreversibly acetylates COX, inhibiting thromboxane A2 (TXA2) synthesis, thus inhibiting platelet aggregation	Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily	Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h (platelet inhibition lasts 7-10 d)	GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye's syndrome in pediatric patients	Indicated for stroke/MI prophylaxis Reduce incidence of recurrent MI Decrease mortality in post-MI patients Contraindicated in patients with GI ulcers
Aggrenox® (ASA + Dipyridamole)	Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation	1 capsule PO BID	Peak: 75 min	H/A Dyspepsia N/V Abdominal pain Cardiac failure Hemorrhoids	More effective than ASA in secondary prevention of stroke Dipyridamole potentiates antiplatelet action of ASA
Clopidogrel (Plavix®)	Irreversibility inhibits ADP binding to platelets, thus decreasing platelet aggregation	Loading dose 300 mg PO, then 75 mg daily	Onset: 2 h (loading dose) Peak: 6 h (loading dose) Duration: 5 d	URI Chest pain H/A Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia May cause TTP	Prevention of cardiovascular events in high-risk patients Clopidogrel is a prodrug requiring two-step activation to active metabolite CYP2C19 poor metabolizers have diminished response to clopidogrel Caution with hepatic/renal impairment
Prasugrel (Effient®)	Same as clopidogrel	Loading dose 60 mg, then 5-10 mg PO daily	Onset: 30 min (loading dose) Peak: 4 h (loading dose) Duration: 5-10 d	Dizziness H/A Nervousness Blurry vision	Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients Higher potency compared to clopidogrel No significant drug-drug interactions, although more data is required

Table 39. Antiplatelet Therapy

	Mechanism of Action	Typical Dose/ Route of Administration	Onset/Peak/ Duration	Specific Side Effects	Remarks
Ticagrelor (Brilinta®)	Reversibly inhibits ADP binding to platelets	Loading dose 180 mg, then 90 mg PO BID	Onset: 30 min (loading dose) Peak: 1.5 h for prodrug, 2.5 h for active metabolite	Difficulty or laboured breathing Shortness of breath Tightness in chest Dizziness	Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients Higher potency compared to clopidogrel Ticagrelor does not need metabolic activation to serve its antiplatelet function Drug-drug interactions with CYP3A4 inhibitors and inducers Prasugrel is a prodrug requiring metabolic activation mainly by CYP3A5 and CYP2B6
Glycoprotein IIb/IIIa Inhibitors Reopro® (abciximab), Integrilin® (eptifibatide)	Blocking GPIbII/IIIa receptor inhibits fibrinogen and VWF binding, leading to decreased platelet aggregation	Variable IV	Variable	Hypotension Back pain N/V Chest pain Abdominal pain Thrombocytopenia	Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time

Anticoagulant Therapy

Table 40. Anticoagulant Therapy

	Mechanism of Action	Dose/Route of Administration	Onset/Peak/ Duration	Reversing Agent	Monitoring	Specific Side Effects	Remarks
Heparin	Inhibition of Factor Xa and Factor IIa, mediated via antithrombin	Variable, depends on indication; can be used IV or SC	Onset: Immediate (IV); 20-30 min (SC)	Protamine sulfate	aPTT (intrinsic pathway), UFH (anti-Xa) levels	Hemorrhage HIT Increased liver enzymes	Pregnancy: safe (does not cross placenta)
Warfarin	Vitamin K antagonist: inhibits production of Factors II, VII, IX, X, proteins C and S	Individualized dosing by monitoring PT/INR; PO	Onset: 24-72 h Peak: 5-7 d Duration: 2-5 d	Vitamin K PCC FP	INR: maintain 2-3 (2.5-3.5 for certain mechanical valves)	Hemorrhage Cholesterol embolism syndrome Intraocular hemorrhage	Pregnancy: not used, can cross placenta (teratogenic)
LMWH (enoxaparin, dalteparin, tinzaparin)	Mainly Factor Xa inhibition, some FIIa inhibition, both mediated via antithrombin	Variable, weight-based dose, depends on indication; SC/IV	Onset: 1-2 h Peak: 3-5 h Duration: 12-24 h	Partial reversibility with protamine sulfate	Anti-Xa levels in pediatrics, extremes of weight, or renal insufficiency	Hemorrhage Fever Increased liver enzymes <1% HIT	Higher bioavailability than heparin Can accumulate in patients with low CrCl (<30 mL/min) Standard treatment of VTE in pregnancy and patients with malignancy
Fondaparinux	Selective Factor Xa inhibition, mediated via antithrombin	Variable SC daily	Onset: 2 h Peak: 2-3 h	Not reversible	None	Anemia Fever Nausea Rash	Long half-life (17-21 h) Contraindicated in renal failure
Rivaroxaban	Direct Factor Xa inhibitor	Variable, depends on indication; PO	Onset: 1-3 h Peak: 1-3 h	Andexanet α	Anti-Xa levels validated for rivaroxaban may be used to detect presence of drug only	Syncope GI hemorrhage Menorrhagia Gastroentritis Cough	Indicated for treatment of acute VTE, secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl>30 mL/min; must be taken with food; contraindicated in mechanical heart valves
Apixaban	Direct Factor Xa inhibitor	PO BID	Onset: 1-3 h Peak: 1-3 h	Andexanet α	Anti-Xa levels validated for apixaban may be used to detect presence of drug only	Hemorrhage Nausea Anemia	Indicated for treatment of acute VTE, secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl >25 ml/min; contraindicated in mechanical heart valves
Edoxaban	Direct Factor Xa inhibitor	PO daily	Onset: 1-2 h Peak: 1-2 h	Andexanet α	Not typically available	Hemorrhage Rash	Indicated for treatment of acute VTE, secondary VTE prevention, stroke prophylaxis in non-valvular AFib; contraindicated in mechanical heart valves; dose reduction in renal insufficiency, avoid in CrCl <15 mL/min
Argatroban	Direct thrombin inhibitor	Variable IV	Onset: 5-10 min Duration: 20-40 min	Not reversible	aPTT	Dyspnea Hypotension Fever	Indicated for treatment of heparin-induced thrombocytopenia, PCI; contraindicated in mechanical heart valves
Dabigatran	Direct thrombin inhibitor	150 mg PO BID	Onset: 1-3 h Peak: 1-3 h	Idarucizumab	Dilute thrombin time may be used to detect presence of drug only; TT also sensitive for drug presence	GI upset Dyspepsia	Indicated for treatment of acute VTE (after 5-10 d parenteral therapy), secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl >30 mL/min; should be stored in original packaging; contraindicated in mechanical heart valves

Adverse Reactions to Heparin

- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- HIT a hematologic emergency associated with venous or arterial thrombosis (see *Table 22, H30*)
- osteoporosis: with long-term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- increased bioavailability compared to unfractionated heparin
- increased duration of action
- SC route of administration

- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30 mL/min) can accumulate LMWH, therefore may need to adjust dose
- only partially reversible with protamine sulfate
- HIT is less common

Table 41. Recommended Management of a Supratherapeutic INR

INR	Bleeding Present	Recommended Action
>Therapeutic to 4.5	No	Lower warfarin dose or omit a dose and resume warfarin at a lower dose when INR is in therapeutic range or no dose reduction needed if INR is minimally prolonged
>4.5 to 10.0	No	Omit the next 1-2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range OR omit a dose and administer oral vitamin K 1-2.5 mg in patients with increased risk of bleeding
>10.0	No	Hold warfarin and administer oral vitamin K 2.5 to 5 mg; monitor INR more frequently and administer more vitamin K as needed; resume warfarin at a lower dose when INR is in therapeutic range
Any	Serious or life threatening	Hold warfarin and administer vitamin K 10 mg by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed

Adapted from: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;(2 suppl):e152S

Chemotherapeutic and Biologic Agents Used in Oncology

Table 42. Selected Chemotherapeutic and Biologic Agents

Class	Example	Mechanism of Action or Target
Alkylating Agent	chlorambucil, cyclophosphamide, melphalan (nitrogen mustards) carboplatin, cisplatin dacarbazine, procarbazine busulfan bendamustine	Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage
Antimetabolites	methotrexate (folic acid antagonist) 6-mercaptopurine, fludarabine (purine antagonist) 5-fluorouracil (5-FU) (pyrimidine antagonist) hydroxyurea cytarabine	Inhibit DNA synthesis
Antibiotics	adriamycin (anthracycline) bleomycin mitomycin C daunorubicin	Interfere with DNA and RNA synthesis
Taxanes	paclitaxel docetaxel	Stabilize microtubules against breakdown once cell division complete
Vinca-alkaloids	vinblastine vincristine vinorelbine	Inhibit microtubule assembly (mitotic spindles), blocking cell division
Topoisomerase Inhibitors	irinotecan, topotecan (topo I) etoposide (topo II)	Interfere with DNA unwinding necessary for normal replication and transcription
Steroids	prednisone dexamethasone	Immunosuppression
Purine Analogues	fludarabine cladribine	Interferes with DNA synthesis
Monoclonal Antibodies	trastuzumab (Herceptin®) bevacizumab (Avastin®) rituximab (Rituxan®), ofatumumab (Arzerra®), obinutuzumab (Gayzva®) cetuximab (Erbitux®) daratumumab	HER2 antagonist VEGF antagonist CD20 antagonist EGFR antagonist CD38 antagonist
Small Molecule Inhibitors	imatinib mesylate (Gleevec®) dasatinib nilotinib bosutinib erlotinib (Tarceva®) gefitinib (Iressa®) bortezomib (Velcade®) sunitinib (Sutent®) ibrutinib (Imbruvica®) idealasib (Zyedlig®) ruxolitinib (Jakavi®) venetoclax lenalidomide, pomalidomide	BCR-ABL inhibitor BCR-ABL inhibitor BCR-ABL inhibitor BCR-ABL inhibitor EGFR antagonist EGFR antagonist 26S proteasome inhibitor VEGFR, PDGFR antagonist BTK inhibitor P13K inhibitor JAK2 inhibitor BCR-ABL inhibitor Bcl-2 inhibitor Immunomodulators
CAR T cell therapy	tisagenlecleucel (Kymriah®) axicabtagene ciloleucel (Yescarta®)	Target CD19

Landmark Hematology Trials

Trial Name	Reference	Clinical Trial Details
Hematologic Malignancies and Related Disorders		
Long-term outcomes of imatinib treatment for chronic myeloid leukemia	NEJM 2017;376:917-927	**Title:** Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia **Purpose:** To compare the efficacy of imatinib with that of IFN-α plus low-dose cytarabine in newly diagnosed chronic-phase CML. **Methods:** 1106 patients with Ph-positive CML in the chronic phase were randomized 1:1 to imatinib or interferon α plus cytarabine. Crossover to imatinib were allowed if no response by 6 mo or major cytogenetic response by 12 mo. **Results:** Assessing the imatinib arm after a median of 11 yr of follow-upspecifically at the sixth year point, the complete cytogenetic response rate was 83%. Among patients who attained a major molecular response after 18 mo of imatinib therapy, the overall survival at 10 yr was 93% and freedom from CML-related death 100%. **Conclusions:** This 116-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.
Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. Byrd et al. 2014	NEJM 2014;371:213-23	**Title:** Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia **Purpose:** To evaluate the efficacy of ibrutinib in patients with CLL and small lymphocytic lymphoma (SLL) at risk for poor outcomes. **Methods:** 391 patients with relapsed or refractory CLL or SLL were randomly assigned to daily ibrutinib or ofatumumab. **Results:** Ibrutinib significantly improved progression-free survival (hazard ratio, 0.22; P<0.001), overall survival (0.43; P=0.005) with a higher overall response rate (42.6% vs. 4.1%, P<0.001) as compared with patients on ofatumumab. Overall survival was 90% in the ibrutinib group and 81% in the ofatumumab group at 12 mo. **Conclusion:** Ibrutinib significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL.
POLLUX	NEJM 2016;375:1319-31	**Title:** Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma **Purpose:** To assess if daratumumab lengthens PFS when added to lenalidomide and dexamethasone therapy in patients with relapsed or refractory myeloma. **Methods:** 569 patients with MM who had been previously treated were randomly assigned to either lenalidomide and dexamethasone (control group) or daratumumab plus lenalidomide and dexamethasone (daratumumab group). The primary endpoint was PFS. **Results:** PFS at 12 mo was 83.2% in the daratumumab group and 60.1% in the control group. Daratumumab had a significantly higher overall response as compared to the control group (P <0.001). Neutropenia was more frequent in the daratumumab group (51.9% vs. 37.0%). **Conclusion:** PFS was significantly lengthened by addition of daratumumab to lenalidomide and dexamethasone for patients with relapsed or refractory MM but was associated with higher rates of neutropenia.
GALLIUM	NEJM 2017;377:1331-44	**Title:** Obinutuzumab for the First-Line Treatment of Follicular Lymphoma **Purpose:** To compare rituximab-based chemotherapy with obinutuzumab-based chemotherapy in patients with untreated advanced-stage follicular lymphoma. **Methods:** 1202 patients were randomly assigned to receive induction treatment with obinutuzumab-based chemotherapy (obinutuzumab) or rituximab-based chemotherapy (rituximab). **Results:** Risk of progression, relapse, or death was significantly lower on obinutuzumab vs.rituximab (estimated 3-yr PFS, 80.0% vs. 73.3%; hazard ratio for progression, relapse, or death, 0.66; 95% CI, 0.51-0.85; P=0.001). There were more adverse events in the obinutuzumab group (grade 3-5: 74.6% vs. 67.8%; serious events: 46.1% vs. 39.9%). **Conclusion:** Obinutuzumab-based chemotherapy resulted in longer PFS than rituximab-based therapy but more frequent high-grade adverse events.
Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. Park et al. 2018	NEJM 2018;378:449-59	**Title:** Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia **Purpose:** To investigate the use of CAR-T in relapsed B-cell ALL. **Methods:** Phase 1 trial including 53 adults with relapsed B-cell ALL received an infusion of autologous T cells expressing the 19-28z CAR. **Results:** Severe cytokine release syndrome occurred in 26% of patients following infusion (95% CI, 15-40); 1 patient died. 83% of patients experienced complete remission. At median 29 mo follow-up, median overall survival was 12.9 mo (8.7-23.4) and median event-free survival was 6.1 mo (5.0-11.5). **Conclusion:** Median overall survival was 12.9 mo in the entire cohort. More adverse events occurred in patients with high disease burden.
Thrombosis		
CLOT	NEJM 2003;349:146-53	**Title:** Low-Molecular-Weight Heparin Versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer **Purpose:** To compare the efficacy of LMWH with an oral anticoagulant for preventing recurrent thrombosis in cancer patients. **Methods:** Cancer patients with acute, symptomatic proximal DVT, PE, or both were randomly assigned to dalteparin (LMWH) for 5-7 d plus a coumarin derivative for 6 mo or dalteparin alone for 6 mo. **Results:** At 6 mo, the rate of recurrent thromboembolism was 17% in the oral-anticoagulant group and 9% in the dalteparin group. Rates of major bleeding were not significantly different between groups (6% vs. 4%, respectively); any bleeding (14% vs. 19%). **Conclusions:** Dalteparin was superior to an oral anticoagulant in cancer patients for reducing recurrent thromboembolism rates without increasing bleeding risk
Influence of Preceding Length of Anticoagulant Treatment and Initial Presentation of Venous Thromboembolism on Risk of Recurrence After Stopping Treatment: Analysis of Individual Participants' Data From Seven Trials. Boutitie et al. 2011	BMJ 2011;342:d3036	**Title:** Influence of Preceding Length of Anticoagulant Treatment and Initial Presentation of Venous Thromboembolism on Risk of Recurrence After Stopping Treatment: Analysis of Individual Participants' Data From Seven Trials **Purpose:** To determine how length of anticoagulation of VTE influences recurrence risk after treatment is stopped. CAR: Individual participants' data was pooled from 7 RCTs including 2925 men or women with a first VTE who did not have cancer and had varying durations of anticoagulant treatment. **Results:** Recurrence was higher if anticoagulation was stopped at 1-1.5 mo vs. at ≥3 mo (hazard ratio 1.52, 1.14-2.02) and similar if treatment was stopped at 3 mo vs. ≥6 mo (1.19, 0.86-1.65). **Conclusion:** Risk of recurrent VTE was similar when anticoagulation was stopped after 3 mo vs. stopping after a longer course of treatment.
EINSTEIN-PE	NEJM 2012;366:1287-97	**Title:** Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism **Purpose:** To investigate the efficacy and safety of a fixed-dose rivaroxaban regimen for the treatment of PE. **Methods:** 4832 patients who had acute symptomatic PE ± DVT were randomly assigned to rivaroxaban or standard therapy with enoxaparin followed by a vitamin K antagonist. **Results:** Rivaroxaban was noninferior to standard therapy for the primary efficacy outcome (symptomatic recurrent VTE), 2.1% in rivaroxaban vs. 1.8% in standard-therapy (hazard ratio, 1.12; 95% CI, 0.75-1.68). Clinically relevant bleeding occurred in 10.3% of patients on rivaroxaban and 11.4% of those on standard-therapy (0.90; 0.76-1.07; P=0.23). **Conclusion:** For initial and long-term treatment of PE, fixed-dose rivaroxaban alone was noninferior to standard therapy with a potentially better benefit-risk profile.

Trial Name	Reference	Clinical Trial Details
AMPLIFY	NEJM 2013;369:799-808	**Title:** Oral Apixaban for the Treatment of Acute Venous Thromboembolism **Purpose:** To investigate the efficacy and safety of fixed-dose apixaban for the treatment of VTE. **Methods:** 5395 patients with acute VTE were randomly assigned to receive apixaban or conventional therapy (SC enoxaparin, followed by warfarin). **Results:** Apixaban was noninferior to conventional therapy for the primary efficacy outcome (symptomatic recurrent VTE or death from VTE) (P<0.001). Major bleeding or clinically relevant nonmajor bleeding occurred in 4.3% of patients on apixaban vs. 9.7% of those on conventional-therapy (RR, 0.44; 95% CI, 0.36-0.55; P<0.001). **Conclusion:** For the treatment of acute VTE, fixed-dose apixaban alone was noninferior to conventional therapy with significantly less bleeding.
RE-VERSE AD	NEJM 2015;373:511-20	**Title:** Idarucizumab for Dabigatran Reversal **Purpose:** To investigate the efficacy and safety of idarucizumab for reversing the anticoagulant effects of dabigatran. **Methods:** 90 patients with either a serious bleed or one requiring an urgent procedure secondary to dabigatran received idarucizumab. **Results:** Idarucizumab normalized test results in 88-98% of patients, which was evident within minutes. Unbound dabigatran concentrations remained <20 ng/mL at 24 h in 79% of patients. **Conclusion:** The anticoagulant effect of dabigatran was completely reversed by idarucizumab within minutes.
CACTUS	Lancet Haematol 2016;3:e556-e562	**Title:** Anticoagulant Therapy for Symptomatic Calf Deep Vein Thrombosis (CACTUS): A Randomised, Double-Blind, Placebo-Controlled Trial **Purpose:** To investigate the efficacy and safety of anticoagulant treatment in patients with acute symptomatic DVT of the calf. **Methods:** 259 low-risk outpatients without active cancer or previous VTE with a first acute symptomatic calf DVT were randomly assigned to receive either nadroparin (LMWH) or placebo for 6 wk. **Results:** No significant difference between groups was seen in the composite primary outcome (extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic pulmonary embolism at day 42). Bleeding occurred in 4% of patients on nadroparin and no patients on placebo (risk difference 4.1, 95% CI 0.4-9.2; p=0.0255). **Conclusion:** In low-risk outpatients with symptomatic calf DVT, nadroparin was non-superior to placebo in reducing the risk of proximal extension or VTE, but it did increase bleeding risk.
Blood Products and Transfusion		
FOCUS	NEJM 2011;365:2453-2462	**Title:** Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery (FOCUS) **Purpose:** To determine whether a higher threshold for blood transfusion would improve recovery in patients who had undergone surgery for hip fracture. **Methods:** 2016 patients >50 yr with a history of or risk factors for cardiovascular disease and Hb level below 10 g/dL after hip-fracture surgery were randomly assigned to a liberal transfusion strategy (a Hb threshold of 10 g/dL) or a restrictive transfusion strategy (anemia symptoms or at physician discretion for a Hb level less than 8 g/dL). **Results:** The primary outcome was death or inability to walk across a room without human assistance on a 60 d follow-up. Primary outcome rates were 35.2% in the liberal transfusion strategy group and 34.7% in the restrictive transfusion strategy group. Rates of complications were similar in the two groups. **Conclusion:** A liberal transfusion strategy did not reduce mortality rates or the inability to walk independently on 60 d follow-up compared to a restrictive transfusion strategy in elderly patients with high cardiovascular risk factors after hip surgery.
TRICC BP	NEJM 1999;340:409-17	**Title:** A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group **Purpose:** To determine if equivalent results can be achieved by a restrictive strategy of red-cell transfusion and a liberal strategy in critically ill patients. **Methods:** 838 critically ill patients with euvolemia (after initial treatment and Hb <9 g/dL within 72 h of ICU admission) received either (1) a restrictive strategy (transfusion if Hb <7.0 g/dL, maintained at 7-9 g/dL) or (2) a liberal strategy (transfusions if Hb <10.0 g/dL, maintained at 10-12 g/dL). **Results:** Mortality rates at 30 d were similar between groups. However, among less acutely ill patients and those <55 yr of age, mortality rates were significantly lower in RS than LS: 8.7% vs. 16.1%, P=0.03 and 5.7% vs. 13%, P=0.02, respectively. **Conclusion:** In critically ill patients, a RS of red cell transfusion is as effective as a LS transfusion.
Therapeutic Platelet Transfusion Versus Routine Prophylactic Transfusion in Patients With Haematological Malignancies: An Open-Label, Multicentre, Randomised Study. Wandt et al. 2012	Lancet 2012;380:1309-16	**Title:** Therapeutic Platelet Transfusion Versus Routine Prophylactic Transfusion in Patients With Haematological Malignancies: An Open-Label, Multicentre, Randomised Study **Purpose:** To investigate the influence of a novel therapeutic platelet transfusion strategy on the number of transfusions and safety in patients with hypoproliferative thrombocytopenia. **Methods:** Patients (16-80 yr) undergoing chemotherapy for AML or autologous haemopoietic stem-cell transplantation were randomly assigned to receive either platelet transfusion when bleeding occurred (therapeutic strategy) or when morning platelet counts were $<10\times10^9$/L (prophylactic strategy; current standard of care). **Results:** In all patients, the therapeutic strategy reduced the mean number of platelet transfusions by 33.5% (95% CI 22.2-43.1; p<0.0001). Major haemorrhage was not increased in patients who had undergone autologous transplantation. Risk of non-fatal grade 4 bleeding was increased in patients with AML. **Conclusion:** The therapeutic strategy should be considered for patients following autologous stem-cell transplantation but not for patients with AML.
Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. Villanueva et al. 2013	NEJM 2013;368:11-21	**Title:** Transfusion Strategies for Acute Upper Gastrointestinal Bleeding **Purpose:** To compare the efficacy and safety of a restrictive transfusion strategy with a liberal transfusion strategy in patients with acute upper GI bleeds. **Methods:** 921 patients with severe acute upper GI bleeding were assigned to either a restrictive strategy (transfusion when Hb <7 g/dL; target Hb = 7-9 g/dL) or a liberal strategy (transfusion when Hb <9 g/dL; target Hb = 9-11 g/dL). **Results:** Survival at 6 wk was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio, 0.55; 95% CI, 0.33-0.92; P=0.02). Further bleeding was more common in patients on restrictive-strategy than liberal-strategy (10% vs.16%; P=0.01); adverse events were also more common (40% vs. 48%; P=0.02). **Conclusion:** A restrictive transfusion strategy led to better outcomes than a liberal strategy in patients with acute upper GI bleeding.

Trial Name	Reference	Clinical Trial Details
Anemia		
CHOIR	NEJM 2006;355:2085-98	**Title:** Correction of Anemia with Epoetin α in Chronic Kidney Disease **Purpose:** To determine the optimal level of hemoglobin correction by recombinant human erythropoietin (epoetin α) in anemic CKD patients. **Methods:** 1432 patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g/dL or a dose targeted to achieve a level of 11.3 g/dL. **Results:** 125 composite events (death, MI, hospitalization for CHF, or stroke) were seen in the high-hemoglobin group, as compared with 97 events in the low-hemoglobin group (hazard ratio,1.34; 95% CI, 1.03-1.74; P=0.03). **Discussion:** In patients with anemia and CKD, targeting a lower Hb reduced incidence of death, MI, CHF-related hospitalization, and stroke.
Other		
CRASH-2	Health Technol Assess 2013;17(10):1-79	**Title:** The CRASH-2 Trial: A Randomised Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion Requirement in Bleeding Trauma Patients **Purpose:** To assess how early administration of a short course of tranexamic acid (TXA) influences rates of death, vascular occlusive events and blood transfusions in trauma patients. **Methods:** 20211 adult trauma patients within 8 h of injury that had, or were at risk for, significant bleeding were randomized to receive TXA or matching placebo. **Results:** TXA significantly reduced all-cause mortality at 28 d (14.5% in TXA vs. 16.0% in placebo; p=0.0035). Death rates caused by bleeding were significantly reduced (4.9% vs. 5.7%; p=0.0077). The risk of death due to bleeding was increased by treatment given after 3 h (4.4% vs. 3.1%; p=0.004). **Conclusion:** The risk of death was safely reduced by early TXA in bleeding trauma patients. Beyond 3 h of injury, treatment is likely ineffective.

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ID Infectious Disease

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Acronyms

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ANC	absolute neutrophil count
AOM	acute otitis media
ARDS	acute respiratory distress syndrome
ARV	anti-retroviral
ART	anti-retroviral therapy
BAL	bronchoalveolar lavage
BCG	Bacille Calmette-Guérin
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFU	colony forming units
CLIA	ChemiLuminescent ImmunoAssay
CLL	chronic lymphocytic leukemia
CMIA	ChemiLuminescent Microparticle ImmunoAssay
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
DEET	N,N-Diethyl-meta-toluamide
DM	diabetes mellitus
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EHEC	enterohemorrhagic *E. coli*
EIA	enzyme immunoassay
EIEC	enteroinvasive *E. coli*
ETEC	enterotoxigenic *E. coli*
FDP	fibrinogen degradation products
FTA-ABS	fluorescent *Treponema* antibody-absorption
FUO	fever of unknown origin
GAS	group A *Streptococcus*
GBS	group B *Streptococcus*
GC	gonococcus
GI	gastrointestinal
GN	Gram-negative
GNB	Gram-negative bacilli
GP	Gram-positive
HAART	highly active anti-retroviral treatment
HAV	hepatitis A virus
HBc	HBV core antigen
HBeAg	HBV envelope antigen
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HHV	human herpes virus
Hib	*Haemophilus influenzae* b
HIV	human immunodeficiency virus
HPF	high power field
HPV	human papillomavirus
HRIg	human rabies immunoglobulin
HSV	herpes simplex virus
HTLV-1	Human T-lymphotropic virus 1
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
IDU	injecting drug use
IE	infective endocarditis
IFN	interferon
Ig	immunoglobulin
ILI	influenza-like illness
INH	isoniazid
INSTI	integrase strand transfer inhibitor
IVDU	intravenous drug use
IVIG	intravenous immunoglobulin
KOH	potassium hydroxide
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated herpes virus
LDL	low-density lipoprotein
LOC	level of consciousness
LP	lumbar puncture
MERS	Middle Eastern respiratory syndrome
MDR	multidrug resistance
MHA-TP	microhemagglutination assay *T. pallidum*
MMR	measles/mumps/rubella
MRSA	methicillin-resistant S. aureus
MSM	men who have sex with men
MSSA	methicillin-sensitive S. aureus
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
O&P	ova and parasites
PCP	*Pneumocystis pneumonia*
PCR	polymerase chain reaction
PI	protease inhibitor
PJP	*Pneumocystis jirovecii* pneumonia
PMN	polymorphonuclear leukocytes
PNS	peripheral nervous system
PPD	purified protein derivative
PWID	people who inject drugs
RA	rheumatoid arthritis
mRNA	messenger ribonucleic acid
RPR	rapid plasma reagin
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcription-PCR
SARS	severe acute respiratory syndrome
SCID	severe combined immunodeficiency
SIADH	syndrome of inappropriate antidiuretic hormone secretion
Sn	sensitivity
Sp	specificity
spp.	species
SRI	severe respiratory illness
STEC	Shiga toxin-producing *E. coli*
STI	sexually transmitted infection
TB	*Mycoplasma tuberculosis*
TG	triglycerides
TIg	tetanus immune globulin
TMP/SMX	trimethoprim-sulfamethoxazole
TNF	tumour necrosis factor
TORCH	toxoplasmosis, other, rubella, cytomegalovirus, HSV
TPI	*T. pallidum* immobilization test
TPPA	*T. pallidum* particle agglutination assay
TSS	toxic shock syndrome
TST	tuberculin skin test
URTI	upper respiratory tract infection
U/S	ultrasound
UTI	urinary tract infection
VDRL	venereal disease research laboratory
VRE	vancomycin-resistant Enterococcus
VZV	varicella-zoster virus

Principles of Microbiology

Bacteriology

Bacteria Basics

- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - GP: thick, rigid layer of peptidoglycan
  - GN: thin peptidoglycan layer + outer membrane composed of lipoproteins and lipopolysaccharides
  - clinical significance: Gram stain results are used to guide tailored empiric treatment prior to availability of culture and susceptibility testing results
- acid-fast bacilli (AFB): high mycolic acid content in cell wall, called "acid fast" because they resist stain decolourization despite acid-alcohol washes (e.g. *Mycobacteria*)
- partially AFB: bacteria with moderate mycolic acid content that will decolourize with the acid alcohol used in AFB stains but are considered partially acid-fast positive based on a modified acid-fast stain with a weaker acid during the washout phase (e.g. *Nocardia*)
  - note that *Nocardia* will be acid-fast stain negative and modified acid-fast stain positive, while *Mycobacteria* will be positive on both acid-fast and modified acid-fast stains
- "atypical" bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. *Chlamydia*
  - bacteria lacking a cell wall: e.g. *Mycoplasma*
  - spirochetes: e.g. *Treponema pallidum*
- O_2 can be either vital or detrimental to growth
  - obligate aerobes: require O_2
  - obligate anaerobes: require environment without O_2
  - facultative anaerobes: can survive in environments with or without O_2

Mechanisms of Bacterial Disease

1. adherence to and colonization of skin or mucous membranes
   - fimbriae (pili): microfilaments extending through the cell wall attach to epithelial cells (e.g. *E. coli* in the urinary tract)
2. invasion or crossing epithelial barriers
3. evasion of host defense system through:
   - inhibition of phagocytic uptake via polysaccharide capsule (e.g. *S. pneumoniae, N. meningitidis, H. influenzae*)
   - presence of surface proteins (e.g. *Staphylococcus, Streptococcus*)
4. toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria are not present (e.g. *Clostridium*)
   - endotoxins are structural components of GN bacterial cell walls and may be shed by live cells or released during cell lysis
5. intracellular growth
   - obligate intracellular: *Rickettsia, Chlamydia*
   - facultative intracellular: *Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella*
6. biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices such as IV catheters

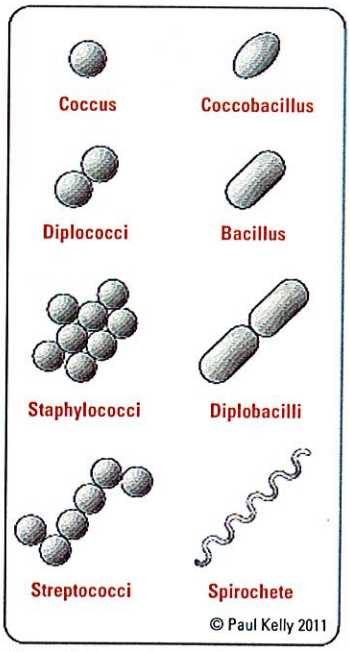


Figure 1. Bacteria morphology

Table 1. Common Bacteria

	GP Bacteria		GN Bacteria		Not Seen on Gram Stain	
	Cocci (round)	**Bacilli (rod-like)**	**Diplococci**	**Bacilli (rod-like)**	**Acid-Fast**	**Others**
Aerobes	*Staphylococcus* *S. aureus* *S. saprophyticus* *S. epidermidis* *S. lugdunensis* *Streptococcus* *S. pneumoniae* *S. pyogenes* (GAS) *S. agalactiae* (GBS) *S. anginosus group* *Enterococcus* *E. faecalis*	Bacillus *B. anthracis* *Listeria* *Nocardia* (modified acid-fast positive)	*Neisseria* *N. meningitidis* *N. gonorrhoeae* *Moraxella* *M. catarrhalis*	*Enterobacterales* *E. coli* *Klebsiella* *Salmonella* *Shigella* *Yersinia* *Campylobacter* *Legionella* *Pseudomonas* *Haemophilus* *H. influenzae*	*Mycobacteria* *M. tuberculosis* *M. leprae* *M. avium* complex	Obligate intracellular *Rickettsiae* *Chlamydia* *C. trachomatis* *C. pneumoniae* No cell wall *Mycoplasma* Spirochete (spiral) *Treponema pallidum*
Anaerobes	*Peptostreptococcus*	*Clostridioides difficile* *Clostridium* *C. tetani* *C. botulinum* *C. perfringens* *Cutibacterium (Propionibacterium) acnes*		*Bacteroides* *B. fragilis*		

Table 2. Commensal Flora

Site	Organisms
Skin	Coagulase-negative staphylococci, *Corynebacterium*, *C. acnes*, *Bacillus*, *S. aureus*
Oropharynx	Viridans group streptococci, *Haemophilus*, *Neisseria*, anaerobes (*Peptostreptococcus*, *Bacteroides*, *Veillonella*, *Fusobacterium*, *Actinomyces*, *Prevotella*)
Small Bowel	*E. coli*, anaerobes (low numbers)
Colon	*E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*, anaerobes (*Bacteroides*, *Peptostreptococcus*, *Clostridium*)
Vagina	*Lactobacillus acidophilus*, viridans group streptococci, coagulase-negative staphylococci, facultative anaerobes

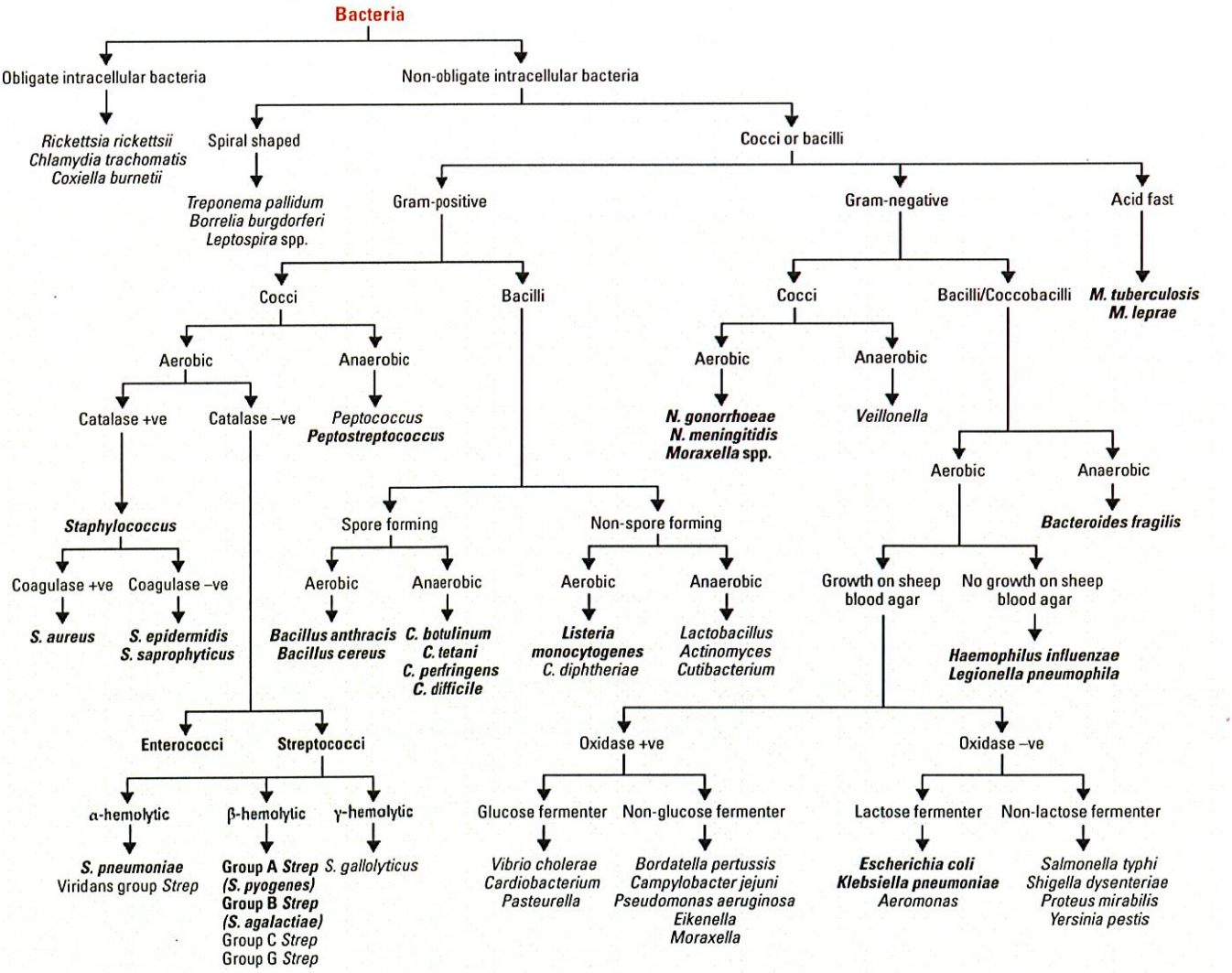


Figure 2. Laboratory identification of bacterial species
Bold = commonly encountered bacteria

Virology

Viral Basics

- viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - infect cells and use host metabolic machinery to replicate
  - nucleic acid can be double stranded (ds) or single stranded (ss)
  - nucleic acid can be positive sense (+) or negative sense (-)
  - can be enveloped or naked
- virions are mature virus particles that can be released into the extracellular environment
- host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

Viral Disease Patterns

1. acute infections (e.g. adenovirus)
   - host cells are lysed in the process of virion release
   - some produce acute infections with late sequelae (e.g. measles virus-induced subacute sclerosing panencephalitis)
2. chronic infections (>6 mo) (e.g. HBV, HIV)
   - host cell machinery is used to produce and chronically release virions
3. latent infections
   - viral genome remains latent in host cell nucleus
   - can reactivate (e.g. HSV, VZV)

Table 3. Common Viruses

Nucleic Acid	Enveloped	Virus Family	Major Viruses	Medical Importance
dsDNA	No	Adenoviridae	Adenovirus	URTI Conjunctivitis Gastroenteritis
	No	Papillomaviridae	HPV1,4 HPV6,11 HPV16,18, etc.	Plantar warts Genital warts Cervical/anal dysplasia and cancer
	Yes	Herpesviridae	HHV1=HSV1 HHV2=HSV2 HHV3=VZV HHV4=EBV HHV5=CMV HHV6* HHV8=KSHV	Oral, ocular, and genital herpes; encephalitis Genital, oral, and ocular herpes; encephalitis Chicken pox, shingles Mononucleosis, viral hepatitis Retinitis, pneumonitis, hepatitis, encephalitis Roseola Kaposi's sarcoma, multicentric Castleman's disease, body cavity lymphoma
	No	Polyomaviridae	JC virus	Progressive multifocal leukoencephalopathy
	Yes	Hepadnaviridae	Hepatitis B	Hepatitis
	Yes	Poxviridae	Monkeypox Smallpox	Monkeypox Smallpox
ssDNA	No	Parvoviridae	Parvovirus B19	Erythema infectiosum (Fifth disease)
(+) ssRNA	No	Caliciviridae	Noroviruses Hepatitis E	Gastroenteritis Acute hepatitis
	No	Picornaviridae	Poliovirus Echovirus Rhinovirus Coxsackie virus Hepatitis A	Poliomyelitis URTIs, viral meningitis URTIs Hand-foot-and-mouth, viral meningitis, myocarditis Acute hepatitis
	Yes	Coronaviridae	Coronavirus	URTIs, SARS, MERS, COVID-19
	Yes	Flaviviridae	Yellow fever Dengue fever Hepatitis C West Nile Zika	Yellow fever Dengue fever Hepatitis Encephalitis, flaccid paralysis Zika virus disease
	Yes	Togaviridae	Rubella Chikungunya	Rubella (German measles) Chikungunya
(+) ssRNA-RT	Yes	Retroviridae	HIV HTLV-1	AIDS T-cell leukemia and lymphoma
(-) ssRNA	Yes	Arenaviridae	Lassa	Lassa fever
	Yes	Filoviridae	Ebola, Marburg	Hemorrhagic fever
	Yes	Orthomyxoviridae	Influenza A, B, C	Influenza
	Yes	Paramyxoviridae	Measles Mumps Parainfluenza RSV	Measles Mumps URTIs, croup, bronchiolitis Bronchiolitis, pneumonia
	Yes	Rhabdoviridae	Rabies	Rabies
dsRNA	No	Reoviridae	Rotavirus	Gastroenteritis

Note: ___viridae = family, ___virus = genus, # = species (e.g. Retroviridae HIV-2)
*Roseolovirus, Herpes lymphotropic virus

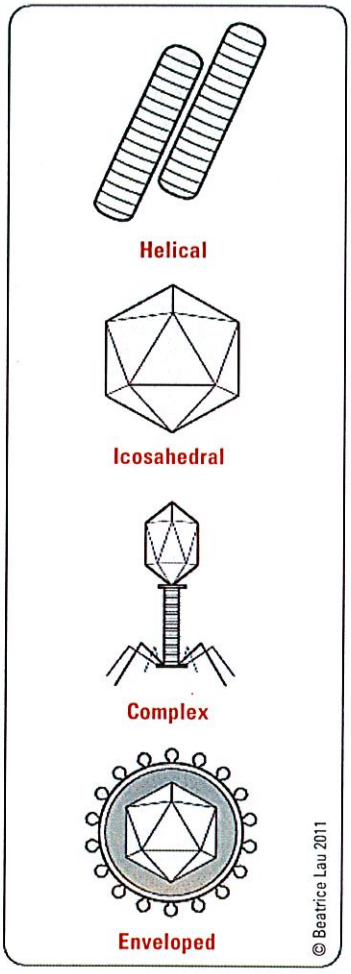


Figure 3. Virus morphology

DNA Viruses: Families

HHAPPPPy
Hepadnaviridae
Herpesviridae
Adenoviridae
Papillomaviridae
Parvoviridae
Polyomaviridae
Poxviridae

Mycology

Fungal Basics

- fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. moulds, i.e. filamentous fungi (multicellular with hyphae)
  3. dimorphic fungi (found as mould at room temperature but grow as yeast-like forms at body temperature)

Table 4. Membrane and Cell Wall Compositions

	Membrane Sterol	Cell Wall
Bacteria	–	Peptidoglycan
Human Cell	Cholesterol	–
Fungi	Ergosterol	Chitin (complex glycopolysaccharide)

Mechanisms of Fungal Disease

- primary fungal infection by:
  - overgrowth of normal flora (e.g. *Candida* spp.)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion of aflatoxins)
- allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

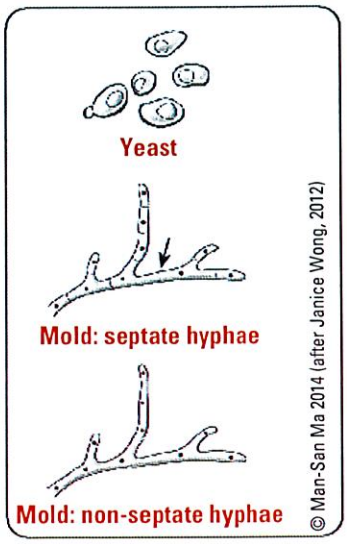


Figure 4. Common fungus morphology

Parasitology

Parasite Basics

- parasite: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycles require more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed through the larval stages
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see *Table 25, ID33* and *Table 26, ID39* for examples of clinically important parasites

Table 5. Differences Between Protozoa and Helminths

Protozoa	Helminths
Unicellular	Multicellular
Motile trophozoite, inactive cyst	Adult → egg → larva
Multiplication	No multiplication in human host
Eosinophilia unusual	Eosinophilia (proportional to extent of tissue invasion)*
Indefinite life span	Definite life span

*Adult *Ascaris* (roundworm) does not cause eosinophilia; migratory larval phases of *Ascaris*, however, cause high-grade eosinophilia

Characteristics of Parasitic Disease

- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic worm infection

Mechanisms of Parasitic Disease

1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B_{12} deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
   - acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
   - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
   - cytokine-mediated (e.g. systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
   - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
   - immune complex (e.g. nephritis of malaria, schistosomiasis)

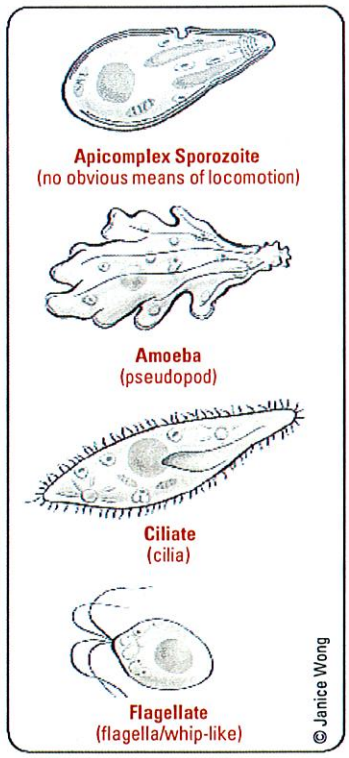


Figure 5. Classification of protozoa based on movement

Parasite sampling may need to be repeated on several occasions before infection can be ruled out

Transmission of Infectious Diseases

Table 6. Mechanism of Transmission

Mechanism	Mode of Transmission	Examples	Preventative Measure
Contact	Direct physical contact, or indirect contact with a fomite	Skin-to-skin (MRSA) Sexual (*N. gonorrhoeae, C. trachomatis*, HSV, HIV) Blood-borne (HIV, HBV, HCV)	For patients in healthcare facilities: Contact precautions Barrier precautions Safe needlestick/sharp practices
Droplet/Contact	Respiratory droplets (>5 µm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids	Influenza, mumps, *N. meningitidis, Bordetella pertussis*	For patients in healthcare facilities: Contact/droplet precautions
Airborne	Airborne droplet nuclei (<5 µm) remain infectious over time and distance	*M. tuberculosis*, disseminated VZV, measles	For patients in healthcare facilities: Airborne precautions
Food/ Waterborne	Ingestion of contaminated food or water	*V. cholerae, Salmonella*, HAV, HEV	Prophylactic vaccinations where available Ensure clean food/water supply For patients in healthcare facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers
Zoonotic/Vector-borne	Disease transmission from animals to humans either directly or via an insect vector, or disease transmission from human to human via an insect vector	Direct animal transmission (rabies, Q fever) Arthropod mediated transmission (malaria, Lyme disease, West Nile virus)	Prophylactic medications, vaccinations Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection
Vertical	Spread of disease from parent to offspring	Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)	Prenatal screening Prophylactic treatment

Nosocomial Infections

- **definition**: infections acquired >48 h after admission to a healthcare facility OR within 30 d from discharge
- **risk factors**: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, and immunodeficiency
  - patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- hand hygiene is an essential precaution

Table 7. Common Nosocomial Infectious Agents

Bacteria	Characteristics	Manifestation	Investigations	Management
MRSA	GP cocci	Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis	Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR	Contact precautions For infection: vancomycin, daptomycin, or linezolid To decolonize: chlorhexidine 2% wash once daily (+ rifampin + (doxycycline or TMP/SMX) + mupirocin cream BID to nares) x 7 d
VRE	Majority are *E. faecium* Resistant if minimum inhibitory concentration of vancomycin is ≥32 µg/mL	Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis	Rectal or perirectal swab OR stool culture for colonization Culture of infected site	Contact precautions* Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified
Clostridioides difficile (*C. difficile*)	Releases exotoxins A and B Hypervirulent strain (NAP1/B1/027) has been responsible for increase in incidence and severity	Fever, nausea, abdominal pain Watery diarrhea Pseudomembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis	Stool PCR for toxin A and B genes Stool immunoassay for toxins A and B (less sensitive than PCR) Abdominal x-ray (may see colonic dilatation) Sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation	Contact precautions Stop culprit antibiotic therapy (primarily fluoroquinolones and clindamycin) Supportive therapy (IV fluids) Empiric treatment with either vancomycin or fidaxomicin If access to empiric treatment is limited, then metronidazole may be used For fulminant *C. difficile* infection (previously called severe), oral vancomycin is used. IV metronidazole added to regimen if ileus present
Extended Spectrum β-lactam Producers (e.g. ESBL producing *E. coli, K. pneumoniae*)	Resistant to most β-lactam antibiotics except carbapenems e.g. penicillins, aztreonam**, and cephalosporins	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Contact precautions* Carbapenems or non-β-lactam antibiotics can be used for empiric therapy
Carbapenemase-producing Enterobacterales (CPE)	Resistant to β-lactam antibiotics including carbapenems	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Contact precautions Colistin, tigecycline can be used varying on susceptibility Cefiderocol, ceftazidime-avibactam, or plazomicin are other options available through the Special Access Program

*The use of contact precautions for VRE and ESBL varies depending on institutional policies. **Not available in Canada

Respiratory Infections

Pneumonia

- see Pediatrics, P68

Definition

- infection of the lung parenchyma

Etiology and Risk Factors

- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
  - impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia)
- mechanical obstruction
- no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

Table 8. Common Organisms in Pneumonia

Community-Acquired	Nosocomial	Aspiration	Immunocompromised Patients	Alcohol Use Disorder
Typical Bacteria *Streptococcus pneumoniae* *Moraxella catarrhalis* *Haemophilus influenzae* *Staphylococcus aureus* GAS Atypical Bacteria *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Legionella pneumophila* Viral *Influenza virus* *Adenovirus* *SARS-CoV-2*	Enteric GNB (e.g. *E. coli*) *Pseudomonas aeruginosa* *S. aureus* (including MRSA)	Oral anaerobes (e.g. *Bacteroides*) Enteric GNB *S. aureus* Gastric contents (chemical pneumonitis)	*Pneumocystis jirovecii* Fungi (e.g. *Cryptococcus*) *Nocardia* CMV HSV TB	*Klebsiella* Enteric GNB *S. aureus* Oral anaerobes (aspiration) TB

*See Pediatrics, P87, Table 45, *Common Causes and Treatment of Community-Acquired Pneumonia*

Clinical Features

- cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, and tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, and crackles)
- features of parapneumonic effusion (decreased air entry, dullness to percussion)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, and pleuritis ± hemorrhage

Investigations

- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, creatinine, arterial blood gas (ABG) (if respiratory distress)
- sputum Gram stain/C&S, blood C&S, ± viral detection (influenza testing), ± serology, and ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR ± CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
- bronchoscopy ± washings for: (1) severely ill patients refractory to treatment and (2) immunocompromised patients

Treatment

- airway/breathing/circulation, O_2, IV fluids, consider salbutamol (nebulized or metered-dose inhaler)
- determine prognosis and need for hospitalization and antibiotics

Criteria for Hospitalization

- along with clinical judgment, validated clinical prediction rules for prognosis can be used to determine the need for hospitalizations in adults diagnosed with community-acquired pneumonia (e.g. the CURB-65 Score or Pneumonia Severity Index (PSI))

Table 9. CURB-65 Score – Pneumonia Clinical Prediction Tool

Component*	Measurement(s)	Points	Total Score	Mortality	Disposition
Confusion	Altered mental status	1	0-1	<5%	Can treat as outpatient
Urea/BUN	Urea >7 mmol/L or BUN >20 mg/dL	1	2-3	5-15%	Consider hospitalization
Respiratory Rate	>30 breaths/min	1	4-5	15-30%	Consider ICU
Blood Pressure	sBP <90 mmHg or dBP <60 mmHg	1			
Age	65 or older	1			

*A CRB-65 score may also be applied in community acquired pneumonia. Its criteria depends on clinical assessment alone



When Klebsiella causes pneumonia: see red currant jelly sputum



3 As of *Klebsiella*
Aspiration pneumonia
Alcohol use disorder and patients with diabetes
Abscess in lungs



Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger calibre and more vertical orientation of the right bronchus



Healthcare-Associated Infections and Antimicrobial Resistance in Canadian Acute Care Hospitals
Can Commun Dis Rep 2020;46:99-112
Purpose: To describe the trends of healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) from 2014 to 2018 using surveillance data from the Canadian Nosocomial Infection Surveillance Program.
Methods: Data were collected from 70 Canadian sentinel hospitals regarding Clostridioides difficile infection (CDI), MRSA bloodstream infections, VRE bloodstream infections, and carbapenemase-producing Enterobacteriaceae.
Results: Rates per 10,000 patient-days increased for MRSA (59%; 0.66-1.05, P=0.023) and VRE bloodstream infections (143%; 0.14-0.34, P=0.023). However, CDI rates decreased by 12.5% (from 6.16-5.39, P=0.042). Carbapenemase-producing Enterobacteriaceae colonization increased by 375% (0.04-0.19; P=0.014) but infection rates remained low and stable.
Conclusion: Standardized surveillance data from acute care hospitals in addition to antimicrobial stewardship will be crucial for the ongoing prevention of HAIs and AMR in Canada.



For a report on nosocomial infections in the US, please refer to: NEJM 2014;370:1198-208. Consult your local hospital statistics for the most applicable information for your workplace.



Diagnosis of Ventilator-Associated Pneumonia in Critically Ill Adult Patients: A Systematic Review and Meta-Analysis
Intensive Care Med 2020;46:1170-79
Purpose: To identify and compare the accuracy of the following measures for diagnosing VAP: physical examination, chest radiography, endotracheal aspirate (ETA), bronchoscopic sampling cultures (protected specimen brush (PSB) and bronchoalveolar lavage (BAL)), and CPIS >6.
Study Selection: Eligible observational studies and RCTs included ≥90% patients over 16 y/o with measures conducted in the ICU, including patients with minimum 48 h of invasive mechanical ventilation.
Results: The collective sensitivity and specificity of VAP physical examination findings were poor: fever (66.4% and 53.9%, respectively) and purulent secretions (77.0%, 39.0%); any infiltrate on chest radiography (88.9%, 26.1%); ETA (75.7%, 67.9%). Among bronchoscopic sampling methods, PSB (61.4%, 76.5%); BAL (71.1%, 79.6%). CPIS>6 (73.8%, 66.4%).
Conclusion: VAP misdiagnosis and potentially unnecessary antimicrobial use may result from reliance on classical clinical measures used in isolation.

Table 10. Pneumonia Severity Index – Clinical Prediction Rule for Prognosis

Risk Factor	Points	Total Score	Risk Class	Mortality	Recommendation
Demographics		<51	I	0.1%	Consider outpatient
Men	Age (yr)				
Women	Age (yr) – 10				
Nursing home resident	+10				
Coexisting Illness		51-70	II	0.6%	Consider outpatient
Neoplastic disease	+30				
Liver disease	+20				
Congestive heart failure	+10				
Cerebrovascular disease	+10				
Renal disease	+10				
Physical Exam		71-90	III	0.9-2.8%	Consider outpatient
Altered mental status	+20				
Respiratory rate ≥30 breaths/min	+20				
sBP <90 mmHg	+20				
T <35°C or ≥40°C	+15				
HR ≥125 bpm	+10				
Investigations		91-130	IV	8.2-9.3%	Hospitalize
Arterial pH <7.35	+30				
BUN ≥30 mg/dL	+20				
Sodium <130 mmol/L	+20	>130	V	27.0-29.2%	Hospitalize
Glucose ≥250 mg/dL	+10				
Hematocrit <30%	+10				
Partial pressure of arterial O_2 <60 mmHg	+10				
Pleural effusion	+10				

Adapted with permission from Diagnosis and Treatment of Community-Acquired Pneumonia, February 1, 2006, Vol 73, No 3, American Family Physician Copyright © 2006 American Academy of Family Physicians. All Rights Reserved

Table 11. IDSA/ATS Community-Acquired Pneumonia Treatment Guidelines 2019

Setting	Circumstances	Treatment
Outpatient	No comorbidities or risk factors for MRSA or *P. aeruginosa* [1]	Amoxicillin OR Doxycycline OR Macrolide (local pneumococcal resistance <25%)[2]
	Comorbidities [3]	Amoxicillin/clavulanate or cephalosporin[4] AND Macrolide[2] or doxycycline OR Respiratory fluoroquinolone[5]
Inpatient	Nonsevere inpatient pneumonia[6] and no risk factors for MRSA or *P. aeruginosa*[1]	β-lactam[7] ± macrolide [2] OR respiratory fluoroquinolone[5]
	Severe inpatient pneumonia[6] and no risk factors for MRSA or *P. aeruginosa*[1]	β-lactam[7] + macrolide [2] OR β-lactam[7] + fluoroquinolone [5]

Given different regional resistance patterns, therapy should be based on local epidemiology and site-specific recommendations
Refers to empiric treatment to be started. Appropriate antibiotic therapy should be tailored if pathogen is identified
1. Previous respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND parenteral antibiotic use in last 3 mo ± locally validated risk factors
2. **Macrolide:** use azithromycin or clarithromycin
3. **Comorbidities:** chronic heart, lung, liver, or renal disease, DM, alcohol use disorder, malignancy, asplenia
4. **Cephalosporin:** cefpodoxime or cefuroxime
5. **Respiratory fluoroquinolone:** moxifloxacin, levofloxacin
6. Severe = 1 major criterion or ≥3 minor criteria. Minor criteria: respiratory rate ≥30 breaths/min, PaO_2/FiO_2 ratio ≤250, multilobar infiltrates, confusion/disorientation, BUN ≥20 mg/dL, WBC <4000/μL due to infection, Plt <100000/μL, T <36°C, hypotension with aggressive fluid resuscitation. Major criteria: septic shock with vasopressors, respiratory failure with mechanical ventilation
7. **β-lactam:** ampicillin sulbactam*, cefotaxime, ceftriaxone, ceftaroline*
IDSA: Infectious Diseases Society of America
ATS: American Thoracic Society
*Available in Canada through the Special Access Program

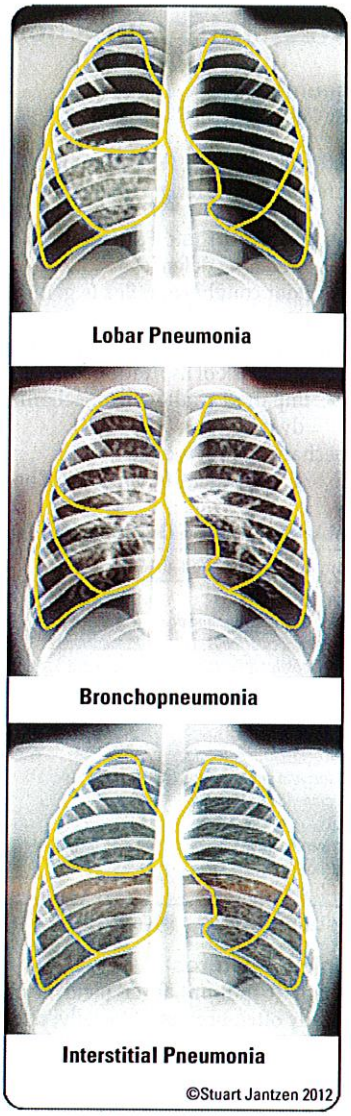


Figure 6. Lobar, broncho-, and interstitial pneumonia

Diagnosis and Treatment of Adults with Community-Acquired Pneumonia: An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America
Am J Respir Crit Care Med 2019;200:e45-e67

- The Pneumonia Severity Index is preferred over the CURB-65 tool for determining inpatient vs. outpatient treatment.
- Test for influenza with a rapid influenza molecular assay when it is circulating in the community.
- Obtaining blood C&S or sputum Gram stain/C&S routinely in adults with CAP managed in the outpatient setting is not recommended.
- Obtaining pre-treatment blood C&S and sputum Gram stain/C&S is recommended in adults with CAP managed in the hospital setting who (1) are classified as severe CAP or (2) are being empirically treated for MRSA or P. aeruginosa or (3) were previously infected with MRSA or P. aeruginosa or (4) were hospitalized and received parenteral antibiotics in the last 90 d.

Table 12. IDSA/ATS Hospital-Acquired (HAP) and Ventilator-Associated (VAP) Pneumonia Clinical Practice Guidelines 2016

Setting	Treatment
Clinically suspected **HAP** (non-VAP) with no increase in likelihood of MRSA and not at high-risk of mortality	**One of:** piperacillin-tazobactam OR cefepime OR levofloxacin OR imipenem OR meropenem
Clinically suspected **HAP** (non-VAP) with increasing likelihood of MRSA and not at high-risk of mortality	**One of:** piperacillin-tazobactam OR cefepime or ceftazidime OR levofloxacin or ciprofloxacin OR imipenem or meropenem OR aztreonam* **PLUS one of:** vancomycin or linezolid for MRSA coverage
Clinically suspected **HAP** (non-VAP) with high-risk of mortality or recipient of IV antibiotics in last 90 d	**Two of the following (avoid 2 β-lactams):** piperacillin-tazobactam OR cefepime or ceftazidime OR levofloxacin or ciprofloxacin OR imipenem or meropenem OR aztreonam* OR amikacin or gentamicin or tobramycin **PLUS either MRSA or MSSA coverage:** MRSA: vancomycin or linezolid OR MSSA: piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem
Clinically suspected **VAP** in units where empiric MRSA coverage and double antipseudomonal/GN coverage are appropriate	**One of:** β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) OR antipseudomonal cephalosporin (cefepime or ceftazidime) OR antipseudomonal carbapenem (imipenem or meropenem) OR monobactam (aztreonam*) **PLUS one of:** antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside (amikacin, gentamicin, or tobramycin) OR polymyxins (colistin or polymyxin B) **PLUS one of:** vancomycin or linezolid for MRSA coverage

Refers to empiric treatment to be started. Appropriate antibiotic therapy should be tailored if pathogen is identified
*Available in Canada through the Special Access Program
Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock
Risk factors for MDR VAP: prior IV antibiotic use within 90 d, septic shock at time of VAP, ARDS preceding VAP, 5+ d of hospitalization prior to VAP onset, acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP, MRSA VAP/HAP, or MDR *Pseudomonas* VAP/HAP: Prior IV antibiotic use within 90 d
Note: Indications for MRSA coverage includes IV antibiotic treatment during the prior 90 d and treatment in a unit where prevalence of MRSA of *S. aureus* isolates is not known or is >20%
Note: These guidelines may be less applicable in Canada given lower rates of antibiotic resistance among common nosocomial pathogens



Does this Patient have Community-Acquired Pneumonia?
Diagnosing Pneumonia by History and Physical Examination
JAMA 1997;278:1440-1445
Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult community-acquired pneumonia.
Results: The presence of fever or immunosuppression had a positive likelihood ratio (+LR) of 2, while a history of dementia had a +LR of 3; however, these traits are not confirmatory. The presence of an abnormality in any vital sign, including tachycardia, tachypnea, or fever had a +LR ranging from 2-4, which was not significantly affected by different cut-points. The absence of vital sign abnormality had a –LR ranging from 0.5-0.8. The combination of respiratory rate <30 breaths/min, heart rate <100 bpm, and temperature <37.8°C had a –LR of 0.18. Findings on chest exam raised the likelihood of diagnosis but were uncommonly seen in studies (e.g. presence of asymmetric respirations essentially confirmed the diagnosis but was only present in 4% of patients). In patients with a clinical diagnosis but normal radiograph, only ~10% will develop radiographic findings in 72 h.
Conclusions: Evidence suggests no single item on clinical history or physical exam is sufficient to rule in or out pneumonia without CXR. Vital sign abnormalities were correlated with a diagnosis of pneumonia. Findings on chest exam significantly raised the likelihood of pneumonia but were uncommonly seen in studies.

Prevention

- Public Health Agency of Canada recommends the following:
  - vaccine for influenza A and B annually for all ages ≥6 mo
  - pneumococcal polysaccharide vaccine (Pneumovax®) for all adults ≥65 yr and in younger patients ≥24 mo at high-risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia, congenital or acquired immunodeficiency)
  - pneumococcal conjugate vaccine (Prevnar-13®) for children and adolescents ages 5-17 yr at high risk for invasive pneumococcal disease and who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high-risk for invasive pneumococcal disease)
  - mRNA COVID-19 vaccine (Moderna (Spikevax®) or Pfizer-BioNTech (Comirnaty®)) for all ages ≥6 mo who do not have contraindications, with boosters as per public health guidance



Beware! Do Not Confuse *H. influenzae* with Influenza Virus
H. influenzae: a bacterium (Types A, B, C, D, E, and F refer to capsule)
Influenza: a virus (Types A and B refer to strain)

Influenza

Definitions and Etiology

- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: influenza A (H1N1), influenza A (H3N2), and influenza B
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne



Vaccines for Preventing Influenza in Healthy Adults
Cochrane DB Syst Rev 2018;CD001269
Study: 52 RCTs and quasi-RCTs evaluating influenza vaccines compared to placebo or no intervention in healthy individuals 16-65 yr. Observational comparative studies were not included.
Results: Inactivated influenza vaccines reduce influenza in healthy adults from 2.3% to 0.9% and reduce influenza-like illness (ILI) from 21.5% to 18.1%. The preventative effect of vaccination is small, with 71 healthy adults needing to be vaccinated to prevent one from experiencing influenza, and 29 needing to be vaccinated to prevent one from experiencing ILI. Vaccination leads to a small reduction in the risk of hospitalization from 14.7% to 14.1%, and a small reduction in days off work. Effectiveness of the influenza vaccine is less in mothers and newborns compared to the general population.
Conclusions: Influenza vaccines have a very modest effect in reducing influenza, associated symptoms, hospitalization, and days off work in healthy adults.

Table 13. Difference Between Influenza Strains

	Influenza A	Influenza B
Host(s)	Humans, birds, mammals	Humans only
Antigenic Drift	Yes, new strains	Yes, new strains
Antigenic Shift	Yes, new subtypes	No
Epidemics	Yes	Yes
Pandemics	Yes	No

Clinical Features
- incubation period 1-4 d and symptoms typically resolve in 7-10 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, headache, and fatigue) and respiratory symptoms (cough, dyspnea, and pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, and sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, and Guillain-Barré syndrome)
- severe disease more likely in the elderly, children, pregnant women, immunocompromised patients, asthma, COPD, cardiovascular disease (CVD), DM, and obesity

Investigations
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for RT-PCR (gold standard), or rapid antigen detection (DFA, direct fluorescent antibody) which has lower sensitivity
- lower respiratory specimens for RT-PCR
- serology: rarely used for clinical management

Treatment and Prevention
- primarily supportive unless severe infection or high-risk for complications
- neuraminidase inhibitors: oseltamivir (Tamiflu®) or zanamivir (Relenza®) for treatment and prophylaxis against types A and B or peramivir (Rapivab™) for the treatment against types A and B
  - decreases duration (by ~1 d) and severity of symptoms if given within 48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- vaccine for influenza A and B viruses is recommended annually for all ages ≥6 mo
- vaccine is reformulated each year to reflect circulating influenza A and B strains

High-risk for Complications
- anyone who is hospitalized, patients with severe illness/chronic medical conditions, immunocompromised patients, children <2 yr, elders ≥65 yr, pregnant women or women ≤2 wk postpartum

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection
NEJM 2018;378:345-353
Purpose: To investigate the association between laboratory-confirmed influenza infection and acute MI.
Methods: Self-controlled case-series. Risk interval defined as first 7 d after respiratory specimen collection and control interval as 1 yr before and 1 yr after the risk interval.
Results: Increased incidence ratio of an admission for acute MI during risk interval vs. control interval (6.05, 95% CI 3.86-9.50). No increased incidence after 7 d. Increased incidence ratios for acute MI within 7 d after detection of influenza B (10.11, 95% CI 4.37-23.38), influenza A (5.17, 95% CI 3.02-8.84), and respiratory syncytial virus (3.51, 95% CI 1.11-11.12).
Conclusions: Significant association between respiratory infections, especially influenza, and acute MI.

COVID-19

Definitions and Etiology
- an acute infectious respiratory disease caused by the SARS-CoV-2 virus
- SARS-CoV-2 is an enveloped, positive-sense, ssRNA virus
- transmission: droplet and airborne transmission
- incubation period 2-14 d, usually ~5 d

Pathophysiology
- invasion of host cells via the viral spike protein which binds to angiotensin-converting enzyme 2 (ACE2) expressed on the surface epithelium of the lungs
- virus induced cytotoxic damage particularly to the alveolar epithelium
- dysregulated immune response can lead to a cytokine storm causing organ failure or death

Clinical Features
- can be asymptomatic (estimated to be 1 in 3 of those infected)
  - children are more likely to be asymptomatic or to have mild disease
- most common: fever, fatigue, and dry cough
- common: dyspnea, loss of smell and/or taste (may vary depending on the variant circulating), loss of appetite, and myalgia
- less common: nausea, vomiting, abdominal pain, sore throat, headache, and thromboembolic events
- course: can range from mild disease (lasts 1-2 wk) to severe or critical disease (lasts 3+ wk); may be complicated by post-COVID condition which is associated with a wide range of diverse symptoms across multiple organ systems that may fluctuate in intensity, often exacerbated by mental and physical overexertion

Diagnosis
- nasopharyngeal swabs for RT-PCR (gold standard) or nasal/oral-nasal swabs for rapid antigen detection point of care tests which have lower sensitivity
- lower respiratory specimens for RT-PCR

Treatment (accurate as of July 2023)
- please see updated guidance through the Ontario Science Table (https://covid19-sciencetable.ca/science-briefs/#infectious-diseases-clinical-care)

- for critically ill adults >18 yr requiring ventilatory and/or circulatory support:
  - dexamethasone PO or IV for 10 d (or until discharge)
  - tocilizumab if on recommended steroid dose + admitted to hospital or diagnosed with COVID-19 in hospital within 14 d
  - prophylactic low molecular-weight or unfractionated heparin
- for adults >18 yr requiring low-flow supplemental O_2:
  - dexamethasone PO or IV for 10 d (or until discharge)
  - remdesivir IV for 5 d
  - tocilizumab if serum CRP ≥ 75 mg/L + disease progression despite 24-48 h of recommended steroid dose + admitted to hospital or diagnosed with COVID-19 in hospital within 14 d
  - prophylactic low molecular-weight or unfractionated heparin
- for mildly ill adults >18 yr who do not require supplemental O_2 in any setting:
  - stratify by risk of severe disease (i.e. ≥5% risk of hospitalization)
  - for patients with ≥5% risk of hospitalization:
    - nirmatrelvir/ritonavir (Paxlovid) if presenting within 5 d of symptom onset
    - remdesivir if presenting within 7 d of symptom onset
- for patients with <5% risk of hospitalization: reassurance and self-monitoring of symptoms

Table 14. Risk of Hospitalization in Mildly Ill Adults >18 yr with COVID-19 (accurate as of April 1, 2022)

- Higher risk individuals are those who have a ≥5% risk of hospitalization if they develop COVID-19. Standard risk individuals are those who have a <5% of hospitalization.
- Indigenous people, Black people, and members of other racialized communities may be at increased risk of disease progression due to disparate rates of comorbidity, increased barriers to vaccination, and social determinants of health. They should be considered priority populations for access to COVID-19 drugs and therapeutics.

Age (Years)	Number of Vaccine Doses			Risk Factors
	0 Doses	1 or 2 Doses	3 Doses	Obesity (BMI ≥30 kg/m²)
<20[1]	Higher risk if ≥3 risk factors [1]	Standard risk [1]	Standard risk [1]	Diabetes
20 to 39	Higher risk if ≥3 risk factors	Higher risk if ≥3 risk factors	Standard risk	Heart disease, hypertension, congestive heart failure
40 to 69	Higher risk if ≥1 risk factors	Higher risk if ≥3 risk factors	Standard risk	Chronic respiratory disease, including cystic fibrosis
≥70	Higher risk	Higher risk if ≥1 risk factors	Higher risk if ≥3 risk factors	Cerebral palsy
Immunocompromised[2] individuals of any age	Higher risk: Therapeutics should always be recommended for immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying immune status, regardless of age or vaccine status [1,2]			Intellectual disability Sickle cell disease Moderate or severe kidney disease (eGFR <60 mL/min)
Pregnancy	Higher risk[3]	Standard risk	Standard risk	Moderate or severe liver disease (e.g. Child Pugh, Class B or C cirrhosis)

1. Evidence for the safety and efficacy of sotrovimab and nirmatrelvir/ritonavir (Paxlovid) in children <18 years of age is limited. While early evidence on risk factors for moderate and severe COVID-19 in children is emerging, the ability to reliably predict disease progression in children remains very limited, and the frequency of progression is rare. While not routinely recommended in children <18 years of age, the use of these agents may be considered in exceptional circumstances (e.g. severe immunocompromise and/or multiple risk factors, clinical progression) on a case-by-case basis. Multidisciplinary consultation with Infectious Diseases (or Pediatric Infectious Diseases) and the team primarily responsible for the child's care is recommended to review the individual consideration of these medications.
2. Examples of immunocompromised or immunosuppressed individuals include receipt of treatment for solid tumours and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment), receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g. DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e. ≥20 mg prednisone or equivalent per day when administered for ≥2 wk), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumour-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.
3. Therapeutics should always be recommended for pregnant individuals who have received zero vaccine doses.

Prevention (accurate as of July 2023)

- complete series of mRNA COVID-19 vaccine (Moderna (Spikevax®) or Pfizer-BioNTech (Comirnaty®)) for all ages ≥6 mo who do not have contraindications, with boosters as per public health guidance

Skin and Soft Tissue Infections

Cellulitis

Definition

- acute infection of the skin principally involving the dermis and subcutaneous tissue

Etiology

- common causative agents: β-hemolytic streptococci (most common cause of non-purulent cellulitis), *S. aureus*, and occasionally *S. lugdunensis*
- immunocompromised patients or water exposure: may also include GN rods and fungi
- bite wounds: consider skin flora of "bitee" and mouth flora of "biter"
- risk factors
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema, DM, and cracked skin in feet/toes (tinea pedis)

Clinical Features

- pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
- CBC and differential; blood C&S if patient has malignancy, severe systemic features, or unusual predisposing factors, such as immersion injury, animal bites, neutropenia, and severe cell-mediated immunodeficiency
- skin swab ONLY if open wound with pus

Treatment
- consult local guidelines for appropriate antibiotic therapy
- antibiotics: cephalexin (broader coverage if risk factors for GN rods)
- if extensive erythema or systemic symptoms, consider cefazolin IV
- if MRSA is suspected, empiric coverage for MRSA may be considered (see *A Simplified Look at Antibiotics, ID46*)
- limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
- life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
- two main forms
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus, Bacteroides, Enterobacterales*)
  - Type II: monomicrobial infection with GAS, or less commonly *S. aureus*

Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
- edema ± crepitus (subcutaneous gas from anaerobes)
- infection spreads rapidly
- rapid onset of systemic symptoms (e.g. tachycardia, hypotension, lightheadedness, disorientation, lethargy, and fever)
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae
  - loss of sensation in the affected area (paresthesias)

Investigations
- clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum creatine kinase (CK) – elevated CK usually means myonecrosis (a late sign)
- plain film x-ray or CT (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

Treatment
- resuscitation with IV fluids
- emergency surgical debridement to confirm diagnosis and remove necrotic tissue (may require amputation)
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): with confirmed GAS infection, penicillin G + clindamycin IV; with confirmed S. aureus infection, cefazolin (or cloxacillin) + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIG

Acquired Oral Lesions

Etiology
- infection (e.g. candidiasis, gonococcal infection, and HSV)
- malignancy (e.g. adenocarcinoma, leukoplakia)
- poor oral hygiene (e.g. caries, periodontal disease)
- trauma (e.g. abuse)
- toxic ingestion
- xerostomia (e.g. age, medications)
- systemic diseases (e.g. lichen planus, Behçet disease)

Table 15. Comparison between Oral Infection vs. Oral Carcinoma

	Oral Candidiasis	Oral Squamous Cell Carcinoma
Risk Factors	Antibiotics, chemotherapy, and radiation therapy Immunocompromised, inhaled corticosteroids Age – infants, older adults with dentures	Tobacco use (smoked and smokeless) Betel use Alcohol HPV, especially HPV-16
Morphology	Pseudomembranous: confluent, white patches or plaques, can be wiped off with a gauze, exposing an erythematous base Atrophic candidiasis: red patches localized mainly to the palate and dorsum of the tongue	A lesion of three or more weeks duration: Red or red and white lesion Ulcer Lump Especially when in combination or if indurated (firm on palpation)
Diagnosis	Cytology, biopsy, or culture	Biopsy and histopathologic examination
Treatment	Topical antifungal	Referral to ENT

Gastrointestinal Infections

- see Gastroenterology, G31 and Pediatrics, P44

Traveller's Diarrhea

- see Gastroenterology, G18

Chronic Diarrhea

- see Gastroenterology, G19

Peptic Ulcer Disease *(Helicobacter pylori)*

- see Gastroenterology, G13

Bone and Joint Infections

Septic Arthritis

Definition

- infection of one or more joints by pathogenic microbes

Routes of Infection

- hematogenous (most common)
  - from distant infection (e.g. abscesses, wound infection, and bacteremia)
- direct inoculation via skin/trauma
  - iatrogenic (e.g. surgery, arthroscopy, arthrocentesis, joint injection)
  - trauma (e.g. open wounds around the joint, penetrating trauma)
- contiguous spread (e.g. septic bursitis, osteomyelitis)

Etiology

- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* spp. (Group A and B)
  - GNs: affect neonates, elderly, injection drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children <4 yr
  - *Haemophilus influenzae* type B (Hib) now rare due to Hib vaccine: consider in unvaccinated children
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* spp.: prosthetic joints
- if culture-negative: partially treated infection (prior to oral antibiotics), reactive arthritis, rheumatic fever, less common bacterial causes such as *Borrelia* spp. (Lyme disease) or *Tropheryma whipplei* (Whipple's disease), and non-infectious causes



Medical Emergency
Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur



Disseminated Gonococcal Infection Triad
Migratory arthralgias
Tenosynovitis next to inflamed joint
Pustular skin lesions

Risk Factors
- gonococcal
- age <40 yr, multiple partners, unprotected intercourse, MSM
- non-gonococcal
  - most affected children are previously healthy with no risk factors: occasionally preceding history of minor trauma
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (e.g. rheumatoid arthritis, osteoarthritis)
  - immunocompromised (e.g. DM, chronic kidney disease, alcohol use disorder, cirrhosis)
  - loss of skin integrity (e.g. cutaneous ulcer, skin infection)
  - age >80 yr



Intra-articular steroids are contraindicated until septic arthritis has been excluded

Clinical Features of Gonococcal Arthritis
- two forms (although often overlap):
  - septic arthritis form: local symptoms in involved joint (swelling, warmth, pain, inability to weight bear, decreased range of motion)
  - bacteremic form: systemic symptoms of fever, malaise, chills

Clinical Features of Non-Gonococcal Arthritis
- acute onset of pain, swelling, warmth, decreased range of motion ± fever and chills; in children, refusal to weight bear
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)

Investigations
- consider rheumatologic causes for monoarthritis (see Rheumatology, Table 4, RH5)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory, CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15000/mm ^{3}: likelihood of infection increases with increasing WBCs), PMNs >90%, culture positive
  - growth of *N. gonorrhoeae* from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment



IWGDF Guidance on the Diagnosis and Management of Foot Infections in Persons with Diabetes - Recommendations for Diagnosing Osteomyelitis
Diabetes Metab Res Rev 2016;32:45-74
Perform a probe-to-bone test for an infected open wound; a negative test likely rules out osteomyelitis in low-risk patients, while a positive test is likely diagnostic in high-risk patients.
In suspected cases, dramatically elevated serum inflammatory markers (especially ESR) are suggestive of osteomyelitis.
When in doubt, positive results on microbiological or histological exam of an aseptic bone sample are usually required for a definitive diagnosis of bone infection.
Bone infection is probable if there are positive results on a combination of diagnostic tests (probe-to-bone, serum inflammatory markers, plain x-ray, MRI, or radionuclide scanning).
For all cases of non-superficial diabetic foot infection, plain x-rays of the foot should be obtained.
When advanced imaging is required for diagnosis, MRI is preferred.

Treatment
- medical
  - empiric IV antibiotics: specific choice depends on clinical scenario and local guidelines; for most adults, cefazolin ± vancomycin is reasonable; for fully vaccinated children, cefazolin or cloxacillin IV unless MRSA is a consideration – delay may result in joint destruction
  - Gram stain and cultures guide subsequent treatment
  - gonococcal: ceftriaxone (+ azithromycin for concurrent treatment of *C. trachomatis*), 7 d of therapy usually sufficient
  - non-gonococcal: antibiotics against *Streptococcus* spp. (2-3 wk IV followed by PO), *S. aureus* (4 wk IV minimum), or GNB (4 wk, newer evidence suggests early switch to PO is safe and effective)
- surgical intervention if (see Orthopedic Surgery, OR11)
  - would consider surgical intervention on all cases of septic arthritis if possible
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement, especially in paediatric population
  - prosthetic joint
- daily joint aspirations until culture sterile
- physiotherapy



See Landmark Infectious Disease Trials table for more information on the OVIVA trial. It details whether oral antibiotic therapy is noninferior to IV antibiotic therapy for the management of complex orthopaedic infections.

Prognosis
- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: in children, generally good outcome if treated promptly; in adults, up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

Etiology
- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly, and are predisposed to infection
- organisms in mild infection: *Streptococcus* spp., *S. aureus*
- organisms in moderate/severe infection: polymicrobial with aerobes (*S. aureus, Streptococcus, Enterococcus*, GNB) and anaerobes (*Peptostreptococcus, Bacteroides, Clostridium*)

Clinical Features
- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation, loss of protective sensation, renal disease, or history of walking barefoot

- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) OR the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone: osteomyelitis
- infection severity
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fever, tachypnea, leukocytosis, tachycardia, hypotension)

Investigations
- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infections)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI/bone scan if high clinical suspicion
- if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

Treatment
- mild to moderate: cefazolin or cephalexin
- severe: options include: 1. ceftriaxone + metronidazole; 2. piperacillin/tazobactam ± vancomycin; 3. meropenem ± vancomycin
- optimize glycemic control, pressure offloading, wound care, consider revascularization
  - this is empiric treatment, and specific treatment needs to be adjusted based on culture and response to therapy

Osteomyelitis

- see Orthopedic Surgery, OR11

Cardiac Infections

Infective Endocarditis

Definition
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetations are made of platelet-fibrin thrombi, WBCs, and bacteria

Risk Factors and Etiology
- predisposing conditions
  - high-risk: prosthetic cardiac valve, previous infective endocarditis (IE), congenital heart disease (unrepaired, repaired within 6 mo, or repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - low/no risk: secundum atrial septal defect (ASD) or surgically repaired ASD, ventricular septal defect (VSD), patent ductus arteriosus (PDA), mitral valve (MV) prolapse, ischemic heart disease, previous coronary artery bypass graft (CABG)
  - opportunistic bacteremia: IVDU, indwelling venous catheter, hemodialysis, poor dentition, DM, HIV
- frequency of valve involvement MV>>aortic valve (AV)>tricuspid valve (TV)>pulmonary valve (PV)
  - in 50% of IVDU-related IE the tricuspid valve is involved

Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors

Native Valve	IVDU	Prosthetic Valve (recent surgery <2 mo)	Prosthetic Valve (remote surgery >2 mo)
***Streptococcus*[1] (36%)**	***S. aureus* (68%)**	***S. aureus* (36%)**	***Streptococcus* (20%)**
***S. aureus* (28%)**	***Streptococcus* (13%)**	***S. epidermidis* (17%)**	***S. aureus* (20%)**
***Enterococcus* (11%)**	*Enterococcus*	*Enterococcus*	***S. epidermidis* (20%)**
S. epidermidis	GNB	GNB	***Enterococcus* (13%)**
GNB	*Candida*	Other[2]	Other[2]
Other[2]	Other[3]		

Organisms in bold are the most common isolates
1. *Streptococcus* includes mainly viridans group streptococci
2. Other includes less common organisms such as:
   - *Streptococcus gallolyticus* (previously known as *S. bovis*; usually associated with underlying GI malignancy and cirrhosis)
   - Culture-negative organisms including *Abiotrophia, Granulicatella, Bartonella, Coxiella, Chlamydia, Legionella, Brucella*
   - *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella*, and *Kingella* (HACEK)
   - *Candida*
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = *Pseudomonas*, saliva = oral flora, toilet water = GI flora)

Clinical Features
- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia

- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute mitral regurgitation (MR), atrial regurgitation (AR))
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler's nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth's spots (retinal hemorrhage with pale centre)



Clinical Features of Infective Endocarditis

FROM JANE
Fever
Roth's spots
Osler's nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhages (i.e. splinter hemorrhages)
Emboli

Diagnosis

- Modified Duke Criteria
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor

Table 17. Modified Duke Criteria

Major Criteria (2)
1. Positive blood cultures for IE • Typical microorganisms for IE from 2 separate blood cultures (*Streptococcus viridans*, HACEK group, *Streptococcus gallolyticus*, *Staphylococcus aureus*, community-acquired enterococci) OR • Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart OR • All of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR • Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800 2. Evidence of endocardial involvement • Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve); and new valvular regurgitation (insufficient if increase or change in pre-existing murmur)
Minor Criteria (5)
1. Predisposing condition (abnormal heart valve, IVDU) 2. Fever (38.0°C/100.4°F) 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracerebral hemorrhage (ICH), conjunctival hemorrhages, Janeway lesions 4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots 5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE



TEE Transesophageal echo
TTE Transthoracic echo

Investigations

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of an endovascular infection (e.g. IE)
- repeat blood cultures (at least 2 sets) after 48-72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), erythrocyte sedimentation rate (ESR) (increased), rheumatoid factor (RF) (+), urea/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- echo findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) indicated for all suspected IE, inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

Treatment

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment unless patient is septic
  - empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken. Generally, *S. aureus*, coagulase-negative *Staphylococcus* (CNST), and GN coverage is important
    - first line empiric treatment for native valve: vancomycin + ceftriaxone OR gentamicin
    - first line empiric treatment for prosthetic valve: vancomycin + gentamicin + rifampin
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and susceptibilities
  - monitor for complications of IE (e.g. heart failure (HF), conduction block, new emboli) and complications of antibiotics (e.g. renal disease)
  - post-treatment prophylaxis only recommended for high-risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue

- dental/respiratory procedures: amoxicillin single dose 30-60 min prior; clindamycin if truly penicillin-allergic
- infected skin/soft tissue procedures: cephalexin single dose 30-60 min prior; clindamycin if truly penicillin-allergic (modify based on etiology of skin/soft tissue infection)

• surgical
- most common indication is refractory CHF
- other indications include: valve ring abscess, valve perforation, unstable prosthesis, large vegetation >1 cm, recurrent emboli despite adequate antimicrobial treatment, antimicrobial failure (persistently positive blood cultures), fungal etiology, *S. aureus* on a prosthetic valve

Prognosis
• adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status
• mortality: prosthetic valve IE (25-50%), non-IVDU *S. aureus* IE (30-45%), IVDU *S. aureus* or streptococcal IE (10-15%)

CNS Infections

Meningitis

• see Pediatrics, P65

Definition
• inflammation of the meninges

Etiology

Table 18. Common Organisms in Meningitis

Bacterial			Viral	Fungal	Other
Age 0-4 wk	**Age 1-3 mo**	**Age >3 mo**			
GBS *E. coli* *L. monocytogenes* *Klebsiella*	GBS *E. coli* *S. pneumoniae* *N. meningitidis* *H. influenzae*	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* (likely if age >50 and comorbidities)	HSV-1, 2 VZV Enteroviruses Parechoviruses West Nile	Cryptococcus Coccidioides	Lyme disease Neurosyphilis TB

Risk Factors
• lack of immunization against *H. influenzae* type B, *S. pneumoniae*, and *N. meningitidis* in children
• most cases of bacterial meningitis are due to hematogenous spread from a mucosal surface (nasopharynx)
• direct extension from a parameningeal focus (otitis media, sinusitis) less common
• penetrating head trauma or iatrogenic
• anatomical meningeal defects – CSF leaks
• immunodeficiency (e.g. corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency, etc.)
• contact with colonized or infected persons

Clinical Features
• neonates and children: fever, lethargy, irritability, vomiting, poor feeding
• older children and adults: fever, headache, neck stiffness, confusion, lethargy, altered LOC, seizures, focal neurological signs, nausea/vomiting, photophobia, papilledema
• petechial rash in meningococcal meningitis (purpura fulminans), seen more frequently on trunk or lower extremities

Investigations
• blood work: CBC and differential, electrolytes (for SIADH), blood C&S
- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
- AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
- PCR for HSV, VZV, enteroviruses; in infants <6 mo, parechoviruses
- West Nile virus serology in blood and CSF during summer and early fall if viral cause suspected

• imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

Table 19. Typical CSF Profiles for Meningitis

CSF Analysis	Bacterial	Viral
Glucose (mmol/L)	Decreased	Normal
Protein (g/L)	Markedly increased	Increased
WBC	500-10000/μL	10-500/μL
Predominant WBC	Neutrophils	Lymphocytes



See Landmark Infectious Diseases Trials for more information on the POET trial, which investigated the efficacy and safety of shifting from IV to oral antibiotics in patients with IE.



Corticosteroids for Acute Bacterial Meningitis
Cochrane DB Syst Rev 2015;CD004405
Purpose: To examine the effect of adjuvant corticosteroid therapy vs. placebo on mortality, hearing loss, and neurological sequelae with acute bacterial meningitis.
Methods: RCTs of corticosteroids for acute bacterial meningitis.
Results: 25 studies, 4121 participants. Corticosteroids were associated with non-significant mortality reductions (RR 0.90, 95% CI 0.80-1.01). Corticosteroids were associated with lower rates of hearing loss (RR 0.74, 95% CI 0.63-0.87) and neurological sequelae (RR 0.83, 95% CI 0.69-1.00). Corticosteroids were associated with increase in recurrent fever (RR 1.27, 95% CI 1.09-1.47).
Conclusions: Corticosteroids significantly reduced hearing loss and neurological sequelae but did not reduce mortality. Data supports use in high-income countries but no benefit in low-income countries.



Brudzinski's Sign
Passive neck flexion causes involuntary flexion of hips and knees

Kernig's Sign
Resistance to knee extension when hip is flexed to 90°

Jolt Accentuation of Headache
Headache worsens when head turned horizontally at 2-3 rotations; more sensitive than Brudzinski's and Kernig's



CSF Gram Stain Findings
- *S. pneumoniae* – GP diplococci
- *N. meningitidis* – GN diplococci
- *H. influenzae* – Pleomorphic GN coccobacilli
- *L. monocytogenes* – GP rods



Does this Adult Patient have Acute Meningitis?
JAMA 1999;281:175-181
Study: Systematic review of literature analyzing the accuracy and precision of the clinical examination in the diagnosis of adult meningitis.
Results: Clinical history items have a low accuracy for the diagnosis of meningitis in adults. The sensitivity for headaches is 50% and the sensitivity for nausea/vomiting is 30%. On physical examination, absence of fever, neck stiffness, and altered mental status eliminates meningitis with a sensitivity of 99%.
Conclusions: The clinical examination aids in excluding a diagnosis of meningitis in adults with a low-risk clinical presentation. In high-risk patients, clinicians need to proceed directly to lumbar puncture given the serious implications of the infection.

Treatment
- bacterial meningitis is a medical emergency: do not delay antibiotics for CT or LP
- empiric antibiotic therapy
  - age ≤28 d: ampicillin + cefotaxime
  - age 29 d-3 mo: ceftriaxone/cefotaxime + vancomycin ± ampicillin
  - age >3 mo: ceftriaxone + vancomycin
    - add ampicillin IV if risk factors for infection with L. monocytogenes present: age >50, alcohol use disorder, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
  - continue in those patients with proven pneumococcal meningitis
  - not recommended for patients with suspected bacterial meningitis in some resource-limited countries
  - not recommended for neonatal meningitis

Prevention
- see Pediatrics, P65
- immunization
  - children: immunization against *H. influenzae* type B (Pentacel®), *S. pneumoniae* (Synflorix®, Prevnar-13®), *N. meningitidis* (Menjugate®, Menactra®, Nimenrix®, Menveo®, Bexsero®)
  - adults: immunization against *N. meningitidis* in selected circumstances (immunocompromised, outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with H. influenzae type B should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with *N. meningitidis*; meningococcal vaccines are also recommended for post-exposure prophylaxis for close contacts and in outbreak control

Prognosis
- complications
  - death, headache, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

Public Health Agency of Canada Indications for Adult Immunization

Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®)
≥65 yr (option to also give pneumococcal conjugate vaccine; if so, to give polysaccharide vaccine 8 wk after conjugate vaccine)

Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®) and Pneumococcal Conjugate Vaccine
Chronic cardiovascular/respiratory/hepatic/renal disorders, asplenia, sickle cell, or immunosuppression (polysaccharide vaccine to be given 8 wk after pneumococcal conjugate vaccine)

Meningococcal Quadrivalent Vaccine (Menactra® or Menomune®)
Healthy young adults
Asplenia
Travellers to high-risk areas
Military recruits or laboratory personnel
Complement, factor D, or properdin deficiency or acquired terminal complement deficiency through receipt of eculizumab

Multicomponent Meningococcal Serogroup B Vaccine (Bexsero®)
Asplenia
Military recruits or laboratory personnel
Complement, factor D, or properdin deficiency, or acquired terminal complement deficiency through receipt of eculizumab

Encephalitis

Definition
- inflammation of the brain parenchyma

Etiology
- identified in only 40-70% of cases
  - when cause is identified, the most common etiology is viral: HSV, VZV, EBV, CMV, enteroviruses, parechoviruses, West Nile and other arboviruses, influenza and other respiratory viruses, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, mycobacteria, spirochetes (Lyme, syphilis), *Mycoplasma pneumoniae*
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. acute disseminated encephalomyelitis (ADEM))

Pathophysiology
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response viruses may reach the CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial, temporal, and inferior frontal lobes
  - associated with HSV-1, less likely caused by HSV-2
- influenza and other respiratory viruses are associated with acute necrotizing encephalopathy (ANE); likely mediated by pathogen-initiated immune response

Clinical Features
- constitutional: fever, chills, malaise, nausea/vomiting
- meningeal involvement (meningoencephalitis): headache, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behavioural disturbances
  - rare complication: development of encephalopathy and Kluver-Bucy syndrome characteristics 1 mo after completion of treatment for HSV encephalopathy

Meningitis and encephalitis patients can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behaviour, speech or movement disorders), but may be normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes ("meningoencephalitis")

Investigations
- CSF: opening pressure, cell count and differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses/parechoviruses, *M. pneumoniae*, and selectively for other less common etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. EBV, West Nile virus, rabies, *Bartonella henselae*)
- imaging/neurologic studies: CT, MRI, EEG to define affected anatomical sites
- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

Treatment
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out

Generalized Tetanus

Etiology and Pathophysiology
- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wounds, burns, non-sterile surgeries, or deliveries)
- upon inoculation, spores develop into *C. tetani* bacilli that produce tetanus toxins
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

Clinical Features
- generalized tetanus
  - initially present with painful spasms of masseters (trismus or "lockjaw")
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, HTN, fever as illness progresses



Antimicrobial therapy (e.g. metronidazole) may fail to treat C. tetani unless adequate wound debridement is performed

Investigations
- primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
- culture wounds, CK may be elevated

Treatment
- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole (effective alternative: IV penicillin G)
- neutralize unbound toxin with tetanus immune globulin (TIg)
- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket

control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

Prevention
- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see Pediatrics, P65 and Emergency Medicine, ER17)

Rabies

Definition
- acute progressive encephalitis caused by RNA virus (genus Lyssavirus of the Rhabdoviridae family)

Etiology and Pathophysiology
- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoons, skunks, bats, foxes, cats, and dogs; monkeys also a risk in the tropics and sub-tropics
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  - almost all cases due to bites
  - animals can be carriers for several days before manifest signs of disease

- virus travels via retrograde axonal transport from PNS to CNS
- virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
  - infected animal can transmit rabies virus as soon as it shows signs of disease

Clinical Features

- five stages of disease
  1. incubation period
     - 1-3 mo on average (can range from days to years, depending on distance from bite site to CNS)
  2. prodrome (<1 wk)
     - low-grade fever, malaise, anorexia, nausea/vomiting, headache, sore throat
     - pain, pruritus, and paresthesia may occur at wound site
     - once prodromal symptoms develop, there is rapid, irreversible progression to death
       - progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome
  3. acute neurologic syndrome: 2 types (<1 wk)
     a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, hypersalivation, fever, seizures
       - painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia and hydrophobia, respectively

     b. paralytic: quadriplegia, loss of anal sphincter tone, fever
  4. coma
     - complete flaccid paralysis, respiratory, and cardiovascular failure
  5. death (within days to weeks of initial symptoms)

Investigations

- purpose of diagnosis by investigations is to limit patient contact with others and to identify others exposed to the infectious source
- antemortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

Treatment

- post-exposure prophylaxis depends on regional prevalence and circumstances surrounding injury
- mandatory to report animal bite/contact that may result in rabies to Public Health Authority
- if not previously immunized:
  - wound care: clean wound promptly and thoroughly with soap and running water for 15 min
  - passive immunization: rabies immunoglobulin (RIG) infiltrated into wound site, with any remaining volume administered IM in anatomical site distant from vaccine administration
    - due to variable response rates, vaccine should not be administered into gluteal muscle
  - active immunization: inactivated human diploid cell rabies virus vaccine (HDCV) – series of 4 shots post-exposure on d 0, 3, 7, and 14
    - vaccine administered into deltoid
- if previously immunized:
  - wound care: clean wound promptly and thoroughly with soap and running water for 15 min
  - two doses of HDCV into deltoid on d 0 and 3
  - no RIG administered
- treatment is supportive once victim manifests signs and symptoms of disease

Prevention

- pre-exposure vaccination
  - recommended for high-risk persons: laboratory staff working with rabies, veterinarians, animal and wildlife control workers, long-term travellers to endemic areas

Systemic Infections

Sepsis and Septic Shock

- see Respirology, R32

Definitions

- bacteremia: bacteria in blood from primary bloodstream infection or secondary to infection of another body system
- sepsis: severe organ dysfunction resulting from dysregulated host response to infection
  - organ dysfunction identified via acute change in SOFA score ≥2 points
  - qSOFA score used initially to screen patients for suspected sepsis using three criteria:
    1. respiratory rate ≥22/min
    2. sBP ≤100 mmHg
    3. altered mentation (GCS <15)
- septic shock: subset of sepsis with circulatory and cellular/metabolic dysfunction; clinically defined in cases where despite adequate volume resuscitation there is both
    1. persistent hypotension requiring vasopressors to maintain MAP ≥65 mmHg AND
    2. serum lactate >2 mmol/L



SOFA score >2 = 10% mortality risk in patient with suspected infection
Hospital mortality with septic shock >40%



qSOFA score
1. Respiratory rate ≥22/min
2. sBP ≤100 mmHg
3. Altered mentation (GCS <15)

Pathophysiology
- causative agents are identified in only 50-70% of cases
- when organisms are identified, GP and GN organisms are the cause in 90% of cases
- bacteremia → local immune response → pro-inflammatory cytokine release → spread of immune response beyond local environment → unregulated, exaggerated systemic immune response → vasodilation and hypotension → distributive shock and reduced O_2 delivery to tissues → anaerobic metabolism and lactic acid production → metabolic acidosis → multiple organ failure

Clinical Features
- history: symptoms and signs specific to an infectious source (e.g. cough, headache, dysuria, purulent exudate, rash)
- general symptoms of infection: fever, chills, pain, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (e.g. fever, tachypnea, tachycardia, hypotension), flushed skin, altered mental status, local signs of infection (e.g. pharyngitis, septic arthritis, neck stiffness, skin wounds/ulcers, or murmurs)

Investigations
- CBC and differential, electrolytes, urea, creatinine, liver enzymes, ABG, lactate, INR, PTT, troponin, blood C&S x2, urinalysis, urine C&S, and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)
- nasopharyngeal swab/stool/sputum cultures, throat swabs, genital swab, LP as indicated

Treatment (see Respirology, R32)
- respiratory support: O_2 ± intubation
- cardiovascular support: IV fluids ± blood transfusion + vasopressors + ICU
- IV antibiotics (empirical, guided by suspected source)
  - consider broad spectrum antibiotics (e.g. piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology or focus of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant Gram-negatives or vancomycin for MRSA)
  - breadth of empiric coverage should take into account: i) estimated adequacy of spectrum of activity and ii) degree of instability or severity of infection
  - narrow once organism and susceptibilities are known
- source control: procedure to control focus of infection (catheter removal, abscess drainage)
- hydrocortisone IV may be added in patients with septic shock unresponsive to fluid resuscitation and vasopressors

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 re-defined sepsis using the Sequential Organ Failure Assessment (SOFA) score for diagnosis and Quick-SOFA (qSOFA) for screening of end-organ failure. The terms severe sepsis and systemic response inflammatory response syndrome (SIRS) are no longer part of the sepsis definition

Leprosy (Hansen's Disease)

Etiology
- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

Clinical Features
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  - i. paucibacillary "tuberculoid" leprosy (intact cell-mediated immune response)
    - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
    - may be self-limited, stable, or progress over time to multibacillary "lepromatous" form
  - ii. multibacillary "lepromatous" leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  - iii. borderline leprosy
    - lesions and progression lie between tuberculoid and lepromatous forms

Investigations
- skin biopsy down to fat or slit skin smears for AFB staining, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment
- regimens based on WHO recommendations
- paucibacillary: dapsone daily + rifampin monthly + clofazimine monthly AND low dose clofazimine once daily x 6 mo
- multibacillary: dapsone daily + rifampin monthly + clofazimine monthly x 12 mo AND low dose clofazimine once daily for 12 mo

- treatment of leprosy (along with other precipitants of immune responsiveness such as viral illness, immunization, hormonal fluctuations of pregnancy, and parturition) can cause an immune reaction to killed or dying bacteria (e.g. erythema nodosum leprosum [a type of antigen-antibody complex deposition panniculitis] and reversal reaction [upgrading cell-mediated immune response]):
  - symptomatic management with NSAIDs if mild
  - prednisone with 12-24 wk taper if severe
  - thalidomide for erythema nodosum leprosum

Prognosis
- curable with WHO approved treatment regimens
- complications: muscle atrophy, contractures, blindness, trauma/superinfection of lesions, crippling/loss of digits and limbs, erythema nodosum leprosum, social stigmatization due to clofazimine hyperpigmentation
- long post-treatment follow-up warranted to monitor for relapse and immune

Lyme Disease





BAKE a Key Lyme Pie
Bell's palsy
Arthritis
Kardiac block
Lyme
Erythema chronicum migrans

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (North America), *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by *Ixodes* tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- as a result of climate change, Lyme disease has spread into higher latitudes. In Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick, and Nova Scotia, as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white-tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas, but may start earlier in the spring or later in the fall as a result of warmer winters due to climate change
- infection usually requires >36 h tick attachment
- as a result of climate change, other tick-borne diseases are expected to increase in prevalence: Anaplasmosis, Babesiosis, Powassan virus, and B. miyamotoi disease

Clinical Features
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, headache, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) at site of tick bite
- stage 2 (early disseminated stage: weeks post-infection)
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early-stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronicum atrophicans (due to B. afzelii)
  - neurologic: encephalopathy, meningitis, neuropathy

Investigations
- order Public-Health-Lab-approved Lyme disease testing and interpret results on basis of symptoms
- a negative test for Lyme disease does not preclude a tick-borne disease; further testing may be indicated if symptoms are present

Prevention
- early identification, investigation of symptoms, and reporting of tick-borne illnesses
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks, and prompt removal of tick
- doxycycline single dose prophylaxis within 72 h of removal of an engorged Ixodes scapularis tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone or doxycycline

Toxic Shock Syndrome

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- staphylococcal Toxic Shock Syndrome (TSS) involves the production of superantigen toxic shock syndrome toxin 1 (TSST-1)
- streptococcal TSS involves the production of superantigens SPEA, SPEB, SPE

Risk Factors
- staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or cesarean or surgical infections)
- streptococcal: minor trauma, surgical procedures, preceding viral illness (e.g. chickenpox), use of NSAIDs

Clinical Features and Investigations
- acute onset
- staphylococcal TSS
  - T >38.9°C
  - sBP ≤90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
- streptococcal TSS
  - sBP ≤90 mmHg
  - isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

Treatment
- supportive care, fluid resuscitation, surgical debridement of infected tissue
- streptococcal: IV penicillin and clindamycin ± IVIG
- staphylococcal: for methicillin-susceptible *S. aureus*: clindamycin + cloxacillin (IV); for MRSA: clindamycin + vancomycin x 10-14 d

Cat Scratch Disease

Etiology
- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

Clinical Features
- skin lesion appears 30 d post-inoculation
- may be followed by fever, malaise, tender regional lymphadenopathy
- usually self-limited
- in some patients, organism may disseminate causing FUO, hepatosplenomegaly, retinitis, encephalopathy, infective endocarditis, uveitis
- in patients with advanced HIV, can present with violacious nodular skin lesions + underlying bone involvement, known as "bacilliary angiomatosis"

Investigations
- serology, PCR, lymph node biopsy

Treatment
- the disease may be self-limited but treatment is recommended by the Infectious Disease Society of America with a 5 d course of azithromycin for immunocompetent patients with mild to moderate illness
- needle aspiration of painful suppurative lymph nodes may hasten the relief of symptoms
- combination therapy consisting of doxycycline or azithromycin plus rifampin often used for disseminated disease (neuroretinitis, hepatosplenic involvement)

Rocky Mountain Spotted Fever

Etiology
- Rickettsia rickettsii: obligate intracellular GN organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks in North America; *Rhipicephalus* ticks in Mexico and Central America
- organisms cause inflammation of endothelial lining of small blood vessels, leading to small hemorrhages and thrombi
- can cause widespread vasculitis leading to headache, and CNS changes; can progress to death if treatment is delayed

Clinical Features
- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, headache, myalgia, nausea/vomiting, anorexia
- macular rash appearing on d 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally "spotless" (10% of patients)

Investigations
- skin biopsy and serology (indirect fluorescent antibody test)

Treatment
- empiric doxycycline, usually 5-7 d (treat for 3 d after defervescence)

West Nile Virus

Epidemiology
- virus has been detected throughout the United States and much of southern Canada (Quebec, Ontario, Manitoba, Saskatechewan, Alberta)
- case-fatality rates in severe cases are ~10%

Transmission
- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation
- rising temperatures linked to increased mosquito survival and geographical range, increased biting rates, increased replication of virus within mosquitoes, shorter reproduction rates, and longer transmission seasons. Climate change also affects bird migration patterns and timing, causing changes in virus spread

Clinical Features
- 80% are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of headache, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis, and acute flaccid paralysis (especially in those >60 yr)

Investigations
- IgM antibody in serum or CSF is the best test (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood, and fluids (all have low sensitivity due to transient viremia)
- CSF: elevated lymphocytes and protein if CNS involvement

Treatment and Prevention
- treatment: supportive
- prevention: mosquito repellant (DEET, picaridin), drain stagnant water, community mosquito control programs

Syphilis





Argyll Robertson Pupil
Accommodates but does not react to light



Those with Untreated 1° or 2° Syphilis
1/3 Cure
1/3 Latent indefinitely
1/3 3° syphilis



Causes of False Positive VDRL and RPR Tests

Viruses (mononucleosis, hepatitis)
Drugs and substance misuse
Rheumatic fever
Lupus and leprosy

Etiology
- *Treponema pallidum*: thick motile spirochetes historically detectable by dark-field microscopy
- transmitted sexually, vertically, or parenterally (rare)

Clinical Features
- see Dermatology, D38 and Gynecology, GY30
- multi-stage disease
  1. primary syphilis (3-90 d post-infection)
     - painless chancre at inoculation site (any mucosal surface)
     - regional lymphadenopathy
     - acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  2. secondary syphilis = systemic infection (2-8 wk following chancre)
     - maculopapular non-pruritic rash including palms and soles
     - generalized lymphadenopathy, fever, malaise, headache, aseptic meningitis, ocular/otic syphilis
     - condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious)
  3. latent syphilis
     - asymptomatic infection that follows untreated primary/secondary syphilis
     - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
     - increased transmission risk with early latent; longer treatment duration required for late latent
  4. tertiary syphilis (1-30 yr post-infection)
     - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
     - aortic aneurysm and aortic insufficiency
  5. congenital syphilis
     - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
     - most infected newborns are asymptomatic
     - clinical manifestations in early infancy include rhinitis (snuffles), lymphadenopathy, hepatosplenomegaly, pseudoparalysis (bone pain associated with osteitis), and rash (usually maculopapular and involving palms and soles)

- late onset manifestations (>2 yr of age) include saddle nose, saber shins, Clutton joints, Hutchinson's teeth, mulberry molars, rhagades, CN VIII deafness, interstitial keratitis, juvenile paresis

6. neurosyphilis
   - headache, dementia, difficulty in coordination, paralysis, sensory deficits, personality changes, Argyll-Robertson pupils, tabes dorsalis
   - can occur from secondary stage onward



Patients with 2° or 3° syphilis treated with penicillin may experience a Jarisch-Herxheimer reaction. Lysis of organisms releases pyrogens thought to cause fever, chills, myalgia, and flu-like symptoms that may last up to 24 h

Investigations

- syphilis tests are conducted by Public Health labs. Thus, order set for syphilis is simplified and does not require specification of which test to complete. Below are details on what tests are conducted at the Public Health lab
- initial screening tests: traditionally non-treponemal tests (RPR, VRDL), or treponemal tests in some jurisdictions (EIA, CMIA, CLIA)
- confirmatory tests: treponemal tests (TPPA, FTA-ABS, MHA-TP, TPI)
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others
- for congenital syphilis, LP is essential; long bone x-rays may also be helpful



VDRL Venereal Disease Research Laboratory
RPR Rapid Plasma Reagin
EIA Enzyme Immunoassay
CLIA ChemiLuminescent ImmunoAssay
CMIA ChemiLuminescent Microparticle ImmunoAssay
FTA-ABS Fluorescent Treponema Antibody-Absorption
MHA-TP Microhemagglutination Assay *T. pallidum*
TPPA *T. pallidum* Particle Agglutination Assay
TPI *T. pallidum* immobilization test

Treatment

- for 1°, 2°, early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3°, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if truly allergic to penicillin: doxycycline 100 mg PO BID x 14 d is a second line therapy (x 28 d in late disease)
- for pregnant patients allergic to penicillin, oral desensitization techniques are considered safe
- neurosyphilis: aqueous penicillin G 16-24 million units/d IV x 14 d ± single dose of benzathine penicillin
- for congenital syphilis, penicillin G IV x 10 d
- see Family Medicine, FM47 for generalized STI workup

Tuberculosis

Etiology, Epidemiology, and Natural History

- 1/3 of the world's population is infected with TB
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
- inhalation and deposition in the lung can lead to one of the following outcomes:
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 90% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 1-2 yr of initial infection) at a pulmonary or extra-pulmonary site



Tuberculous Polyserositis
Pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)

Risk Factors

- social and environmental factors
  - birth in or extended travel to a country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - the incidence of TB is 25 times higher in Canadian-born Indigenous peoples (highest in Inuit) compared to Canadian-born non-Indigenous peoples
  - personal/occupational contact, crowded living conditions, low socioeconomic status (SES), people experiencing homelessness, IDU
- host factors
  - immunocompromised (especially HIV), including extremes of age
  - immunosuppressed (TNF-α inhibitors, glucocorticoids)
  - silicosis
  - chronic kidney disease requiring dialysis
  - diabetes
  - malignancy and chemotherapy
  - substance use (e.g. drug use, alcohol use disorder, smoking)

Clinical Features

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms

1. pulmonary TB
   - chronic productive cough + hemoptysis, fever, night sweats, weight loss, chest pain, anorexia
   - CXR consolidation or cavitation, lymphadenopathy, predominantly upper lung findings but variable
   - non-resolving pneumonia despite standard antimicrobial therapy
2. miliary TB
   - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
   - CXR: multiple small 1-5 mm millet seed-like lesions throughout lung

3. extra-pulmonary TB
    - can occur in any organ - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott disease), adrenal (causing Addison disease), renal, ovarian

Investigations

- screening for latent TB may be done via TST or IFN-γ release assay (IGRA)
    - both can be used to diagnose prior TB infection. IGRA has fewer false positives as it does not detect antigens in BCG vaccine or most types of non-tuberculosis mycobacteria
        - neither should be used in adults for active TB diagnosis or monitoring anti-TB treatment response
        - TST preferred when repeat testing planned to assess risk of new infection (e.g. serial testing in healthcare)
- IGRA preferred when BCG vaccine after 1 y/o, vaccination more than once, or unable to return for reading
- diagnostic tests/investigations for active pulmonary TB
    - sputum specimens (either spontaneous or induced) should be collected for AFB smear and culture; the three specimens can be collected on the same day, a minimum of 1 h apart
    - BAL if other lung pathology (e.g. lung cancer) also suspected, or TB suspected despite negative sputum samples
    - CXR
        - classic triad: apical-posterior infiltrates, lung volume loss, cavitation
        - atypical features: hilar/mediastinal lymphadenopathy, non-cavitary infiltrates
        - signs of complications: endobronchial spread, pleural effusion, pneumothorax
        - Ghon complex: a parenchymal granuloma, indicating a previous tuberculosis infection, and a calcified hilar lymph node on the same side



Positive TST Test
If induration at 48-72 h
>5 mm if immunocompromised, close contact with active TB
>10 mm all others; positive PPD; CXR; decision to treat depends on individual risk factors
False(–): poor technique, anergy, immunosuppression, infection <10 wk or remotely
False(+): BCG after 12 mo of age in a low-risk individual, nontuberculous mycobacterial (NTM)
Booster effect: initially false(–) result boost to a true(+) result by the testing procedure itself (usually if patient was infected long ago so had diminished delayed type hypersensitivity reaction or if history of BCG)

Prevention

- primary prevention
    - airborne isolation for active pulmonary disease
    - BCG vaccine
        - ~80% effective against paediatric miliary and meningeal TB
        - effectiveness in adults debated (anywhere from 0-80%)
        - recommended in high-incidence communities in Canada for infants in whom there is no evidence of HIV infection of immunodeficiency; widely used in other countries
- prevention of reactivation of latent infection
    - rifampin (RIF) (10 mg/kg (600 mg maximum)) daily for 4 mo (active disease must be ruled out)
    - isoniazid (INH) (15 mg/kg (900 mg maximum)) + pyridoxine (B6) and rifapentine (RPT) (dose by weight) weekly for 3 mo
    - INH (5 mg/kg (300 mg maximum)) + pyridoxine (B6) daily for 9 mo (previous standard regimen, recommended when rifamycin regimens cannot be used)
    - INH (5 mg/kg (300 mg maximum)) + pyridoxine (B6) daily for 6 mo
    - INH (5 mg/kg (300 mg maximum)) + pyridoxine (B6) and RIF (10 mg/kg (600 mg maximum)) daily for 3 mo



TB Treatment

RIPE
Rifampin
INH
Pyrazinamide
Ethambutol

Treatment of Active Infection

- given the nuances of TB treatment, active TB infection should be managed by an experienced TB clinician

pulmonary TB: INH + rifampin + pyrazinamide + ethambutol x 2 mo (initiation phase), then INH + rifampin x 4 mo in fully susceptible TB (continuation phase), total 6 mo. Extend continuation phase to 7 mo if >65 y/o, pregnant, or risk of hepatotoxicity

- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- for patients taking INH, pyridoxine should be added in cases of diabetes, renal failure, malnutrition, substance use disorders, seizure disorders, pregnancy/breastfeeding, risk of neuropathy
- empiric treatment of suspected MDR or extensively drug-resistant (XDR) TB requires referral to a specialist
    - MDR = resistance to INH and rifampin ± others
    - XDR = resistance to INH + rifampin + fluoroquinolone + >1 of injectable, second-line agents
        - very difficult to treat, global public health threat, 5 documented cases in Canada from 1997-2008
    - suspect MDR TB if previous treatment failed, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information)

HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2016)
- estimated 65040 Canadians living with HIV infection at the end of 2016, 20% unaware of HIV-positive status
- 2090 new infections were reported in 2013: MSM account for 53% of cases, people who inject drugs (PWID) 19%%

Global Situation (WHO and UNAIDS Core Epidemiology Slides, July 2018)
- estimated 36.7 million people living with HIV/AIDS at the end of 2016
- estimated 1.8 million newly infected in 2016
- estimated 1 million AIDS-related deaths in 2016

Etiology

- HIV is a retrovirus that causes progressive immune system dysfunction, predisposing patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17), and capsid (p24), enclosing 2 single-stranded copies of RNA plus enzymes in its core
- virion glycoproteins bind CD4 and CCR5/CXCR4 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by viral reverse transcriptase; dsDNA is integrated into host genome by viral integrase
- virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes
- newly produced virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virion is considered infectious
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, and increased cell turnover

Modes of Transmission

Table 20. Modes of Transmission in Adolescents and Adults by Site and Medium

HIV Invasion Site	Sub-Location	Transmission Medium	Transmission Probability per Exposure Event
Female genital tract	Vagina, ectocervix, endocervix	Semen	1 in 200 to 1 in 2000
Male genital tract	Inner foreskin, penile urethra	Cervicovaginal and rectal secretions and desquamations	1 in 700 to 1 in 3000
Intestinal tract	Rectum	Semen	1 in 20 to 1 in 300
	Upper GI tract	Semen	1 in 2500
		Maternal blood/genital secretions (intrapartum)	1 in 5 to 1 in 10
		Breastmilk	1 in 5 to 1 in 10
Placenta	Chorionic villi	Maternal blood (intrauterine)	1 in 10 to 1 in 20
Blood stream		Contaminated blood products Sharp/needlestick injuries	95 in 100 to 1 in 150

Adapted with permission from Macmillan Publishers Ltd., Hladik F, McElrath MJ. Setting the stage: host invasion by HIV. Nat Rev Immunol 2008;8:447-457.
NOTE: these estimates are for "all comers" i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study)

p24 = capsid protein
gp41 = fusion and entry
gp120 = attachment to host T-cell

Homozygosity for A32 mutation in CCR5 gene confers relative resistance to HIV infection
Heterozygosity for A32 mutation in CCR5 gene associated with slower disease course

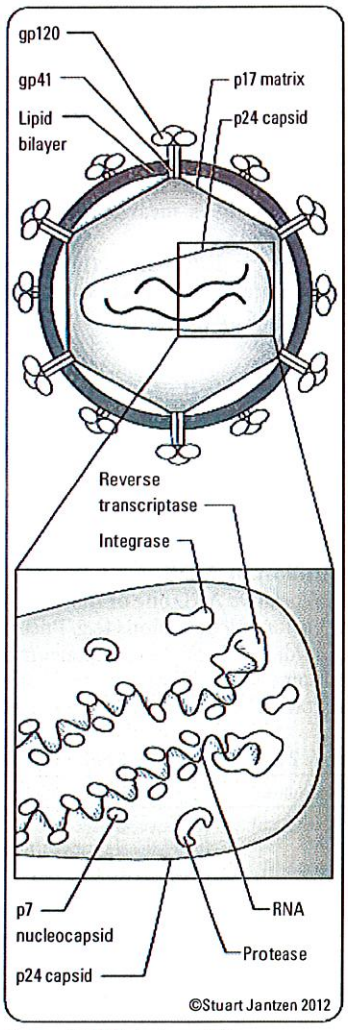


Figure 7. HIV viral particle

Natural History

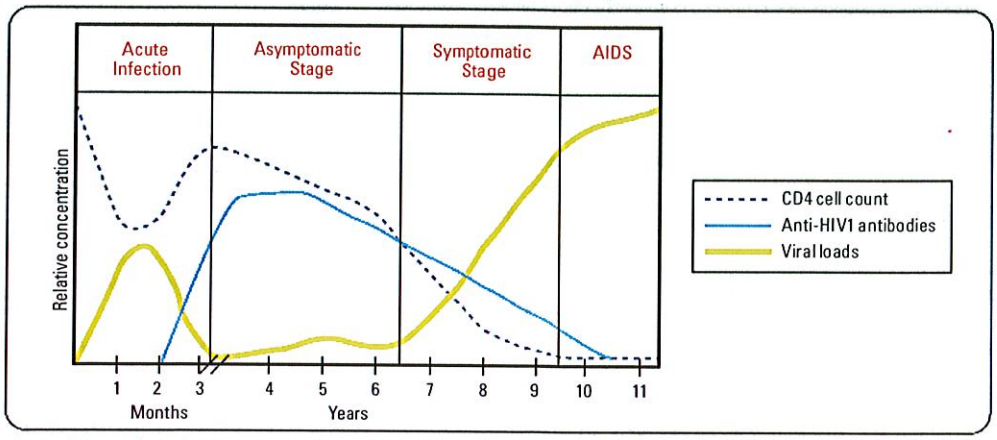


Figure 8. Relationships between CD4 T-cell count, viral load, and anti-HIV1 antibodies

Acute (Infection) Retroviral Syndrome

- 40-90% experience an acute non-specific illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, headache, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis, CN palsies, or other neurological presentations; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high-risk of transmission

Asymptomatic (Latent) Stage

- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count in adults: 500-1100 cells/mm^3
- CD4 count drops 60-100 cells/mm ^{3}per yr but is variable
- by 10 yr post-infection, 50% have advanced HIV (i.e. AIDS), 30% demonstrate milder symptoms, and <20% are asymptomatic if untreated

Definition of AIDS

- HIV-positive AND one or more of the clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. Pneumocystis jiroveci pneumonia (PJP, previously PCP), esophageal candidiasis, CMV, Mycobacterium avium complex (MAC), TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome OR CD4 <200 (or <15%); this is largely historical because ART can reverse CD4 count decline

Table 21. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

CD4 Counts	Possible Manifestations
<500 cells/mm^3	Often asymptomatic Constitutional symptoms: fever, night sweats, fatigue, weight loss Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), KS Recurrent bacterial infections, especially pneumonia Pulmonary and extrapulmonary tuberculosis Lymphoma
<200 cells/mm^3	*Pneumocystis jiroveci* pneumonia (formerly PCP) KS Oral thrush Local and/or disseminated fungal infections: *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*
<100 cells/mm^3	Progressive multifocal leukoencephalopathy (PML) – JC virus CNS toxoplasmosis
<50 cells/mm^3	CMV infection: retinitis, colitis, cholangiopathy, CNS disease MAC Bacillary angiomatosis (disseminated *Bartonella*) Primary CNS lymphoma (PCNSL)

Laboratory Diagnosis

- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): ELISA detects serum antibody to HIV; sensitivity >99.5%
- increasingly, combination p24 antigen/HIV antibody tests (4th generation) used for screening; improved sensitivity in early or acute infection and sensitivity/specificity approach 100% for chronic infection
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%

Sexual Activity without Condoms and Risk of HIV Transmission in Serodifferent Couples when the HIV-Positive Partner is using Suppressive Antiretroviral Therapy
JAMA 2016;316(2):171-181
Purpose: To evaluate the rate of within-couple HIV transmission (heterosexual and MSM) during periods of sex without condoms and when the HIV+ partner had HIV-1 RNA <200 copies/mL.
Methods: Prospective, observational PARTNER study, enrolled 1166 HIV serodifferent couples (in which the HIV+ partner was taking ART) who reported having condomless sex. Primary outcome was risk of within-couple HIV transmission to HIV- partner.
Results: Enrolled couples provided 1238 eligible couple-years of follow-up. Couples reported condomless sex for a median of 2 yr and condomless sex with other partners was reported by 108 HIV- MSM and 21 heterosexuals. While 11 HIV- partners became HIV+ (10 MSM; 1 heterosexual), no phylogenetically linked transmissions occurred over eligible couple-years of follow-up (within-couple HIV transmission = 0, 95% CI 0.30-0.71 per 100 couple-years).
Conclusions: Among serodifferent heterosexual and MSM couples in which HIV+ partner was using ART and who reported condomless sex, during median 1.3 yr/couple follow-up, there were no documented cases of within-couple transmission.

Seroconversion: Development of detectable anti-HIV antibodies

Window Period: Time between infection and development of anti-HIV antibodies; when serologic tests (ELISA, Western blot) are negative

All infants born to HIV-infected mothers have positive enzyme linked immunosorbent assay (ELISA) tests because of circulating maternal anti-HIV antibodies, which disappear by 18 mo; early diagnosis is made by detection of HIV RNA in plasma

HLA-B*5701 Testing
Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of White individuals, lower prevalence in other ethnic groups)
Routine screening for HLA-B*5701 at baseline and definitely prior to abacavir use

HIV Status
CD4 count: progress and stage of disease
Viral load: rate of progression

HIV Non-disclosure Laws in Ontario
In 2017, Ontario changed HIV non-disclosure laws for people living with HIV, where non-disclosure of HIV status to a sexual partner is no longer considered a criminal offense if one of the following criteria is met:

- On antiretroviral therapy with a viral load <200 copies/mL for at least 6 mo
- Viral load between 200-1500 copies/mL and a condom is used properly and does not break

- rapid (point-of-care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during "window period"

Management of the HIV-Positive Patient

- verify positive HIV test
- complete baseline history and physical exam, then follow-up every 3-6 mo
- laboratory evaluation
  - if non-stable and non-suppressed viral load, order routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load) also important indicator of effect of ART
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B*5701 genetic test to screen for abacavir hypersensitivity if considering abacavir in treatment regimen
  - CCR5 tropism testing if considering CCR5 antagonist in treatment regimen
  - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B, and C, syphilis, toxoplasmosis, CMV, VZV)
  - routine biochemistry and hematology, CXR, urinalysis
  - annual fasting lipid profile and fasting glucose (due to ART side effects)
- education
  - regular follow-up on viral loads (q3-6 mo) as well as strict adherence to ART improves prognosis; routine monitoring of CD4 counts until consistently over 500 cells/mm^{3}with suppressed viral load
  - prevention of further transmission through safer sex and clean needles for IDU
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) can rarely occur so barrier protection during sex is still recommended
  - discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non-disclosure in jurisdictions where applicable
  - connect to relevant community groups and resources
- health care maintenance
  - assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  - vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative), HPV
  - annual screening (PAP smear), regular STI screening
  - management of comorbid conditions and provision of general primary care

Table 22. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

Pathogen	Indication for Prophylaxis	Preferred Prophylactic Regimen
Pneumocystis jirovecii	CD4 count <200 cells/mm^3	TMP/SMX 1 SS or DS once daily
Toxoplasma gondii	IgG antibody to *Toxoplasma* and CD4 count <100 cells/mm^3	TMP/SMX 1 DS once daily
Mycobacterium tuberculosis	PPD reaction >5 mm or contact with case of active TB	INH + pyridoxine daily x 9 mo
Mycobacterium avium complex	CD4 count <50 cells/mm^3	No prophylaxis if patients are started on ARTs

SS = single strength; DS = double strength
See USPHS/IDSA guidelines for preventing opportunistic infections among HIV-infected persons (Relevant Sections updated 2013, 2015). Available from: http://aidsinfo.nih.gov/

1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 mo while on ART

Anti-Retroviral Pre-Exposure Prophylaxis for Preventing HIV in High-Risk Individuals
Cochrane DB Syst Rev 2012;7:CD007189
Purpose: To evaluate the efficacy of oral anti-retroviral prophylactic therapy in preventing HIV infection.
Study: Systematic review of 12 randomized controlled trials with 6 trials forming the core analysis.
Population: 9849 HIV-uninfected patients at high risk of contracting HIV including MSM, serodiscordant couples, and others.
Outcome: New infection with HIV.
Results: Daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) reduced the risk of HIV acquisition compared to placebo (RR 0.49; 95% CI 0.28-0.85). TDF alone also showed significant risk reduction in trials with fewer patients (RR 0.33; 95% CI 0.20-0.55). There was no significant increase in adverse events in any of the treatment groups. Sexual practices and adherence did not differ between treatment and placebo arms.
Conclusions: Pre-exposure prophylaxis with TDF with or without FTC effectively reduces the risk of HIV acquisition in high-risk, HIV-uninfected patients without causing significant adverse effects.

Reasons for Deterioration of a Patient with HIV/AIDS
- Opportunistic infections
- Neoplasms
- Medication-related toxicities
- Co-infections (e.g. HBV, HCV, STIs)
- Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)

Treatment Failure
- Assess adherence
- Assess drug interactions
- Resistance testing
- Rule out opportunistic infections
- Rule out marrow suppression
- Construct new combination drug regimen

Anti-Retroviral Treatment

Overall Treatment Principles

- recommended that all HIV-positive patients initiate combination ART to restore and preserve immune function, reduce morbidity, prolong survival, and prevent transmission
- patients starting ART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of clinical and psychosocial factors on case-by-case basis
- consider results of baseline resistance testing and complete ART history before initiating or re-initiating ART
- goal: keep viral load below limit of detection i.e. <20 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo, and restore immunological function
- strong evidence against intermittent ART or 'drug holidays'
- patient with undetectable viral load adhering to ART does not transmit HIV to sexual partners

ART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 INSTI or "boosted" PI (combined with ritonavir or cobicistat for improved pharmacokinetics)
- note: guidelines are subject to frequent change. Combination therapy is suggested, preferably with single pill regimens

Treatment Failure

- defined primarily by viral load (persistently >200 copies/mL)
- ensure that viral load >20 is not just a transient viremia or 'blip'; confirm medication adherence, assess drug interactions, perform resistance testing

Table 23. Anti-Retroviral Drugs

Class	Drugs	Mechanism	Adverse Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	abacavir (ABC) emtricitabine (FTC) lamivudine (3TC) tenofovir disoproxil fumarate (TDF) tenofovir alafenamide (TAF) zidovudine (AZT) didanosine (ddI) stavudine (d4T) **Combination Tablets:** AZT/3TC (Combivir®) AZT/3TC/ABC (Trizivir®) ABC/3TC (Kivexa®) TDF/FTC (Truvada®) TAF/FTC (Descovy®)	Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth	Lactic acidosis (often secondary to mitochondrial toxicity) Lipodystrophy Rash Nausea/vomiting/diarrhea Bone marrow suppression (AZT) Peripheral neuropathy (ddI, d4T) Drug-induced hypersensitivity (ABC) Pancreatitis (ddI/d4T) Myopathy (AZT)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	delavirdine (DLV) doravirine (DOR) efavirenz (EFZ) etravirine (ETR) nevirapine (NVP) rilpivirine (RPV)	Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication	Rash, Stevens-Johnson syndrome CNS: dizziness, insomnia, somnolence, abnormal dreams (EFZ) Hepatotoxicity (NVP – avoid in females with CD4 >250, men with CD4 >400) CYP3A4 interactions
Protease inhibitors (PIs)*	atazanavir (ATV) amprenavir (APV) darunavir (DRV) darunavir/cobicistat (DRV/c) lopinavir/ritonavir (LPV/r) nelfinavir (NFV) ritonavir (RTV) tipranavir (TPV) indinavir	Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins	Lipodystrophy, metabolic syndrome Nausea/vomiting/diarrhea Nephrolithiasis (indinavir) Rash (APV) Hyperbilirubinemia (ATV, indinavir) CYP3A4 interactions Hyperlipidemia
Integrase strand transfer inhibitors (INSTIs)	bictegravir cabotegravir dolutegravir (DTG) elvitegravir (EVG) raltegravir (RAL)	Inhibits integration of HIV DNA into the human genome thus preventing HIV replication	
Fusion inhibitor (only used if resistance)	enfuvirtide (T-20)	Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection	Injection site reactions, rash, infection, diarrhea, nausea, fatigue
CCR5 antagonist	maraviroc (MVC)	Inhibit viral entry by blocking host CCR5 co-receptor	Fever, cough, dizziness

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations



Lactic Acidosis

Occurs secondary to mitochondrial toxicity

Symptoms include abdominal pain, fatigue, nausea/vomiting, muscle weakness



Lipodystrophy

Body fat redistribution (mainly with old ARVs)

Lipohypertrophy (e.g. dorsal fat pad, breast enlargement, increased abdominal girth) thought to be caused primarily by protease inhibitors

Lipoatrophy (e.g. facial thinning, decreased adipose tissue in the extremities) is thought to be caused by thymidine analogue NRTIs such as d4T and AZT

Metabolic abnormalities: lipids (increased LDL, increased TGs), glucose (insulin resistance, T2DM), increased risk of CVD

Single Tablet ART Regimens

- reduces pill burden and increases adherence
- generally better tolerated

Table 24. Single Tablet ART Regimens

Name	Contents	Common Side Effects
Biktarvy®	bictegravir/emtricitabine/tenofovir alafenamide	good side effect profile
Genvoya®	tenofovir/emtricitabine/elvitegravir/cobicistat	good side effect profile
Complera®	rilpivirine/emtricitabine/tenofovir	good side effect profile
Odefsey®	rilpivirine/emtricitabine/tenofovir alafenamide	good side effect profile
Stribild®	elvitegravir/cobicistat/emtricitabine/tenofovir	good side effect profile
Triumeq®	dolutegravir/abacavir/lamivudine	good side effect profile; use only in HLAB*5701 negative patients
Atripla®	efavirenz/tenofovir/emtricitabine	psychiatric events, vivid dreams

Recommended ARV Regimens for Treatment-Naïve HIV-infected Adults

- initial regimens for treatment (most include an integrase inhibitor and a pair of NRTIs):
  1. bictegravir/TAF/FTC
  2. DTG/ABC/3TC (in patients confirmed to be HLB*5701 negative)
  3. DTG + (TAF or TDF)/(FTC or 3TC)
  4. raltegravir + TAF (or TDF)/FTC
  5. DTG/3TC
- note: not all regimens are available in all regions

Recommended ARV Regimens for Individuals of Childbearing Potential

- there is an increased risk of neural tube defects in infants born to women on dolutegravir at time of conception
- it is not known if other INSTIs also increase risk of neural tube defects
- therefore, before beginning an INSTI-containing treatment regimen in individuals of childbearing potential, the following should be considered:
  - completing a pregnancy test
  - a discussion on risks and benefits of dolutegravir, and lack of information on other INSTIs
  - for individuals attempting to conceive: RAL + TDF/FTC, TDF/3TC, or ABC/3TC are preferred regimens; DTG regimens to be used as an alternative only
  - for individuals not attempting to conceive but are sexually active and not using contraception, consider effectiveness/tolerability, patient preferences in decision
  - for individuals using effective contraception, treatment approach is similar to that of individuals in the general population with HIV

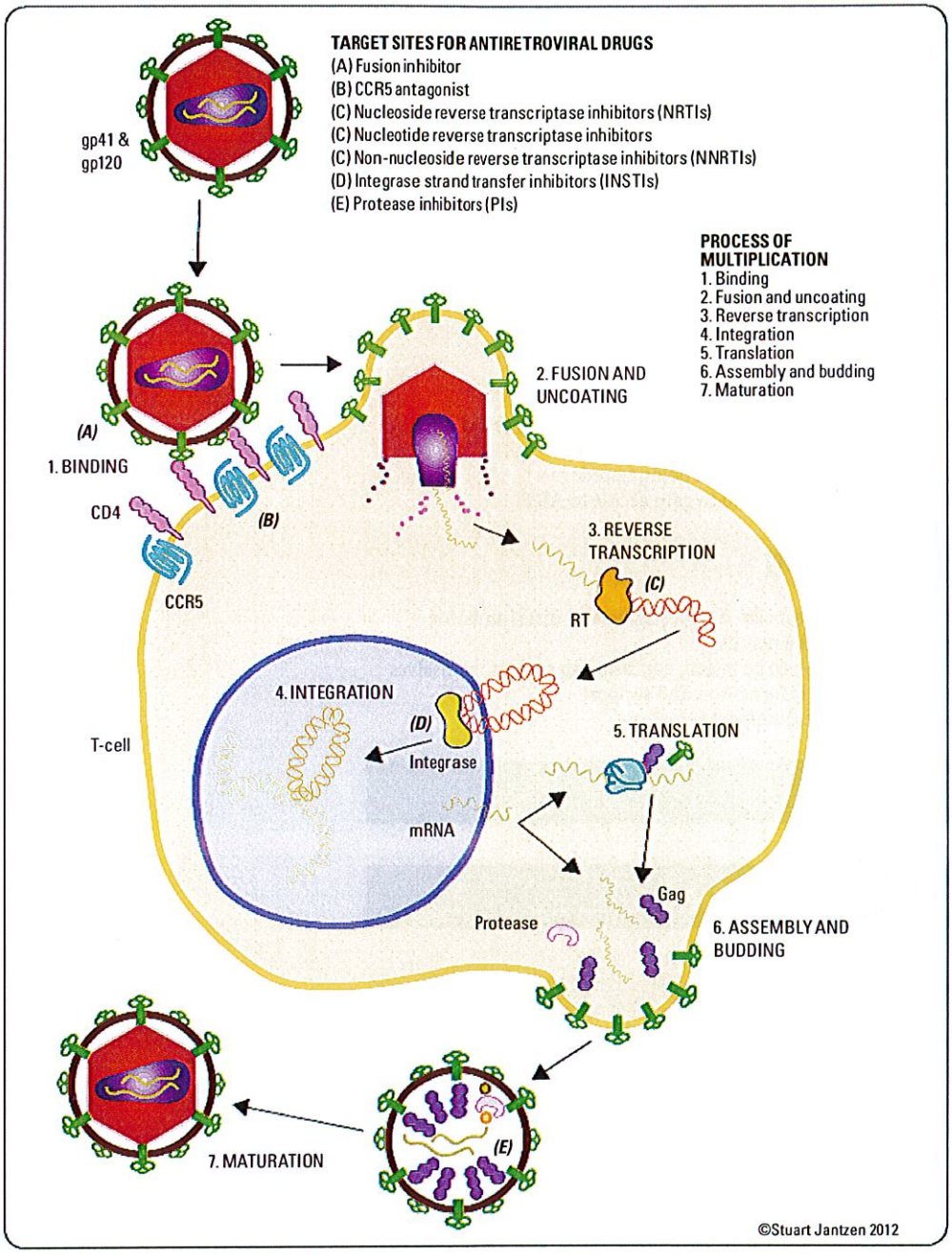


Figure 9. Mechanism of HIV replication

Prevention of HIV Infection

- education, including harm reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for IVDU: avoid sharing needles
- prevention of vertical HIV infection: treatment with ART should be initiated prior to pregnancy or as early as possible during pregnancy. The risk of vertical HIV transmission can be reduced to <1% if maternal ART is started in a timely manner and the maternal viral load is undetectable prior to delivery
- universal blood and body precautions for healthcare workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV
  - PrEP strategies include daily TDF/FTC or TAF/FTC and "PrEP on demand", where medication is taken as a double dose 12-24 h before anticipated exposure and then for 2 more doses 24 and 48 h later (i.e. 2-1-1 dosing)
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation

Early identification of HIV is essential for patients to receive the maximal benefit from ART

Efficacy, Safety, and Effect on Sexual Behaviour of On-Demand Pre-Exposure Prophylaxis for HIV in Men who have Sex with Men: An Observational Cohort Study
Lancet HIV 2017;4:402-410
Purpose: Assess the efficacy, safety, and effect of on-demand pre-exposure prophylaxis (PrEP) on sexual behaviour.
Methods: Men and transgender women who have sex with men, previously enrolled in the placebo-controlled ANRS IPERGAU trial. On demand tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) to be taken before and after sexual intercourse and participants assessed for incidence of HIV, PrEP adherence, safety, and sexual behaviour.
Results: HIV incidence was 0.19/100 person-years (95% CI 0.01-1.08) vs. 6.60/100 person-years (95% CI 3.60-11.05) in the placebo group, relative risk reduction of 97%. Drug-related GI events were reported in 14% of participants but were self-limiting. Participants reporting condomless sex at their last receptive anal intercourse increased from 77 to 86% at 18 mo follow-up.
Conclusions: On-demand oral PrEP is highly effective at preventing HIV infection among high-risk MSM. This represents an alternative to daily PrEP.

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women
NEJM 2016;375:2121-2132
Purpose: To evaluate whether longer-acting methods of anti-retroviral therapy (i.e. vaginal rings) may simplify use of medications and provide HIV-1 protection.
Methods: Phase 3, randomized, double-blind, placebo-controlled trial of monthly vaginal ring containing dapivirine in women (aged 18-45) in Malawi, South Africa, Uganda, and Zimbabwe.
Results: Among 2629 women enrolled, the incidence of HIV-1 infection was 3.3/100 person-years in dapivirine group and 4.5/100 person-years in placebo group. Post hoc analysis identified higher rates of HIV-1 protection in women >21 yr (56%, 95% CI 31-71) but not among those <21 yr (-27%, 95% CI -133-31), which correlated with reduced adherence.
Conclusions: Monthly vaginal ring containing dapivirine reduced risk of HIV-1 infection among African women.

Types of Testing

1. Nominal/Name-Based HIV Testing
- person ordering the test knows the identity of the person being tested for HIV
- HIV test is ordered using the name of the person being tested
- person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
- test result is recorded in the healthcare record of the person being tested

2. Non-Nominal/Non-Identifying HIV Testing
- similar to nominal/name-based testing on all points except:
  - HIV test is ordered using a code or the initials of the person being tested

3. Anonymous Testing
- available at specialized clinics
- person ordering the HIV test does not know the identity of the person being tested
- HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
- test results are not recorded on the healthcare record of the person being tested
- patient identification and notification of Public Health required to gain access to ART

HIV Pre- and Post-Test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV-positive individuals should be connected with local support services

FUNGAL INFECTIONS

Skin and Subcutaneous Infections

Superficial Fungal Infections

- see Dermatology, D32, D33, D37, D45 D46, and D49

Dermatophytes

- see Dermatology, D31

Subcutaneous Fungal Infections

Etiology
- subcutaneous inoculation by fungi that naturally reside in the soil, including *Sporothrix schenckii*, which usually occurs in gardeners injured by a rose thorn or splinter

Clinical Features
- causes subcutaneous nodules at the point of entry, may develop into an ulcer
- fungi may migrate up lymphatic vessels creating nodules along the way – "nodular lymphangitis"

Treatment
- oral azole
- IV amphotericin B for severe or disseminated infection

Endemic Mycoses

Etiology

- fungal infection that occurs through the inhalation of spores (from soil, bird droppings, vegetation) or inoculation injury
- thermally dimorphic organisms: mould in cold temperature (e.g. soil), and yeast at higher temperature (e.g. tissue)
- in North America, the three major endemic mycoses are: histoplasmosis, blastomycosis, and coccidioidomycosis
- NB. Previously defined regions of endemicity are expanding and can no longer be used to definitively rule out infections with specific organisms



Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts, and bat caves

Clinical Features

- may be asymptomatic
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromised states

Table 25. Endemic Mycoses

Disease	Endemic Region	Clinical Features	Investigations
Histoplasma capsulatum	Ohio and Mississippi River valleys in central USA, Ontario, Quebec; widespread	Asymptomatic (in most people) Primary pulmonary Fever, cough, chest pain, headache, myalgia, anorexia CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy CXR (chronic): pulmonary infiltrates, cavitary disease Disseminated (rare) Occurs primarily in immunocompromised patients Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS	Fungal culture, fungal stain Antigen detection (urine and serum) Serology
Blastomyces dermatitidis	States east of Mississippi River, Northern Ontario, and along the Great Lakes	May be asymptomatic Primary: acute or chronic pneumonia Fever, cough, chest pain, chills, night sweats, weight loss CXR (acute): lobar or segmental pneumonia CXR (chronic): lobar infiltrates, fibronodular interstitial disease Disseminated Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), genitourinary tract (prostatitis, epididymitis)	Sputum smear and culture Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material)
Coccidioides immitis	Deserts in southwest USA, northwest Mexico	"Valley fever": subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for wk to mo Can develop hypersensitivity with arthralgias, erythema nodosum Disseminated Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis) Common opportunistic infection in patients with HIV	Sputum culture Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material)

Opportunistic Fungi

Pneumocystis jirovecii (formerly *P. carinii*) Pneumonia: PJP or PCP

Etiology

- respiratory exposure to unicellular fungus (previously classified as a protozoan)
- can be transmitted from person to person
- without prophylaxis, HIV-positive patients with a CD4 count <200 cells/mm3 have an 80% lifetime risk of PJP
- most cases of PJP occur in patients who are unaware of their HIV infection, do not seek medical care for HIV, or who do not use prophylaxis
- in HIV-negative patients, PJP occurs almost exclusively in immunocompromised patients (e.g. organ transplant patients, inflammatory conditions, hematological malignancies)



CXR in *P. jirovecii*
Bilateral, diffuse opacities
CXR may be normal (20-30% cases)
CT shows cysts (hence the name Pneumocystis) but almost never pleural effusions

Clinical Features

- symptoms of pneumonia: fever, non-productive cough, progressive dyspnea (and hypoxia)
- classic CXR findings of interstitial pneumonia
- most clinical disease is due to reactivation of latent infection or reinfection by a different genotype in immunocompromised patients (steroid use, HIV)

Investigations

- CXR: bilateral symmetrical interstitial infiltrates
- ABG: reduced pO_2 and elevated alveolar-arterial (A-a) gradient
- serum LDH: elevated (>220 IU/L)
- induced sputum or lower airway sampling: positive for Pneumocystis, traditional test was immunofluorescence however many labs using quantitative PCR

Treatment and Prevention
- oxygen to keep SaO_2 >90%
- antimicrobial options
  - TMP/SMX (PO or IV) is preferred therapy, even for those taking this for prophylaxis
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV) is second line in severe disease
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia (pO_2 <70 mmHg or A-a gradient O_2 >35 mmHg)
- prophylactic TMP/SMX for those at high-risk of infection (HIV patients when CD4 <200 cells/mm ^{3}or non-HIV immunocompromised patients under specific conditions)

Cryptococcus spp.

Etiology
- inhalation of airborne encapsulated yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gatti*)
- *C. neoformans* tends to affect immunocompromised hosts vs. *C. gatti* which tends to affect immunocompetent hosts



C. gattii has a limited geographical distribution including Vancouver Island, Northern Australia, and Papua New Guinea

Clinical Features
- asymptomatic
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*
  - other: bone, lymph nodes, bone marrow, soft tissues, eyes, prostate

Investigations
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain or cryptococcal antigen test, culture to confirm
- lateral flow cryptococcal antigen assay from serum and CSF
- LP with measurement of opening pressure



India-ink sensitivity for Cryptococcus is only 50% (higher in HIV patients); now replaced by cryptococcal antigen test in most laboratories

Treatment
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance
  - serial lumbar puncture or other method of managing increased ICP an important adjunct to therapy

Candida albicans



Etiology
- overgrowth of *C. albicans* (normally found as part of the microbiome of the skin, mouth, vagina, and GI tract)
- risk factors for overgrowth:
  - immunocompromised state (DM, corticosteroids)
  - critically ill patients (broad-spectrum antibiotic use, central venous catheters, total parenteral nutrition)
  - obesity: maceration and moisture in intertriginous areas, pannus, under breasts

Clinical Features
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY26), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

Treatment
- thrush: clotrimazole troches, miconazole mucoadhesive buccal tablets, or nystatin suspension or pastilles for mild disease, fluconazole for severe or refractory disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

Aspergillus spp.

Etiology
- infection with *Aspergillus* fungi (*A. fumigatus, A. flavus*) which is found ubiquitously in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains, and rice

Clinical Features
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a pre-existing lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia or transplantation
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass ("halo" sign)
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver hemorrhage, necrosis, and hepatocellular carcinoma formation

Treatment Options
- voriconazole or amphotericin B for invasive aspergillosis
- surgical resection for aspergilloma; a bronchial artery embolization for severe hemoptysis due to erosion of bronchial arteries from aspergilloma
- corticosteroids ± itraconazole for ABPA



See Landmark Infectious Disease Trials table for more information on the voriconazole vs. amphotericin B for invasive aspergillosis trial. It compared voriconazole with amphotericin B for primary therapy of invasive aspergillosis.

PARASITIC INFECTIONS

Protozoa – Intestinal/Genitourinary Infections

Entamoeba histolytica (Amoebiasis)

Etiology
- infection with *E. histolytica* occurs when the cysts are transmitted via the oral-fecal route in areas of poor sanitation that have been contaminated by other infected humans, or via sexual activity
- seen in migrants, travellers, institutionalized individuals, Indigenous peoples, MSM

Clinical Features
1. asymptomatic carriers
2. amoebic dysentery
   - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction, and ulceration of large intestine
3. amoebic abscesses (liver abscesses, see General and Thoracic Surgery, GS52)
   - most common in liver (hematologic spread); presents with right upper quadrant pain, weight loss, fever, hepatomegaly
   - can also occur in lungs and brain

Investigations
- serology, fecal/serum antigen testing, stool microscopic exam (for cysts and trophozoites), colon biopsy, single stool for multiplex enteric parasite PCR
- *E. histolytica* indistinguishable microscopically from the non-pathogenic *E. dispar* (distinguish by specific stool antigen detection or multiplex stool PCR assay)

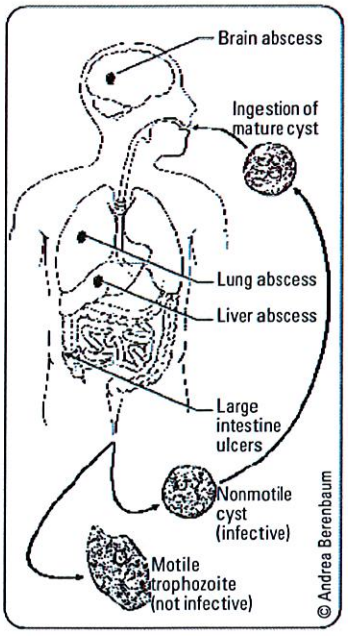


Figure 10. Entamoeba life cycle

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of abscess rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst shedding: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

Giardia lamblia

Etiology
- infection with G. lamblia occurs via the fecal-oral route with the ingestion of cysts from water/food contaminated by infected humans and other mammals (especially in the Rockies)
- risk factors: travel, camping, institutions, daycare centres, MSM

Clinical Features
- giardiasis ("beaver fever")
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats the small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucous in stool

Investigations
- multiple stool samples (daily x 3 d) for microscopy; single stool for multiplex enteric parasite PCR; stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

Treatment and Prevention
- metronidazole; nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

Trichomonas vaginalis

Etiology
infection with *T. vaginalis* occurs via sexual contact



Trichomonas causes 25% of vaginitis

Clinical Features
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- *Trichomonas* vaginitis (see Gynecology, GY26)
- vaginal discharge (profuse, malodorous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

Investigations
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

Treatment
- metronidazole for patient and partner(s)

Cryptosporidium spp.

Etiology
- infection with Cryptosporidium spp. via the fecal-oral route occurs with the ingestion of cysts from water contaminated by infected humans and other animals (including cows)
- risk factors: summer and fall, young children (daycare), MSM, contact with farm animals, immunodeficiency

Clinical Features
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with nausea/vomiting, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

Investigations
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody, single stool for multiplex enteric parasite PCR

Treatment and Prevention
- supportive care
- in HIV+ patients, (re)initiate ART and try to increase their CD4 count to >100; if fails, try nitazoxanide or macrolides
- good personal hygiene, water filtration

Blood and Tissue Infections

Plasmodium spp. (Malaria)

Etiology

- transmission of *Plasmodium* spp. (*P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi*) primarily occurs during the blood meal of an infected female Anopheles mosquito
- sporozoites injected during the blood meal then infect human liver cells, where they multiply and are released as merozoites; merozoites infect red blood cells and cause disease
- infection with malaria parasites can also occur via vertical transmission (rare) or blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features

- flu-like prodrome (may include fever, chills, fatigue, diaphoresis, cough, rash, arthralgias, myalgias, headache, GI symptoms)
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of red blood cells) that can last several hours
  - *P. vivax* and *P. ovale*: chills and fever x 48 h but can be variable
  - *P. malariae*: chills and fever x 72 h but can be variable
  - *P. falciparum*: less predictable fever interval, can be highly variable
- abdominal pain, diarrhea, myalgia, headache, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis
- >90% of patients infected with *P. falciparum* are ill within 30 d
- relapsing malarial attacks may occur after many months due to the reactivation (entering the erythrocytic cycle) of dormant liver hypnozoites of either *P. ovale* or *P. vivax*
- complications:
  - *P. falciparum* (most common and most lethal): CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute kidney injury, ARDS, primarily responsible for fatal disease
  - *P. knowlesi*, and rarely *P. vivax*, can be fatal

Investigations

- CBC screen (assess for triad of: thrombocytopenia, elevated LDH, and anemia)
- microscopy: blood smear q12-24 h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests
- PCR

Treatment and Prevention

- all spp. of malaria can lead to severe infection (*P. falciparum* most likely to cause severe disease and death)
  - markers of severity: clinical features + parasitemia
  - in any patient with clinical evidence of severe disease: parenteral treatment (artemisinin combination therapy)
- *P. falciparum*: most areas of the world show chloroquine resistance – check local resistance patterns
  - artemisinin combination therapy (e.g. artesunate + doxycycline or artemether-lumefantrine)
  - atovaquone/proguanil combination (Malarone®)
  - quinine + doxycycline or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- *P. vivax, P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: atovaquone/proguanil + primaquine or quinine and doxycycline + primaquine
- *P. malariae, P. knowlesi*: chloroquine
- prevention with antimalarial prophylaxis (although quality may vary regionally), covering exposed skin, insecticide-treated bed nets, insect repellent
- prevention of relapse for *P. vivax*: primaquine or the newly FDA-licensed tafenoquine (in patients ≥16 yr who are receiving appropriate antimalarial therapy for acute P. vivax infection)

Mefloquine for Preventing Malaria during Travel to Endemic Areas
Cochrane DB Syst Rev 2017;CD006491
Purpose: To summarize efficacy and safety of mefloquine used as prophylaxis for malaria in travellers.
Methods: Randomized control trials (for efficacy and safety) and non-randomized cohort studies (for safety) to compare prophylactic mefloquine with placebo, no treatment, or alternative antimalarial agent.
Results: Participants were more likely to discontinue mefloquine (6%) vs. atovaquone-proguanil (3%) due to adverse effects (including nausea, vomiting, abnormal dreams, insomnia, anxiety, and depressed mood during travel). No difference in serious adverse effects or discontinuation due to adverse effects was found between mefloquine and doxycycline or mefloquine and chloroquine.
Conclusions: Absolute risk of malaria during short-term travel appears low with mefloquine, doxycycline, and atovaquone-proguanil therapy. Choice of agent depends on how individual travellers assess importance of specific adverse effects, pill burden, and cost.

Malaria is the most common fatal infectious disease worldwide

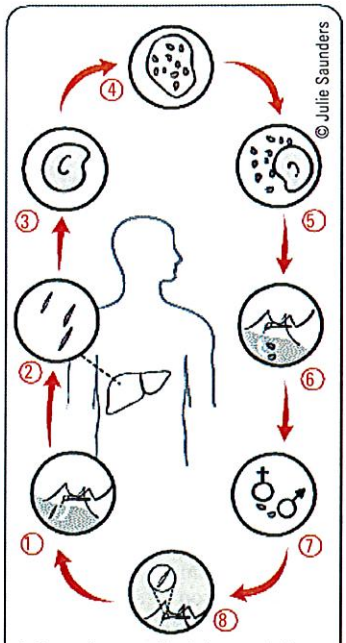


Figure 11. Life cycle of *Plasmodium* spp.

Trypanosoma cruzi

Etiology
- found in Mexico, South America, and Central America
- transmission by reduviid insect vector ("Kissing Bug"), which defecates on skin and trypomastigotes in the stool are rubbed into bite site or intact mucous membranes by host
- trypomastigotes can penetrate intact buccal mucosa when orally inoculated (e.g. via sugar cane-sweetened unpasteurized juices)
  - also transmitted via placental transfer, organ transplantation, blood transfusion, and ingestion of food or drink contaminated by an infected triatomine
  - congenital acquisition increasingly recognized as a risk factor for Chagas disease being detected in non-endemic areas

Clinical Features
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation (Chagoma) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - if inoculation via conjunctiva: "Romana's sign;" usually unilateral
  - acute myocarditis, pericardial effusion, meningoencephalitis in severe cases
  - chronic indeterminate phase: asymptomatic but increasing levels of antibody in blood; most infected persons (60-70%) remain in this phase, and do not go on to manifest a determinate form of Chagas disease
  - chronic determinate: leads to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

Investigations
- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

Treatment and Prevention
- acute: benznidazole or nifurtimox
- indeterminate: increasing trend to treat as acute infection for children and adults under age 50
- chronic determinate: symptomatic therapy, surgery as necessary including heart transplant, esophagectomy, and colectomy; there is unlikely a clinical benefit to antiparasitic treatment at the determinate stage of disease
- insect control, bed nets



See Landmark Infectious Disease Trials table for more information on the BENEFIT trial. It details the role of trypanocidal therapy in patients with established Chagas cardiomyopathy.



Classic Triad of Congenital Toxoplasmosis
Chorioretinitis
Hydrocephalus
Intracranial calcifications

Toxoplasma gondii

Etiology
- infection with *T. gondii* occurs through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), transplacental transmission, organ transplantation, gardening without gloves (cat oocyst exposure), whole blood transfusions, contaminated water sources

Clinical Features
- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult- blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (headache and focal neurological signs)
  - lymph node, liver, spleen enlargement, and pneumonitis
  - chorioretinitis

Investigations
- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination

Treatment and Prevention
- no treatment if: immunocompetent, not pregnant, no severe organ damage
- immunocompromised: pyrimethamine + sulfadiazine + folinic acid
- pregnancy: spiramycin if fetal status unknown, pyrimethamine + sulfadiazine + folinic acid if confirmed or highly suspected fetal infection, avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: TMP/SMX
- proper hand hygiene, cook meat thoroughly to proper temperature

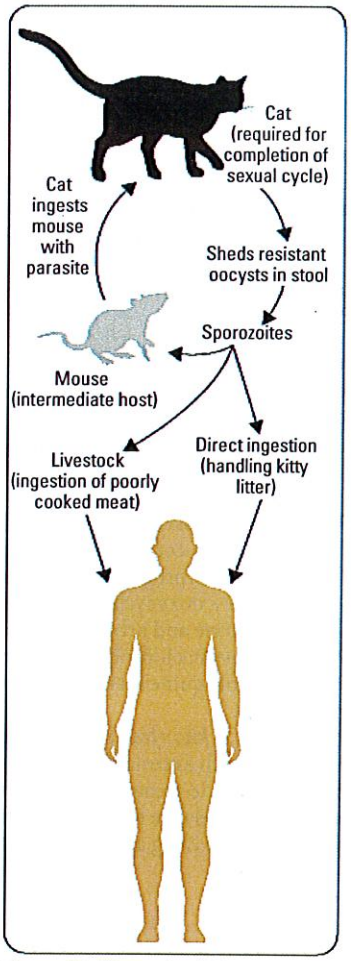


Figure 12. Life cycle of *Toxoplasma gondii*



1/3 of Ontario's population is infected with *Toxoplasma gondii*

Helminths

Roundworms – Nematodes

Table 26. Nematodes (Roundworms)

Nematode	Epidemiology	Transmission	Clinical Presentation	Management
Ascaris lumbricoides	Worldwide (most common in tropical and subtropical areas)	Human feces, ingestion of contaminated food or water containing eggs	Often asymptomatic, abdominal discomfort Heavy infections may cause intestinal blockage, growth impairment Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löffler's syndrome)	Mebendazole OR albendazole OR pyrantel pamoate OR ivermectin
Trichuris trichiura (whipworm)	Worldwide (most common in tropical areas)	Ingestion of eggs in soil	Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth	Mebendazole OR albendazole
Onchocerca volvulus	Sub-Saharan Africa, Latin America	Blackfly bite	River blindness (onchocerciasis), dermatitis	Ivermectin + doxycycline
Wuchereria bancrofti	Tropics	Mosquito bite	Damage to lymphatics causes lymphadenopathy, lymphedema, lymphatic filariasis (elephantiasis), hydrocele Tropical pulmonary eosinophilia	Diethylcarbamazine + doxycycline
Loa loa	West and Central African rainforest (e.g. Cameroon, Central African Republic)	Deerfly bite	Loiasis mostly asymptomatic. Can have episodic angioedema (Calabar swellings), eye pain and itching from subconjunctival migration	Surgical removal of adult worms, diethylcarbamazine, albendazole
Enterobius vermicularis (pinworm)	Worldwide	Human host: fecal-oral self-inoculation and fomite person-to-person transfer Adult worms live in cecum and deposit eggs in peri-anal skin	Asymptomatic carriers or severe nocturnal peri-anal itching (pruritus ani) Occasional vaginitis, ectopic migration to appendix or other pelvic organs Abdominal pain, nausea/vomiting with high worm burden	Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out) Examination of perianal skin at night may reveal adult worms Usually no eosinophilia as no tissue invasion Mebendazole, albendazole; pyrantel in pregnancy Change underwear, bathe in morning, pajamas to bed, wash hands, trim fingernails Treat all family members simultaneously Reinfection common
Strongyloides stercoralis (threadworm)	Subtropical, tropical, and temperate (including southern US)	Fecal contamination of soil: transmission via unbroken skin, walking barefoot Autoinfection: penetration of larvae through GI mucosa or perianal skin Adult worms live in mucosa of small intestine	One of few worms able to multiply in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler's syndrome) Abdominal pain, diarrhea, pruritus ani, larva currens (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunoablative therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection	Ivermectin and/or albendazole

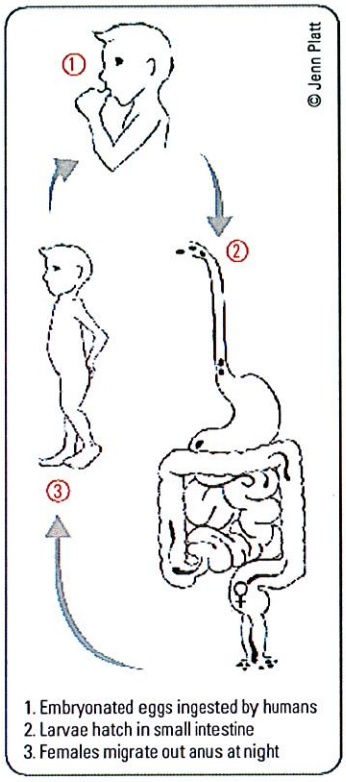


Figure 13. Life cycle of Enterobius

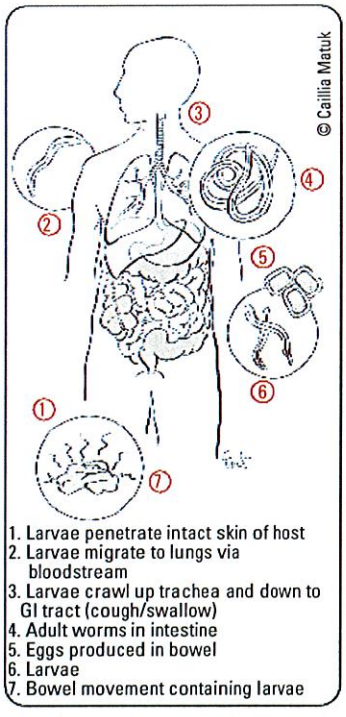


Figure 14. Life cycle of Strongyloides

Flatworms – Cestodes/Trematode

Table 27. Cestodes/Trematodes (Flatworms)

	Epidemiology	Transmission	Clinical Presentation	Treatment
CESTODES				
Taenia solium **(pork tapeworm)**	Worldwide, but more common in places with poor sanitation	Undercooked pork (larvae), human feces (eggs)	Taeniasis: mild GI symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures	Corticosteroids + albendazole + praziquantel for most cysticercosis Antiepileptics if seizures Praziquantel for taeniasis
Taenia saginata **(beef tapeworm)**	Worldwide, but more common wherever contaminated raw beef is eaten	Undercooked beef (larvae)	Taeniasis: mild GI symptoms	Praziquantel
Diphyllobothrium latum	Europe, North America, Asia	Raw fish	Vitamin B_{12} deficiency leading to macrocytic anemia and posterior column deficits	Praziquantel
Echinococcus granulosus	Rural areas, sheep-raising countries	Dog feces (eggs)	Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation	Albendazole ± praziquantel alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole
TREMATODES				
Clonorchis sinensis	Japan, Taiwan, China, Southeast Asia	Raw fish	Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma	Praziquantel
Schistosoma spp.	Africa, Southeast Asia, focal in Western Hemisphere	Fresh water exposure	Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, squamous cell carcinoma (SCC) of the bladder)	Praziquantel

Schistosoma spp.

Etiology

infection with Schistosoma spp. (*S. mansoni, S. haematobium, S. japonicum*) occurs following penetration of unbroken skin by their larvae (cercariae) which are found in infested fresh water

- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- schistosomes cannot multiply in or pass between humans
- more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

Clinical Features

- most asymptomatic; symptoms seen in travellers (nonimmune)
- swimmer's itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, headache, weight loss, cough, abdominal pain, chronic diarrhea, high-grade eosinophilia
- chronic schistosomiasis (can persist for years):
  - *S. mansoni, S. japonicum*
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegaly (2° to portal HTN), hepatomegaly
  - *S. haematobium*
    - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
    - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
  - neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
  - pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement

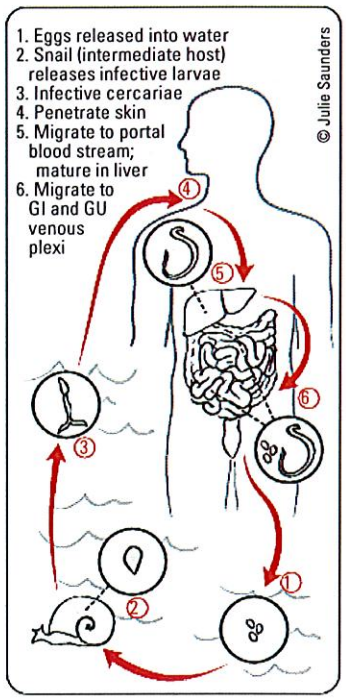


Figure 15. Life cycle of Schistosoma

Investigations

- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia), loop-mediated isothermal amplification, circulating serum antigen test
- *S. mansoni, S. japonicum*: eggs in stool, liver U/S shows peri-portal fibrosis, rectal biopsy
- *S. haematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

Treatment and Prevention

- praziquantel
- add prednisone if acute schistosomiasis or neurologic complications develop
- proper disposal of human waste, molluscicide (pesticide against molluscs), avoidance of infested fresh water while travelling

Ectoparasites

- scabies, lice
- see Dermatology, D33

Table 28. Important Exposures

Insect Bites	
Mosquito	*Plasmodium* spp. (malaria) Dengue Chikungunya *Wuchereria bancrofti* (lymphatic filariasis, aka elephantiasis) West Nile encephalitis Yellow Fever Japanese encephalitis Zika
Tick	*Borrelia burgdorferi* (Lyme disease) *Rickettsia rickettsii* (Rocky Mountain spotted fever)
Fly	*Trypanosoma brucei* spp. (human African trypanosomiasis (HAT), aka African sleeping sickness) *Leishmania* spp. (Leishmaniasis) *Bartonella bacilliformis* (bartonellosis)
Flea	*Yersinia* (Plague) *Tunga penetrans* (Tungiasis)
Mammal Bites	
Dog/Cat	Rabies, Pasteurella, anaerobes, *Streptococcus* spp., *S. aureus*, *Bartonella henselae*, *Clostridium tetani* (tetanus)
Human	*Streptococcus* spp., *S. aureus*, oral anaerobes, *Eikenella* spp.
Oral Exposures	
Unpasteurized Milk	*Brucella* spp., non-tuberculous Mycobacteria, *Salmonella* spp., *E. coli*, *Listeria* spp.
Undercooked Meat/Fish	Enteric bacteria, helminths, protozoa (e.g. Toxoplasma)
Water	Hepatitis A/E, norovirus, V. cholerae (cholera), *Salmonella*, *Shigella*, *Giardia*, poliovirus, *Cryptosporidium*, *Cyclospora*
Environmental Exposures	
Fresh Water	*Leptospira* spp., *Schistosoma* spp., *Acanthamoeba*, *Naegleria fowleri*
Soil	Hookworms, *Toxocara* spp. (visceral larva migrans), *Leptospira interrogans* (leptospirosis)

Adapted with permission from Lancet 2003;361:1459-1469

Travel Medicine

General Travel Precautions

- vector-borne: long sleeves, long pants, hats, insecticides (containing permethrin) applied to clothes, belongings, and bed nets; and skin repellents (e.g. DEET, icaridin) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (e.g. Lake Malawi), fresh-water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller's diarrhea (bismuth salicylate, rifaximin)
- standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

Infectious Diseases to Consider

- vector-borne: malaria, dengue fever, chikungunya, yellow fever, spotted fever rickettsioses, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, leishmaniasis, Zika virus, filariasis
- sexually transmitted: HIV, HBV, acute HSV, syphilis, usual STIs, e.g. gonorrhea and chlamydia
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis, Ebola
- airborne: TB, measles, varicella
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller's diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

Fever in the Returned Traveller

Etiology

- commonly identified causes of fever in the returned traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from Salmonella (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller's diarrhea (10-20%), respiratory tract infection (10-15%), UTI/STI (2-3%)
  - Fever in a returned traveller from a malaria endemic area is considered malaria until proven otherwise
- can be caused by routine infections that are common in non-travellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes (e.g. DVT/PE, drug fever, inflammatory disorder unmasked by travel-acquired infection)

History

- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
- persons visiting friends and family are more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals
- exposure history
  - street foods, untreated water: increased risk of traveller's diarrhea, enteric fever
  - uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  - body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  - increased risk of HBV, HCV, HIV, GC, *C. trachomatis*, syphilis
  - animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
- fever pattern
- incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  - <21 d: consider malaria, typhoid fever, dengue fever, chikungunya, Zika, rickettsioses, traveller's diarrhea, respiratory tract infections (e.g. ILI, COVID-19); exclude HBV, TB
  - >21 d: consider malaria, TB, typhoid fever; exclude dengue fever, chikungunya, traveller's diarrhea, rickettsioses
- body systems affected: GI, respiratory, CNS, skin

Investigations

- all travellers with fever should undergo the following tests
  - blood work: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  - urine: urinalysis, urine C&S if dysuria or other localizing signs
- special tests based on symptoms, exposure history, and geography
  - stool: C&S, O&P
  - CXR
  - viral serology (hepatitis, HIV)
  - dengue serology for IgM, dengue PCR

Treatment

- empiric treatment if ongoing fever for 48-72 h and negative malaria smears and all cultures pending
- travelled to India, Southeast Asia: azithromycin ± doxycycline
- travelled elsewhere: ciprofloxacin ± doxycycline

Table 29. Fever in the Returned Traveller

Illness	Geography/ Timing	Pathogen	Incubation Period	Clinical Manifestations	Diagnosis	Treatment
Malaria	Africa, India, Central and South America, Southeast Asia Usually rural, night-biting mosquitoes	*P. falciparum* *P. vivax* *P. malariae* *P. ovale* *P. knowlesi*	7-30 d to mo or yr	Fever and flu-like illness (shaking chills, headache, muscle aches, and fatigue) Nausea/vomiting and diarrhea Anemia and jaundice *Plasmodium falciparum*: (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure	Blood smear (thick and thin) x3 Rapid diagnostic test (with smear or PCR confirmation) Antigen detection PCR	Artesunate (for severe disease) + Malarone®, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine
Dengue	Southeast Asia, Caribbean Usually urban, day-biting mosquitoes	Dengue viruses 1-4	3 d to 2 wk	Sudden onset of fever, headache, retro-orbital pain, myalgias, and arthralgias Leukopenia Thrombocytopenia hemorrhagic manifestations (rare in travellers)	Anti-dengue IgM positivity PCR	Symptom relief: acetaminophen (avoid using NSAIDs and ASA because of antiplatelet properties)
Typhoid (enteric fever)	Global but mostly Indian subcontinent	*Salmonella enterica* serotype *Typhi* or serotype *Paratyphi*	3 to 60 d	Sustained fever 39°-40°C (103°-104°F) Abdominal pain, headache, loss of appetite, cough, constipation	Stool, urine, or blood culture positive for *S.* ser. Typhi or *S.* ser. Paratyphi	Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide
Tick Typhus	Mediterranean, South Africa, India	*Rickettsia*	1 to 2 wk	Fever, headache, myalgia, spotted rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes	Serology Presence of classic tick eschar	Doxycycline
TB	Global	*M. tuberculosis*	Variable	Fever, cough, hemoptysis	CXR Sputum culture and acid-fast stain Nucleic Acid Amplification Test (NAAT)	Isoniazid (INH), rifampin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) + Vitamin B6
Mononucleosis	Caribbean, Central and South America	EBV or CMV	30 to 50 d	Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly	Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test	Acetaminophen or NSAIDs, fluids
Zika Virus Disease	Africa, Southeast Asia, South America; spreading	Zika virus	Unknown, likely 3 to 12 d	Headache, malaise, myalgia, arthralgia, mild fever, rash, conjunctivitis	RT-PCR Serology	Rest, fluids, analgesics/ antipyretics (avoid NSAIDs until dengue ruled out), condom use, avoid pregnancy

Fever of Unknown Origin

Table 30. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on Several Occasions

Classical FUO	Nosocomial FUO	Neutropenic FUO	HIV-associated FUO
Duration >3 wk	Hospitalized patient Infection not present/incubating on admission	Neutrophil count <500/mL or is expected to fall to that level in 1-2 d	HIV infections Duration >4 wk for outpatients, >3 d for hospitalized patients
Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures

Causes of Nosocomial FUO
B, C, D, E

Bacterial and fungal infections of respiratory tract and surgical sites
Catheters (intravascular and urinary)
Drugs
Emboli

Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extrapulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvic, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - other: viral (CMV, EBV, HIV), bacterial (brucellosis, bartonellosis), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin) and leukemias, multiple myeloma, myelodysplastic syndrome
  - solid tumours: renal cell carcinoma (most common), breast, liver (hepatocellular carcinoma), colon, pancreas, or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, polyarteritis nodosa), juvenile RA, Still disease
- miscellaneous (~20%)
  - drugs (e.g. antimicrobials, anti-arrhythmics), factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (e.g. familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
  - unknown in 30-50% despite detailed workup

Approach to Classic FUO

- careful and repeated history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - blood work: CBC and differential, electrolytes, urea, Cr, calcium profile, liver enzymes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, muscle enzymes, rheumatoid factor (RF), antinuclear antibody (ANA), serum protein electrophoresis (SPEP), blood film
  - cultures: blood (x3 sets), urine, sputum, stool C&S and O&P, other fluids as appropriate
  - serology: HIV, Monospot, CMV IgM, syphilis
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established

if no diagnosis with the above, consider empiric therapy vs. watchful waiting

- without intervention: patients that remain undiagnosed despite extensive workup have good prognosis

- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent

Infections in the Immunocompromised Host

Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Table 31. Types of Immunodeficiency

Type	Conditions	Vulnerable To
Cell-Mediated Immunity	HIV, Hodgkin, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome	Latent viruses Fungi Parasites Non-tuberculosis *mycobacterium* (NTM)
Humoral Immunity	CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome	Encapsulated organisms (*S. pneumoniae, H. influenzae, N. meningitidis, Salmonella enterica* serotype *Typhi*, GBS)
Neutrophil Function	Chemotherapy, myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease	Catalase-producing organisms (*Staphylococcus, Serratia, Nocardia, Aspergillus*)

Febrile Neutropenia

Definition

- fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h)
- neutropenia: ANC (absolute neutrophil count) <1.0
- ANC = WBC x (%neutrophils + %bands)
- severe neutropenia: ANC <0.5

Pathophysiology

- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B_{12}, folate
- increased peripheral neutrophil destruction
  - autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

Epidemiology/Etiology

- most common life-threatening complication of cancer therapy
- 8 cases per 1000 cancer patients per yr in the U.S.
- causative organism identified only 1/3 of the time
- GN (especially *Pseudomonas*) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially *Candida, Aspergillus*)
- frequently associated with IV lines, mucosal or GI infection. Typhlitis (inflammation of cecum) is a rare complication, but can lead to serious infection and poor outcomes

Investigations
- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region for perianal abscess
- blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and nasopharyngeal swab for respiratory viruses, stool for testing if diarrhea
- CBC and differential, Cr, urea, electrolytes, AST/ALT, total bilirubin, chest imaging (CXR or CT)

Treatment
- most hospitals have their own specific protocol so check local guidelines first (see *Figure 16*)
- prophylaxis against febrile neutropenia (FN) with granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) decreases hospitalization without affecting mortality (indicated if risk of FN ≥20% or if FN has occurred in a previous chemotherapy cycle)

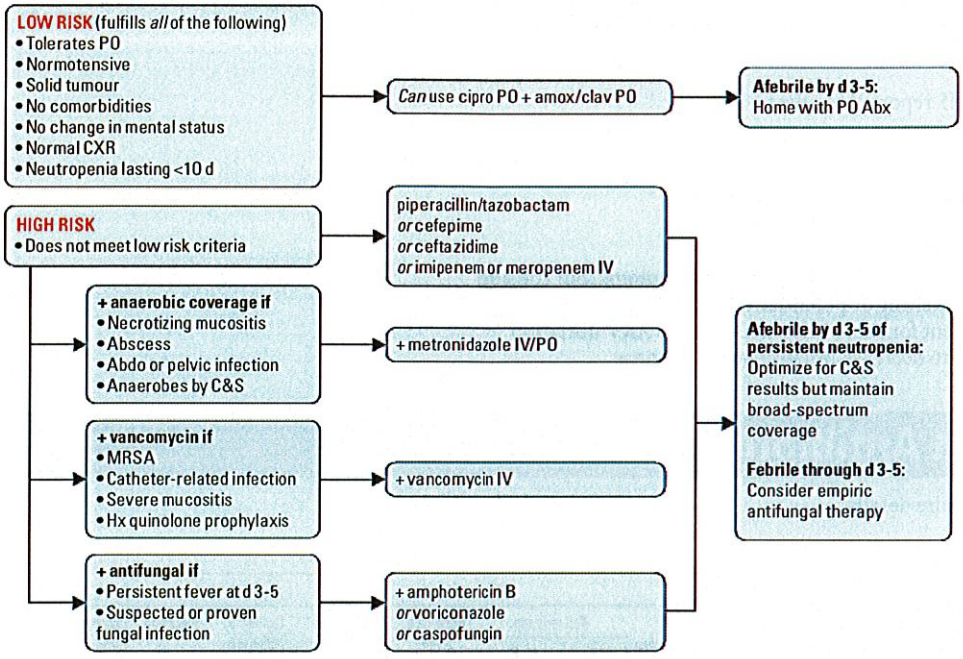


Figure 16. Example of treatment protocol for febrile neutropenia

Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant
  - donor-derived infections
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant
  - viral (especially CMV, EBV, VZV)
  - fungal (especially *Aspergillus, Cryptococcus, P. jirovecii*)
  - protozoan (especially *Toxoplasma*)
  - unusual bacterial/mycobacterial infections (especially TB, *Nocardia, Listeria*)

Prophylactic Vaccinations Given Before Transplant
- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B, COVID-19
- in select patients: MMR, varicella, HPV, herpes zoster

Immune Reconstitution Inflammatory Syndrome

Definition
- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology
- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in patients with advanced HIV or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation

- can occur in response to multiple infections
  - Mycobacteria (*tuberculosis, avium complex*)
  - *Cryptococcus*
  - *Pneumocystis*
  - *Toxoplasma*
  - HBV and HCV
  - herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Molluscum contagiosum
  - COVID-19
- clinical features are dependent on the type and location of the pre-existing infection
- thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
- non-HIV conditions with documented immune reconstitution inflammatory syndrome (IRIS): solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

Epidemiology
- in HIV-positive patients starting ART, IRIS reported to affect ~10%

Investigations
- IRIS is a diagnosis of exclusion
- rule out drug reaction, medication non-adherence, drug resistance

Treatment
- continue ARV therapy in HIV-positive patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to ARV initiation
- consider starting corticosteroids/NSAIDs to decrease inflammatory response

A Simplified Look at Antibiotics

- general overview, see *Table 33, ID49* for more details

Table 32. Antibiotics Overview

Class and Drugs	GP							Anaerobes	GN					Atypicals		Other	
	Streptococcus spp.	*Staphylococcus* spp.			*Enterococcus* spp.		*C. difficile*		*H. influenzae*	*Neisseria* spp.		*Bacilli* (e.g. *E. coli, Klebsiella* spp.)	*Pseudomonas*	*Legionella, Chlamydia pneumoniae, Mycoplasma*	Rickettsia	*Chlamydia trachomatis*	*Syphilis*
		S. saprophyticus	MSSA	MRSA	*E. faecalis*	*E. faecium*				N. meningitidis	*N. gonorrhoeae*						
PENICILLINS																	
Penicillin G (IV)/ Penicillin V (PO)	✓							✓ Oral anaerobes except Gram(-) e.g. B. fragilis		✓							
Ampicillin (IV)/ Amoxicillin (PO)	✓				✓			✓ Oral anaerobes except Gram(-) e.g. B. fragilis									
Cloxacillin		✓	✓														
+β-LACTAM COMBINATION AGENTS																	
Amoxicillin-clavulanate	✓	✓	✓		✓			✓	✓			✓					
Piperacillin/ tazobactam	✓	✓	✓		✓			✓	✓	✓		✓	✓				
ceftolozane-tazobactam									✓			✓	✓				
Ceftrazidime-avibactam*									✓			✓	✓				
Meropenem-vaborbactam*									✓			✓	✓				
Imipenem-relebactam*									✓			✓	✓				
CEPHALOSPORINS (PO/IV)																	
1st generation: cephalexin/ cefazolin/cefadroxil	✓	✓	✓									✓					
2nd generation: cefuroxime/ cefprozil	✓	✓	✓						✓			✓					

Table 32. Antibiotics Overview

Class and Drugs	GP							Anaerobes	GN						Atypicals		Other	
	Streptococcus spp.	*Staphylococcus* spp.			*Enterococcus* spp.		*C. difficile*		*H. influenzae*	*Neisseria* spp.		*Bacilli* (e.g. *E. coli*, *Klebsiella* spp.)	*Pseudomonas*		*Legionella*, *Chlamydia pneumoniae*, *Mycoplasma*	Rickettsia	*Chlamydia trachomatis*	*Syphilis*
		S. saprophyticus	MSSA	MRSA	*E. faecalis*	*E. faecium*				N. meningitidis	*N. gonorrhoeae*							
3rd generation: cefixime/ cefotaxime, ceftriaxone	✓	✓	✓						✓	✓	✓	✓						
3rd generation: ceftazidime									✓			✓	✓					
4th generation: cefepime	✓	✓	✓						✓			✓	✓					
5th generation: ceftobiprole ceftaroline*	✓	✓	✓	✓					✓			✓						
Cefiderocol*									✓			✓	✓					
Aminoglycosides gentamicin tobramycin amikacin plazomicin*												✓	✓					
MACROLIDES																		
Erythromycin Clarithromycin									✓						✓			
Azithromycin									✓		✓				✓		✓	
FLUOROQUINOLONES																		
Ciprofloxacin										✓		✓	✓					
Levofloxacin	✓	✓	✓	✓	✓	✓			✓			✓	✓		✓			
Moxifloxacin	✓	✓	✓	✓	✓	✓		±	✓			✓	✓		✓			
Norfloxacin ‡spontaneous bacterial peritonitis (SBP) prophylaxis			✓		✓				✓		✓	✓	✓					
CARBAPENEMS																		
Imipenem	✓		✓		✓			✓	✓	✓	✓	✓	✓					
Meropenem	✓		✓					✓	✓	✓	✓	✓	✓					
Ertapenem								✓	✓	✓	✓	✓						
TETRACYCLINES																		
Doxycycline/ tetracycline/ minocycline	✓	✓	✓	✓	✓	✓			✓			✓			✓	✓	✓	✓
Tigecycline	✓		✓	✓	✓	✓		✓	✓			✓			✓	✓		
OTHERS																		
Vancomycin	✓		✓	✓	✓ (not VRE)	✓ (not VRE)	✓ (oral vancomycin for *C. difficile* gastroenteritis)											
Daptomycin	✓		✓	✓	✓	✓												
Linezolid	✓		✓	✓	✓	✓												
Metronidazole							✓	✓										
Clindamycin	✓		✓	✓				✓										
TMP/SMX			✓	✓								✓						
Nitrofurantoin		✓			✓	✓						✓						
Fosfomycin			✓	✓	✓	✓						✓						
Colistin									✓			✓	✓					

* Available in Canada through the Special Access Program

Antimicrobials

Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S and clinical response
- if causative organism identified, use antibiotic to which organism is susceptible
- if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

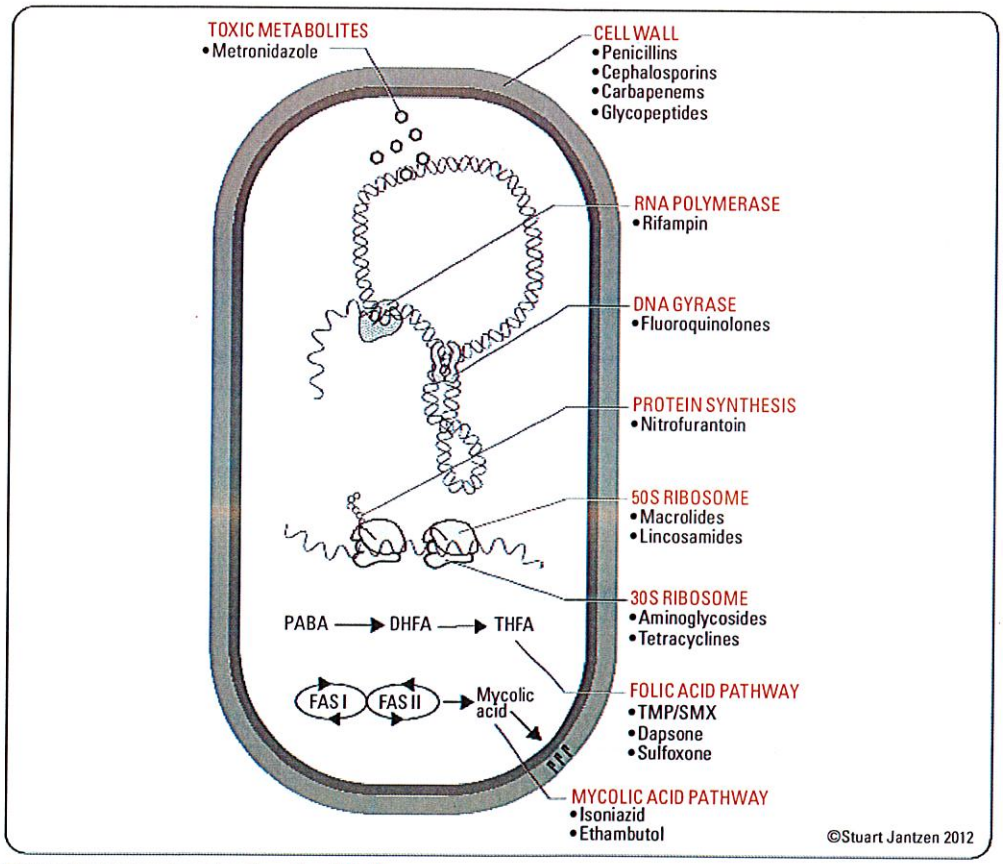


Figure 17. Mechanism of action of antibiotics

Reasons for Combination Therapy

- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. *Enterococcus* spp. causing endocarditis)
- To prevent emergence of resistance

Bactericidal Antibiotics	Bacteriostatic Antibiotics
"Very Finely Proficient At CCell MurDer"	"ECSTaTiC"
Vancomycin	Erythromycin (and other macrolides)
Fluoroquinolones	Clindamycin
Penicillin	Sulfamethoxazole
Aminoglycosides	Trimethoprim
Cephalosporins	Tetracyclines
Carbapenems	Chloramphenicol
Metronidazole	
Daptomycin	

Table 33. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Penicillins					
Benzyl penicillin - penicillin G IV/IM - penicillin V PO	GP except Staphylococcus, Enterococcus, N. meningitidis, Oral anaerobes Syphilis	Bactericidal: β-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan	Immediate allergy (IgE): anaphylaxis, urticaria Late-onset allergy (IgG): urticaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures Diarrhea	Mild to moderately severe infections caused by susceptible organisms including: actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis	Hypersensitivity to penicillin
Aminopenicillin - ampicillin IV - amoxicillin PO (Amoxil®)	Same as penicillin AND *Enterococcus* *Listeria* Some strains of: *H. influenzae, E. coli, K. pneumoniae*	See above	See above	Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for *H. pylori* treatment, Lyme disease, pneumococcal pneumonia, UTI (amoxicillin and ampicillin) for most enterococci and susceptible GN pathogens	Hypersensitivity to penicillin or β-lactam antibiotics
Isoxazolyl penicillin - cloxacillin - methicillin - nafcillin - oxacillin	Methicillin-sensitive *Staphylococcus aureus*; streptococci	See above	See above	Bacterial infections caused by staphylococci and streptococci including skin and soft-tissue infections	Hypersensitivity to cloxacillin or any penicillin
β-lactam combinations - amoxicillin-clavulanate (Clavulin®, Augmentin®) - piperacillin/tazobactam (Tazocin®) -ceftolozane/tazobactam	Same as penicillin AND *Staphylococcus* *H. influenzae* *Enterococcus* Anaerobes (oral and gut) *P. aeruginosa* (piperacillin-tazobactam) Ceftolozane/tazobactam primarily used for resistant GN	β-lactamase produced by certain bacteria inactivate β-lactams Lactamase inhibitors prevent this process, preserving antibacterial effect of β-lactams	See above	Various β-lactamase producing bacteria, amoxicillin-clavulanate-sensitive bacteria including URTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections Ceftolozane-tazobactam, ceftazidime-avibactam, meroepenem-vaborbactam, and imipenem-relebacatam used to treat resistant GN infections	Hypersensitivity to penicillin or cephalosporin History of amoxicillin-clavulate-associated jaundice or hepatic dysfunction
Cephalosporins					
PO 1° cephalexin (Keflex®)	IV cefazolin (Ancef®)	GP Good with the exception of *Enterococcus* and MRSA	GN *E. coli, Klebsiella, Proteus, H. influenzae* (not all isolates)	Bactericidal: β-lactam inhibits PBP, prevents cross-linking of peptidoglycan, less susceptible to penicillinases	10% penicillin allergy cross-reactivity	Skin and soft tissue infections, prevention of surgical site infections (cefazolin); infections caused by susceptible organisms (especially *Staphylococcus* and *Streptococcus* infections)	Hypersensitivity to cephalosporins or other β-lactam antibiotics
2° cefuroxime (Ceftin®) cefprozil (Cefzil®)	cefuroxime (Zinacef®) cefoxitin	Weaker activity than 1°	More coverage than 1° (includes anaerobes)	See above	See above	Upper and lower RTI, pneumococcal pneumonia, soft tissue infections	See above
3° cefixime (Suprax®)	ceftriaxone (Rocephin®) cefotaxime (Claforan®) ceftazidime (Fortaz®)	*S. aureus* + streptococcal coverage (cefotaxime and ceftriaxone) especially *S. pneumoniae*	Broad coverage (includes *Pseudomonas* for ceftazidime only)	See above	~1% penicillin allergy cross-reactivity	Community-acquired pneumonia (cefotaxime, ceftriaxone), gonorrhea (ceftriaxone), community-acquired bacterial meningitis (ceftriaxone, cefotaxime), abdominal and pelvic infections (cefotaxime or ceftriaxone in combination with metronidazole), once-daily administration makes ceftriaxone convenient for outpatient IV therapy	Severe hypersensitivity (Type I) to other β-lactam antibiotics
4°	cefepime (Maxipime®)	Broad spectrum	Broad coverage including *Pseudomonas*	See above	See above	Empiric therapy for febrile neutropenia	See above
5°	Ceftobiprole (Zevtara ®) ceftaroline (Teflaro®)*	Broad coverage including MRSA	Broad coverage (except *Pseudomonas*)	See above	See above	Acute bacterial skin and skin structure infections, community-acquired pneumonia	See above
Other	Cefiderocol*	Broad spectrum	Broad coverage including Pseudomonas	See above	See above	Used to treat resistant GN infections	See above
Carbapenems							
imipenem (Primaxin®)	GP except MRSA GN including *Pseudomonas* + *Enterobacter*, extended-spectrum β-lactamases (ESBLs), anaerobes	β-lactam inhibits PBP and prevents cross-linking of peptidoglycan	Penicillin allergy cross-reactivity Seizures	Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms	Hypersensitivity to imipenem Lowers seizure threshold
meropenem (Merrem®)	See above; does not cover *Enterococcus*	See above	See above	See above	Hypersensitivity to carbapenems
ertapenem (Invanz®)	GP except *Enterococcus*, MRSA GN including *Enterobacter* (but not *Pseudomonas*), anaerobes	See above	See above	See above; once-daily administration makes it convenient for outpatient IV therapy	Hypersensitivity to carbapenems

*Available in Canada through the Special Access Program

Table 33. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Glycopeptides					
vancomycin (Vancocin®)	GP including MRSA, not VRE *C. difficile* if PO	Glycopeptide sterically inhibits cell wall synthesis	Red Man syndrome Nephrotoxicity Ototoxicity Thrombocytopenia	Severe or life-threatening GP infections, patients with β-lactam allergy May only be taken orally for severe *C. difficile* infection	Hypersensitivity to vancomycin
Other					
fosfomycin	GN (some coverage for *Pseudomonas* but lower compared to *Enterobacterales*) and GP (including *Enterococcus*)	Inhibiting cell wall synthesis at the initial step involving phosphoenolpyruvate synthase	PO – mild nausea, diarrhea possible IV – hypokalemia, hypernatremia, liver function test abnormalities	PO – uncomplicated urinary tract infections IV - complicated urinary tract infections, nosocomial lower RTI, osteomyelitis; bacterial meningitis	Hypersensitivity to fosfomycin
PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)					
Macrolides					
erythromycin (Erybid®, Eryc®) †This agent is rarely used due to GI upset	GP except *Enterococcus* GN: *Legionella, B. pertussis* "Atypicals": *Chlamydophila, Mycoplasma*	Binds to 50S ribosomal subunit inhibiting protein synthesis	GI upset Acute cholestatic hepatitis Prolonged QT	Susceptible RTI, pertussis, diphtheria, Legionnaires' disease, skin and soft tissue infections	Hypersensitivity to erythromycin Concurrent therapy with astemizole, terfenadine
clarithromycin (Biaxin®)	See above, some mycobacteria	See above	See above	Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for *H. pylori* treatment	Hypersensitivity to macrolides
azithromycin (Zithromax®)	See above, some mycobacteria	See above	See above	Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, *Campylobacter* infections if treatment indicated, chlamydia	Hypersensitivity to macrolides
Lincosamides					
clindamycin (Dalacin®)	GP except *Enterococcus*, most community-acquired MRSA anaerobes	Inhibits peptide bond formation at 50S ribosome	Pseudomembranous colitis and *C. difficile* GI upset	Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections	Hypersensitivity to clindamycin Infants <30 d Concurrent use or within 2 wk of monoamine oxidase (MAO) inhibitors
chloramphenicol	GP GN Anaerobes	Inhibits peptidyl transferase action of tRNA at 50S ribosome	Aplastic anemia Grey Baby syndrome	Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams	Hypersensitivity to chloramphenicol
linezolid (Zyvoxam®)	GP including VRE + MRSA	Binds 50S ribosome and prevents functional 70S initiation complex	HTN (acts as MAO inhibitor) Risks with prolonged use: myelosuppression, optic neuropathy, peripheral neuropathy	Vancomycin-resistant *Enterococcus faecium* infections including intra-abdominal, skin and skin structure, and urinary tract infections, MRSA infections as outpatient therapy	Hypersensitivity to linezolid, concurrent use or within 2 wk of MAO inhibitors
PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)					
Aminoglycosides					
gentamicin tobramycin amikacin (Amikin®) plazomicin*	GN (includes *Pseudomonas*)	Binds 30S subunit of ribosome inhibiting protein synthesis	Nephrotoxicity (reversible) Vestibular and ototoxicity (irreversible) Vestibular toxicity is the most important aminoglycoside toxicity	GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections	Pre-existing hearing loss and renal dysfunction
Tetracyclines					
tetracycline (Apo-Tetra®, Nu-TetraT®) minocycline (MinocinT®) doxycycline (Doxycin®) tigecycline (Tygacil®)	GP Anaerobes "Atypicals": *Chlamydophila, Mycoplasma, Rickettsia, Borrelia burgdorferi* *Treponema* Malaria prophylaxis (doxycycline) Tigecycline has activity against MRSA, VRE, and ESBL-producing *E. coli/K. pneumoniae*	Binds 30S subunit of ribosome inhibiting protein synthesis	GI upset Hepatotoxicity Fanconi's syndrome Photosensitivity Teratogenic Yellow teeth and stunted bone growth in children	*Rickettsial* infections, *Chlamydophila*, acne (tetracycline, minocycline), Pelvic Inflammatory Disease (PID) (step-down), malaria prophylaxis (doxycycline)	Severe renal or hepatic dysfunction Pregnancy or lactation Children under 12 yr

*Available in Canada through the Special Access Program

Table 33. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
TOPOISOMERASE INHIBITORS					
Fluoroquinolones (FQs)					
ciprofloxacin (Cipro®) norfloxacin (Apo-Norflox®) ofloxacin (Floxin®) Respiratory FQs: levofloxacin (Levaquin®) moxifloxacin (Avelox®)	Variable GP activity GN (includes *Pseudomonas*) "Atypicals" levofloxacin and moxifloxacin cover *S. pneumoniae* moxifloxacin also has additional anaerobic coverage	Inhibits DNA gyrase	Headache, dizziness Allergy Seizures Prolonged QT Dysglycemia (levofloxacin, moxifloxacin) Tendonitis Tendon rupture	Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or management of "low-risk" febrile neutropenia (ciprofloxacin in combination with amoxicillin-clavulanate)	Pregnancy or lactation Children under 18 yr Concomitant use of medications that prolong QT interval
OTHER					
rifampin	GP cocci *N. meningitidis* *H. influenzae* Mycobacteria	Inhibits RNA polymerase	Hepatic dysfunction, P450 enzyme induction Orange tears/saliva/urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment for other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with *N. meningitidis* or HiB meningitis	Jaundice Not to be used as monotherapy (except for prophylaxis)
metronidazole (Flagyl®)	Anaerobes, protozoa	Forms toxic metabolites in bacterial cell which damage microbial DNA	Disulfiram-type reaction with EtOH Seizures Peripheral neuropathy	Protozoal infections (trichomoniasis, amebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections	Pregnancy with trichomoniasis Disulfiram within 2 wk, alcohol within 3 d Active neurological disorders Hypothyroidism Hypoadrenalism
daptomycin	GP, including MRSA and VRE	Binds to cell wall and forms channels leading to intracellular K^+ depletion	Skeletal muscle injury at high doses (elevated creatine phosphokinase) Peripheral neuropathy	Bacteremia, endocarditis, skin and soft tissue, and other infections due to resistant GP infections including MRSA and VRE	Known hypersensitivity Inactivated by surfactant, therefore not used in MRSA pneumonia Tx
colistin	GN	Disrupts bacterial cell membranes	Renal toxicity	Bacteremia, pneumoniae	Hypersensitivity, renal failure
ANTI-METABOLITE					
trimethoprim-sulfamethoxazole (TMP/SMX) (Septra®, Bactrim®)	GP, especially *S. aureus* (including most MRSA) GN: enteric *Nocardia* Other: *Pneumocystis*, *Toxoplasma*	Inhibits folic acid pathway (TMP inhibits dihydrofolate reductase (DHFR) and SMX competes with (para-aminobenzoic acid) PABA)	Hepatitis Stevens-Johnson syndrome Bone marrow suppression Hyperkalemia Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)	Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of *P. jirovedi* pneumonia	Hypersensitivity to TMP-SMX, sulfa drugs Infants <4 wk Hepatic or renal dysfunction Pregnancy and lactation
nitrofurantoin (MacroBID®, (Macrodantin®)	*Enterococcus*, *S. saprophyticus* GN (coliforms)	Reactive metabolites inhibit ribosomal protein synthesis	Cholestasis, hepatitis Hemolysis if G6PD deficiency Interstitial lung disease with chronic use	Lower UTI; not pyelonephritis or bacteremia	Anuria, oliguria, or significant renal impairment During or imminent labour Infants <1 mo of age
ANTI-MYCOBACTERIALS					
isoniazid (INH)	Mycobacteria	Inhibits mycolic acid synthesis	Hepatotoxicity Hepatitis Drug-induced SLE Peripheral neuropathy	Part of multidrug treatment for active TB, alone for treatment of latent TB	Drug-induced hepatitis or acute liver disease
rifampin (RIF)	Mycobacteria	Inhibits RNA polymerase	Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment for other mycobacterial infections, adjunct for treating prosthetic device infection (bacterial biofilm), always use in combination with other antimicrobials to reduce emergence of resistance	Jaundice Not to be used as monotherapy (except for prophylaxis)
ethambutol	Mycobacteria	Inhibits mycolic acid synthesis	Loss of central and colour vision Neuropathy	Part of multidrug treatment for active TB and other mycobacterial infections	Renal failure
pyrazinamide (PZA)	Mycobacteria	Unknown	Hepatotoxicity Gout Gastric irritation	Part of multidrug treatment for active TB	Severe hepatic damage or acute liver disease Patients with acute gout
SULFONES					
dapsone sulfoxone	*M. leprae*, *P. jirovecii*, Toxoplasma	Inhibit folic acid synthesis by competition with PABA	Rash Drug fever Agranulocytosis	Part of multidrug treatment for *M. leprae*, part of treatment for *P. jirovecii* pneumonia (with TMP), *P. jirovecii* pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine	G6PD Deficiency

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Table 34. Antibiotics for Selected Bacteria

Pseudomonas	*S. aureus*	*Enterococcus*	*H. influenzae*	Anaerobes
ciprofloxacin	cloxacillin (MSSA)	ampicillin	amoxicillin-clavulanate	metronidazole
gentamicin tobramycin amikacin	1° cephalosporin (MSSA)	amoxicillin	2°/3° cephalosporin	clindamycin
piperacillin/ tazobactam	clindamycin	vancomycin	macrolides (clarithromycin, azithromycin)	amoxicillin-clavulanate
ceftazidime	cotrimoxazole (including MRSA)	nitrofurantoin (lower UTI)	levofloxacin	cefoxitin
cefepime	vancomycin (including MRSA)	linezolid for VRE	moxifloxacin	piperacillin/tazobactam
imipenem	linezolid (including MRSA)	daptomycin for VRE		moxifloxacin
	daptomycin (including MRSA)	tigecycline for VRE		ertapenem, imipenem, meropenem
	tigecycline (including MRSA)	penicillin		
	doxycycline (MSSA/MRSA)	imipenem		

Antivirals

Table 35. Antivirals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTI-HERPESVIRUS				
acyclovir valacyclovir (Valtrex®) (prodrug of acyclovir)	HSV-1,2 VZV	Guanosine analogue inhibits viral DNA polymerase	PO: well-tolerated IV: nephrotoxicity, CNS	Hypersensitivity to acyclovir or valacyclovir
famciclovir (Famvir®) penciclovir	HSV-1,2 VZV	See above	Headache, nausea	Hypersensitivity to famciclovir or penciclovir
ganciclovir (Cytovene®) valganciclovir (prodrug of ganciclovir)	CMV HSV-1,2, VZV, HHV-6, EBV	See above	Hematologic: neutropenia, thrombocytopenia, anemia	Hypersensitivity to ganciclovir or valgancidovir Possible cross-hypersensitivity between acyclovir and valacyclovir
foscarnet	CMV Acyclovir-resistant HSV, VZV	Pyrophosphate analogue inhibits viral DNA polymerase	Nephrotoxicity Anemia Electrolyte disturbance	Hypersensitivity to foscarnet
OTHER ANTIVIRALS				
(pegylated) interferon-α-2a or-2b	Chronic hepatitis B	Inhibits viral protein synthesis	"Flu-like" syndrome Depression Bone marrow suppression	Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment
lamivudine (Epivir®)	Chronic hepatitis B, HIV	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*
tenofovir	Chronic hepatitis B, HIV	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*
entecavir	Chronic hepatitis B	Deoxyguanosine analogue Inhibits viral DNA polymerase reducing viral DNA synthesis	Increased serum ALT, bilirubin Skin rash Glycosuria, hyperglycemia GI Hematuria Fatigue, headache Increased serum Cr	Hypersensitivity to entecavir or any component of the formulation HIV co-infection (if monotherapy)
glecaprevir and pibrentasvir	Chronic hepatitis C	glecaprevir: HCV NS3/4A protease inhibitor pibrentasvir: HCV Nonstructural protein 5A inhibitor (NS5A) that is essential for viral RNA replication and virion assembly	Nausea, diarrhea Fatigue, headache Pruritus Increased serum bilirubin	Moderate/severe hepatic impairment or history of hepatic decompensation Coadministration: atazanavir, rifampin, atorvastatin, dabigatran, ethinyl estradiol, or simvastatin
sofosbuvir and velpatasvir	Chronic hepatitis C	velpatasvir: HCV NS5A protein inhibitor sofosbuvir: prodrug, inhibits NS5B RNA-dependent RNA polymerase	Fatigue, headache Increased serum creatine kinase Skin rash Increased serum lipase Nausea Insomnia, irritability Asthenia HBV reactivation (in HBV/HCV coinfection)	Hypersensitivity to sofosbuvir, velpatasvir, or any component of the formulation
ribavirin (Virazole®)	Chronic hepatitis C (in combination with direct-acting antivirals), RSV Lassa fever	Guanosine analog with multiple postulated mechanisms of action	Hemolytic anemia Rash, conjunctivitis Highly teratogenic	Pregnant women and partners Hemoglobinopathies Concomitant α interferon use
cidofovir	Adenovirus CMV retinitis Acyclovir and foscarnet resistant HSV	Deoxycytidine analogue Inhibits DNA synthesis	Nephrotoxicity (proximal tubule dysfunction)	Renal failure: probenecid can reduce renal toxicity

Table 35. Antivirals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
Neuraminidase inhibitors: zanamivir (Relenza®) oseltamivir (Tamiflu®)	Influenza A and B: treatment and prophylaxis	Inhibits neuraminidase, an enzyme required for release of virus from infected cells leading to prevention of viral aggregation	GI: nausea/vomiting, diarrhea Bronchospasm with zanamivir	Hypersensitivity to the neuraminidase inhibitors
remdesivir	Hospitalized COVID-19	Adenosine triphosphate analog Inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase Inhibits viral RNA synthesis	Bradycardia, hypotension Increased serum ALT, AST Hypersensitivity reactions (e.g. anaphylaxis, angioedema) Skin rash GI Prolonged prothrombin time Seizure	Hypersensitivity to remdesivir or any component of the formulation
nirmatrelvir/ritonavir (Paxlovid®)	COVID-19 infection within 5 days of symptom onset	nirmatrelvir: Peptidomimetic inhibitor of SARS-CoV-2 protease ritonavir: CYP3A inhibitor, increasing concentrations of nirmatrelvir	Hypertension Diarrhea, Dysgeusia Myalgia	Hypersensitivity to nirmatrelvir, ritonavir or any component of the formulation Co-administration of highly dependent CYP3A substrates or potent CYP3A inducers

Antifungals

Table 36. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
POLYENES				
amphotericin B (liposomal formulation is less toxic)	Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis Pulmonary: Aspergillosis CNS: Cryptococcus	A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death	Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, headache Peripheral phlebitis	Hypersensitivity to amphotericin or any component of the formulation
nystatin (oral, topical)	Candidiasis: mucocutaneous, GI, oral (thrush), vaginal	See above Not absorbed from the GI tract	GI: nausea/vomiting, diarrhea Highly toxic if given IV	Hypersensitivity to nystatin or any component of formulation
IMIDAZOLES				
clotrimazole (Canesten®)	Oral and vulvovaginal candidiasis Dermatomycoses	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Pruritus, skin irritation	Hypersensitivity to clotrimazole or any component of formulation
miconazole (Monistat®, Micozole®)	Vulvovaginal candidiasis Dermatomycoses		Vaginal burning Nausea/vomiting	Hypersensitivity to miconazole, milk protein concentrate, or any component of formulation
ketoconazole (Nizoral®)	Dermatomycoses Seborrheic dermatitis		Pruritus, skin irritation, GI nonspecific Results in decreased androgen and testosterone synthesis	Cross-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant
TRIAZOLES				
fluconazole (Diflucan®)	*Candida* infections (mucosal and invasive) Cryptococcal meningitis (step-down therapy)	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Elevated liver enzymes GI nonspecific	Cross-sensitivity with other azoles unknown Terfenadine of multiple doses ≥400 mg CYP3A4 substrates (QTc prolongation risk)
itraconazole (Sporanox®)	Sporotrichosis Onychomycoses Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis		Elevated liver enzymes Rash GI Nonspecific HTN Hyperkalemia Peripheral edema	Cross-sensitivity with other azoles unknown Severe ventricular dysfunction Pregnant women or planning CYP2D6 inhibitors or eliglustat Hepatic and renal impairment
voriconazole (Vfend®)	Aspergillosis Candidiasis		Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients Prolonged QT Periostitis Neurologic toxicity	Cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids, St. John's wort, venetoclax, ivabradine
posaconazole (Posanol®, Noxafil®)	Candidiasis Aspergillosis Mucormycosis		Elevated liver enzymes Headache Prolonged QT	Coadministration of cisapride, ergot alkaloids, or sirolimus CYP3A4 substrates: HMG-CoA reductase inhibitors (e.g. atorvastatin, lovastatin, simvastatin) QT interval prolonging (e.g. pimozide, quinidine)
isavuconazole	Candidiasis (esophageal) - off label for HIV patients Aspergillosis Mucormycosis		Peripheral edema Headache, fatigue, insomnia Hypokalemia GI Elevated liver enzymes Dyspnea, cough	Hypersensitivity to isavuconazole or any component of the formulation Strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) Strong CYP3A4 inducers (e.g. rifampin, carbamazepine, St. John's wort, long acting barbiturates) Moderate CYP3A4/5 inducers (e.g. efavirenz, etravirine) Familial short QT syndrome Pregnant women or planning

Table 36. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ALLYLAMINES				
terbinafine (Lamisil®)	Dermatomycoses Onychomycoses	Inhibits enzyme needed for ergosterol synthesis	Rash, local irritation GI nonspecific Transaminitis	Active liver disease
ECHINOCANDINS				
caspofungin micafungin anidulafungin	Refractory aspergillosis Candidemia (azole-resistant)	Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall)	Hepatotoxicity infusion and injection site reactions	

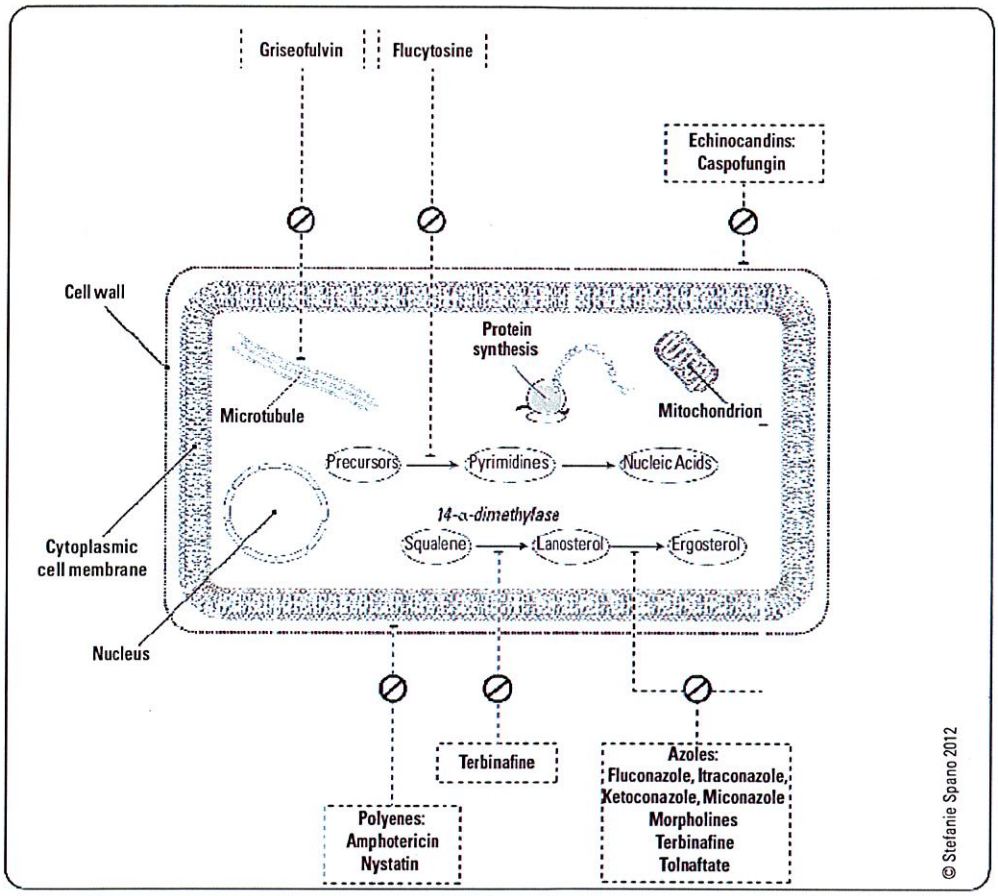


Figure 18. Mechanism of action of antifungals

Antiparasitics

Table 37. Antiparasitics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTIMALARIALS				
chloroquine	Malaria: treatment of erythrocytic phase of all five species of *Plasmodium* that infect humans Note: High resistance of *P. falciparum and P. vivax* in certain geographic areas	Inhibits parasite heme polymerase	CNS: blurred vision, retinopathy, dizziness Nonspecific GI (rare with prophylaxis)	Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes
quinine	Malaria: treatment of all five species of *Plasmodium* that infect humans, including chloroquine-resistant *P. falciparum*		Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (nausea/vomiting, diarrhea), CNS (headache, fever) Hypoglycemia	Hypersensitivity to quinine, may have cross-sensitivity with quinidine Tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use Prolonged QT Myasthenia gravis
mefloquine (Lariam®)	Malaria: prophylaxis		CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, headache	History of seizures, psychosis, anxiety, depression, or other mental health diagnoses
primaquine	Malaria: treatment of liver hypnozoites of *P. vivax* and *P. ovale*; prophylaxis of all *Plasmodium* spp. *Pneumocystis jirovecii* (with clindamycin)	Interferes with mitochondrial function	Hemolytic anemia in G6PD deficient GI upset (take with food)	G6PD deficiency Concurrent or recent use of quinacrine Pregnancy
atovaquone/proguanil (Malarone®)	Malaria: treatment and prophylaxis of *P. falciparum*	Inhibits mitochondrial electron transport and dihydrofolate reductase	Nausea/vomiting, anorexia, diarrhea, abdominal pain (take with food)	Hypersensitivity to atovaquone or proguanil Severe renal impairment
artemisinin derivatives (artemether, artesunate, etc.) Note: marketed throughout the word in both endemic and non-endemic countries; neither licensed nor marketed in Canada, therefore available only via Health Canada Special Access Program	Malaria: treatment of all *Plasmodium* spp. Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above	Binds iron, leading to formation of free radicals that damage parasite proteins	Transient neurologic deficits (nystagmus, balance disturbance) Transient neutropenia (at high doses of oral artesunate) Delayed hemolysis	Hypersensitivity to artemisinins
OTHER ANTI-PROTOZOAL				
iodoquinol (Diodoquin®)	Amebiasis: *E. histolytica, Dientamoeba fragilis, Balantidium coli, Blastocystis hominis*	Contact amebicide that acts in intestinal lumen by uncertain mechanism	GI: nausea/vomiting, diarrhea, abdominal pain CNS: headache, seizures, encephalitis	Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy
metronidazole	Amebiasis: *E. histolytica, T. vaginalis, giardiasis, D. fragilis*	See *Antibiotics, ID50*		
nitazoxanide	*Cryptosporidium*, giardiasis, cyclosporiasis	Interferes with parasite anaerobic metabolism	Nausea/vomiting, diarrhea, abdominal pain, headache	Hypersensitivity to nitazoxanide
ANTI-HELMINTHICS				
praziquantel	*Schistosomiasis* and other flukes Tapeworms	Increases Ca^{2+} permeability of helminth cell membrane, causing paralysis and detachment	Nausea/vomiting, fever, dizziness	Ocular cysticercosis Concomitant use with strong CYP450 inducers
albendazole	Intestinal roundworms *Neurocysticercosis* *Echinococcus* Hydatid disease	Inhibits glucose uptake into susceptible parasites Microtubule inhibitor	Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis	Pregnancy Ocular cysticercosis or intraventricular cysticercosis
mebendazole (Vermox®)	Intestinal roundworms: pinworm, whipworm, hookworm, roundworm (e.g. *Ascaris*)	Inhibits microtubule formation and glucose uptake	Nonspecific GI	Pregnancy Infants
ivermectin	*Strongyloidiasis* *Onchocerciasis* Scabies	Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis	Nausea, bloating, diarrhea, myalgias, lightheadedness, headache	Hypersensitivity to ivermectin Pregnancy
diethylcarbamazine	Wuchereria bancrofti Loa loa	Thought to immobilize microfilariae and disrupt surface membrane to enhance killing by host immune system	Anorexia, nausea/vomiting, headache, drowsiness, encephalitis, retinal hemorrhage Mazzotti reaction if coinfected with onchocerciasis	Pregnancy Onchocerciasis High-grade microfilaremia due to *Loa loa*

Quick Reference: Common Infections and Their Antibiotic Management

- see Family Medicine, FM54

Landmark Infectious Diseases Trials

Trial Name	Reference	Clinical Trial Details
Respiratory Infections		
EPIC-HR	NEJM 2022;386:1397-1408	**Title:** Oral Nirmatrelvir for High-Risk, Non-hospitalized Adults with COVID-19 **Purpose:** To determine whether nirmatrelvir/ritonavir is safe and effective for the treatment of adults who are ill with COVID-19 and do not need to be in the hospital but are at an increased risk of developing severe illness. **Methods:** 2246 participants with confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive nirmatrelvir/ritonavir or placebo orally every 12 h for 5 d (10 doses total). **Results:** Primary outcome measure was proportion of participants with COVID-19 related hospitalization or death from any cause; incidence was lower on day 28 by 6.32% in nirmatelvir group compared to placebo (relative risk reduction of 89.1%; P<0.0001). **Conclusions:** In early treatment of patients with both symptomatic COVID-19 and at high risk of progressing to severe illness, nirmatrelvir/ritonavir significantly reduces hospitalization and death.
PINETREE	NEJM 2022;386:305-315	**Title:** Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients **Purpose:** To determine whether remdesivir in symptomatic, nonhospitalized patients with COVID-19 who are at high risk of disease progress prevents hospitalization. **Methods:** 562 patients were randomized within 7 d of symptoms onset to IV remdesivir (200 mg on day q1 and 100 mg on days 2 and 3) or placebo. Primary efficacy was a composite of COVID-19-reslated hospitalization or death from any cause by day 28. **Results:** COVID-19-related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group. **Conclusions:** Among non-hospitalized patients who were at high risk for COVID-19 progression, a 3-day course of remdesivir resulted in an 87% lower risk of hospitalization or death than placebo.
ACTT-1	NEJM 2020;383:1813-26	**Title:** Remdesivir for the Treatment of Covid-19 — Final Report **Purpose:** To determine if remdesivir is effective against patients hospitalized with COVID-19 lower respiratory tract infection **Methods:** 1062 patients were randomized to either remdesivir (200 mg loading dose on day 1, followed by q100 mg daily for up to 9 additional days) or placebo for up to 10 d. Primary outcome: time to recovery define as either discharge from hospital or hospitalization for infection control purposes only. **Results:** Mean time to recovery for those randomized to remdesivir was 10 d compared to 15 d among those with placebo. Kaplan-Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15. **Conclusions:** Remdesivir was superior to placebo in shortening time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.
RECOVERY	NEJM 2021;384:693-704	**Title:** Dexamethasone in Hospitalized Patients with COVID-19 **Purpose:** To assess if glucocorticoids can protect against inflammation-mediated lung injury and reduce progression to respiratory failure and death. **Methods:** 6425 hospitalized SARS-CoV-2 patients were randomized to receive either (1) dexamethasone (oral or IV, 6 mg daily) for up to 10 d or (2) usual standard of care alone. **Results:** Dexamethasone significantly reduced incidence of death as compared to usual care alone in patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; RR 0.64; 95% CI 0.51-0.81) and among those receiving oxygen (23.3% vs. 26.2%; RR 0.82; 95% CI 0.72-0.94) but not among those without respiratory support (17.8% vs. 14.0%; RR 1.19; 95% CI 0.92-1.55). **Conclusion:** In patients hospitalized with COVID-19, dexamethasone lowers 28-d mortality in those receiving invasive mechanical ventilation or oxygen alone.
PneumA	JAMA 2003;290:2588-98	**Title:** Comparison of 8 vs. 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults: A Randomized Trial **Purpose:** To identify the optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP). **Methods:** 401 patients with VAP diagnosed by quantitative culture of bronchoscopic specimens who had received initial empiric antibiotic therapy were randomly assigned to receive either 8 d or 15 d of antibiotic therapy (regimen selected by treating physician). **Results:** As compared to 15-d therapy, 8-d therapy did not result in a significant difference in mortality (18.8% vs. 17.2% in 8-d and 15-d group, respectively; difference, 1.6%; 90% CI, -3.7% to 6.9%) or recurrent infections (28.9% vs. 26.0%; difference, 2.9%; 90% CI, -3.2% to 9.1%). 8-d therapy was associated with more mean antibiotic-free days (13.1 vs. 8.7; P<0.001). **Conclusion:** 8- and 15-d antibiotic treatment regimens demonstrated comparable dinical efficacy against VAP among patients who had received appropriate initial empiric therapy.
Meningitis		
Dexamethasone in Adults with Bacterial Meningitis. Gans et al. 2002	NEJM 2002;347:1549-56	**Title:** Dexamethasone in Adults with Bacterial Meningitis **Purpose:** To assess the efficacy of corticosteroids as an adjuvant treatment of acute bacterial meningitis in adults. **Methods:** 301 patients were randomly assigned to receive dexamethasone (10 mg) or placebo 15-20 min before or with the first dose of antibiotics and subsequently every 6 h for 4 d. **Results:** Dexamethasone treatment was associated with a significant reduction in the risk of an unfavourable outcome, defined as a score of 1-4 on the Glasgow Outcome Scale at 8 wk (relative risk (RR), 0.59; 95% CI, 0.37-0.94; P=0.03), as well as a significant reduction in in mortality (RR, 0.48, 95% CI, 0.24-0.96; P=0.04). **Conclusion:** In adults with acute bacterial meningitis, early treatment with dexamethasone significantly improves outcomes and does not increase the risk of GI bleeding.
Infective Endocarditis		
POET	NEJM 2019;380:415-24	**Title:** Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis **Purpose:** To investigate whether a change from IV to oral antibiotics in stable left-sided IE would result in efficacy and safety profiles similar to those with continued IV treatment. **Methods:** 400 adults with IE on the left side of the heart, in stable condition, being treated with IV antibiotics (minimum 10 d) were randomized to continue IV treatment or to switch to oral antibiotics. Primary Outcome: Composite of all-cause mortality, embolic events, unplanned cardiac surgery, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 mo following completion of antibiotics. **Results:** The primary composite outcome occurred in 12.1% in the IV group and 9.0% in the oral group (between-group difference, 3.1 percentage points; 95% CI, -3.4 to 9.6; P=0.40), thus meeting noninferiority. **Conclusion:** Shifting to oral antibiotics was noninferior to continued IV antibiotics in patients with IE on the left side of the heart in stable condition.

Trial Name	Reference	Clinical Trial Details
Intraabdominal Infections		
STOP-IT	NEJM 2015;372:1996-2005	**Title:** Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection **Purpose:** To determine the appropriate duration of antimicrobial therapy for intraabdominal infection. **Methods:** 518 patients with complicated intraabdominal infection and adequate source control were randomly assigned to receive a fixed course of antibiotics for 4±1 d (experimental group) or until 2 d following the resolution of fever, leukocytosis, and ileus, up to maximum 10 d (control group). **Results:** There were no significant differences in the rates of surgical-site infection, recurrent intraabdominal infection, or death between treatment groups (21.8% vs. 22.3% in the experimental and control groups, respectively; absolute difference, -0.5; 95% CI, -7.0 to 8.0; P=0.92). The experimental group experienced a significantly shorter median duration of antibiotic therapy (4.0 d vs. 8.0 d; absolute difference, -4.0; 95% CI, -4.7 to -3.3; P<0.001). **Conclusion:** The outcomes after fixed-duration antibiotic therapy were similar to those after a longer course of antibiotics in patients with intraabdominal infections with adequate source control.
HIV and AIDS		
iPrEx	NEJM 2010;363:2587-99	**Title:** Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex With Men **Purpose:** To investigate the efficacy and safety of antiretroviral chemoprophylaxis for the prevention of HIV acquisition. **Methods:** 2499 HIV-seronegative men or transgender women who have sex with men were randomly assigned to receive emtricitabine plus tenofovir disoproxil fumarate (FTC-TDF), or placebo daily. **Results:** During median 1.2 yr follow-up, 100 participants became infected (36 in the FTC-TDF group vs. 64 in the placebo group), representing a 44% reduction in the incidence of HIV (95% CI, 15-63; P=0.005). Similar rates of serious adverse events were observed in both groups (P=0.57). **Conclusion:** Preexposure prophylaxis with antiretrovirals significantly reduced HIV infection risk in HIV-negative men and transgender women who have sex with men.
Prevention of HIV-1 Infection With Early Antiretroviral Therapy. Cohen et al. 2011	NEJM 2011;365:493-505	**Title:** Prevention of HIV-1 Infection With Early Antiretroviral Therapy **Purpose:** To investigate if immediate antiretroviral therapy could limit the transmission of HIV in serodiscordant couples. **Methods:** 1763 HIV-1-positive adults with an HIV-negative partner were randomly assigned to receive antiretroviral therapy either immediately or after a decline in the CD4 count or the onset of HIV-1-related symptoms. **Results:** Of the 39 HIV-1 transmissions observed, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6-1.3). Of the 28 linked transmissions, 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01-0.27; P<0.001). **Conclusion:** Rates of HIV-1 transmission and clinical events were reduced by early initiation of antiretroviral therapy, suggesting personal and public health benefits.
Sepsis and Septic Shock		
CORTICUS	NEJM 2008;358:111-24	**Title:** Hydrocortisone Therapy for Patients With Septic Shock **Purpose:** To investigate the efficacy of hydrocortisone administration in patients with septic shock who were either responsive or unresponsive to corticotropin. **Methods:** 499 patients were randomly assigned to receive 50 mg IV hydrocortisone or placebo every 6 h for 5 d with dose tapering over the following 6 d. **Results:** No significant difference in mortality at 28 d between patients in groups that did not respond to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, P=0.69) or between those that did response to corticotropin (28.8% and 28.7%, P=1.00). **Conclusion:** Survival was not improved by hydrocortisone in patients with septic shock.
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. Brunkhorst et al. 2008	NEJM 2008;358:125-39	**Title:** Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis **Purpose:** To investigate the role of intensive insulin therapy and the choice of either crystalloids or colloids in patients with severe sepsis. **Methods:** Patients received either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch or modified Ringer's lactate for fluid resuscitation. **Results:** Trial stopped for safety reasons. Intensive insulin therapy was associated with increased rates of hypoglycemia (17.0% vs. 4.1%, P<0.001) and serious adverse events (10.9% vs. 5.2%, P=0.01). Higher rates of acute renal failure and renal-replacement were seen in pentastarch as compared to Ringer's lactate. **Conclusion:** In critically ill patients with sepsis, intensive insulin therapy increased the risk of serious adverse events related to hypoglycemia. Pentastarch was harmful.
Bone and Joint Infections		
OVIVA	NEJM 2019;380:425-36	**Title:** Oral versus Intravenous Antibiotics for Bone and Joint Infection **Purpose:** To assess if oral antibiotics are noninferior to IV antibiotic treatment for managing complex orthopaedic infections. **Methods:** Within 1 wk post-surgery, 1054 patients were randomly assigned to receive IV or oral antibiotics for 6 wk. Both groups were permitted follow-on oral antibiotics. **Results:** There was no significant difference in risk of treatment failure between oral and IV groups (-1.4%; 95% CI, -5.6-2.9), indicating noninferiority. There was no significant difference in the rates of serious adverse events between groups. **Conclusion:** Oral antibiotics were noninferior to IV antibiotics for the treatment of complex orthopaedic infections when used for 6 wk.
DATIPO	NEJM 2021;384:1991-2001	**Title:** Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection **Purpose:** To identify the appropriate duration of antimicrobial therapy for the management of prosthetic joint infection. **Methods:** 410 patients with microbiologically confirmed prosthetic joint infection that had been managed with an appropriate surgical procedure were randomly assigned to receive either 6 wk or 12 wk of antibiotic therapy as soon as possible after surgery. **Results:** Rates of persistent infection were significantly higher in the 6-wk group as compared to the 12 wk group (18.1% vs. 9.4%; risk difference, 8.7%; 95% CI, 1.8%-15.6%). **Conclusion:** Antibiotic therapy for 6 wk was not noninferior to 12-wk therapy and resulted in more unfavourable outcomes in patients with prosthetic joint infections managed with standard surgical procedures.

Trial Name	Reference	Clinical Trial Details
Blood and Tissue Infections		
Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. Zongo et al. 2021	NEJM 2021; 385:1005-1017	**Title:** Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention **Purpose:** The study compared the efficacy of RTS,S to that of SMC, which is the standard treatment for children in areas with highly seasonal malaria transmission. **Methods:** Randomly assigned 6861 children 5 to 17 mo of age to receive sulfadoxine-pyrimethamine and amodiaquine (2287 children [chemoprevention-alone group]), RTS,S/AS01E (2288 children [vaccine-alone group]), or chemoprevention and RTS,S/AS01E (2286 children [combination group]) **Results:** Demonstrated that not only is RTS,S comparable to SMC in preventing malaria, but that combining the two interventions is markedly superior to either intervention alone. **Conclusion:** Use of the two interventions together resulted in an approximately 70 percent further reduction in malaria deaths and hospitalizations, and a 60 percent reduction in uncomplicated malaria over use of SMC alone.
BENEFIT	NEJM 2015;373:1295-306	**Title:** Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy **Purpose:** To investigate the efficacy of trypanocidal therapy in patients with Chagas' cardiomyopathy. **Methods:** 2854 patients with Chagas' cardiomyopathy were randomly assigned to receive benznidazole or placebo for up to 80 d. **Results:** Rates of conversion to negative *Trypanosoma cruzi* PCR results were 66.2% in the benznidazole group and 33.5% in the placebo group at the end of treatment, 55.4% and 35.3% at 2 yr, and 46.7% and 33.1% at >5 yr (P<0.001 for all). PCR conversion rates did not correspond to clinical outcomes. **Conclusion:** In patients with Chagas' cardiomyopathy, trypanocidal therapy reduced serum parasite levels but did not improve cardiac deterioration.
Fungal Infections		
Voriconazole Versus Amphotericin B for Primary Therapy of Invasive Aspergillosis. Herbrecht et al. 2002	NEJM 2002;347:408-15	**Title:** Voriconazole Versus Amphotericin B for Primary Therapy of Invasive Aspergillosis **Purpose:** To compare voriconazole vs. amphotericin B for primary therapy of invasive aspergillosis. **Methods:** 277 patients randomly assigned to receive IV voriconazole followed by oral voriconazole BID or IV amphotericin B deoxycholate. **Results:** Successful outcomes occurred in 52.8% of patients on voriconazole and 31.6% on amphotericin B at wk 12 (absolute difference, 21.2%; 95% CI, 10.4-32.9). Rate of survival was 70.8% in the voriconazole group and 57.9% in the amphotericin B group (hazard ratio, 0.59; 95% CI, 0.40-0.88). Voriconazole was associated with significantly fewer severe adverse events. **Conclusion:** Initial therapy with voriconazole is more clinically effective with fewer side effects than the standard approach with amphotericin B.

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MG Medical Genetics

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Acronyms

CF	cystic fibrosis	GA	gestational age	MCADD	medium chain acyl-CoA dehydrogenase deficiency	NGS	next generation sequencing
CNV	copy number variant	GS	genome sequencing	MLPA	multiplex ligation-dependent probe assay	PKU	phenylketonuria
(W)ES	(whole) exome sequencing	GSD	glycogen storage disease	MSUD	maple syrup urine disease	SNP	single nucleotide polymorphism
(W)GS	(whole) genome sequencing	LCHAD	long chain 3-hydroxyacyl-CoA dehydrogenase deficiency			VLCAD	very long chain acyl-CoA dehydrogenase deficiency
FISH	fluorescence in situ hybridization						

Introduction to Genetics

Common Terms

- **penetrance**: probability that a gene variant is observably expressed in an individual who carries it
- **expressivity**: extent of gene expression – refers to the range of variation seen in a phenotype for a certain genotype
- **genetic heterogeneity**: when a phenotype/genetic disorder can be caused by different genotypes, due to genetic variation within the same gene (allelic heterogeneity) or in different genes (locus heterogeneity)
- **phenotypic heterogeneity**: pathogenic variants in the same gene result in multiple clinical manifestations and varying degrees of severity
- **mosaicism**: presence of two or more genotypes (e.g. chromosome patterns or gene variants) in the cells of the same person
- **nondisjunction**: a cell division error in which chromosomes fail to segregate, resulting in daughter cells with fewer or more chromosomes than expected
- **uniparental disomy**: inheritance of two full or partial copies of a chromosome from one parent and no corresponding full/partial chromosome from the other parent
- **allele**: an abnormal number of chromosomes in the cell due to loss or duplication

Genetic Variation

- a variant is a permanent change in the nucleotide sequence that differs from the most common nucleotide sequence (reference sequence)
- variants are classified based on their likelihood of disrupting the function of the gene product. The American College of Medical Genetics and Genomics has created a commonly used method for classifying variants for single gene disorders:
  - benign: not associated with genetic disease
  - likely benign: probably not associated with genetic disease, but insufficient evidence to classify as benign
  - variant of uncertain significance (VUS): insufficient evidence to classify variant as benign or pathogenic
  - likely pathogenic: 90% likely to be pathogenic, and clinically treated as a pathogenic variant
  - pathogenic: known to be associated with genetic disease
- nomenclature no longer used in clinical genetics:
  - mutation: previously synonymous with pathogenic variant. Now this term is only used to describe the actual process of genetic change
  - polymorphism: a variant that is relatively common in the population and not typically associated with a genetic disease. This term is used only in the context of population genetics

Types of Genetic Variation

- deletions or duplications of a whole gene(s) caused by aneuploidy, unbalanced chromosome rearrangements, or copy number variants (e.g. 22q11.2 deletion or DiGeorge syndrome; 17p11.2 duplication or Potocki-Lupski syndrome)
- disruption of a gene: inversions, balanced chromosome rearrangements
- variants that cause alteration in the protein coding sequence: missense (encodes for a different amino acid), nonsense (encodes for a premature stop codon), frameshift (deletion/insertion of a number of nucleotides that is not a multiple of 3, thus shifting the reading frame)
- variants that affect the transcription of a gene
- variants that affect splicing

Single Gene Disorders

- traits or disorders determined by variation occurring in a specific gene, which often follow a Mendelian inheritance pattern
- autosomal inheritance: disorder is caused by pathogenic variants in a gene located on chromosomes 1-22 (the autosomes)
  - autosomal dominant: one copy of a gene with a pathogenic variant is sufficient to cause a trait/disorder
  - autosomal recessive: both copies of a gene must have pathogenic variants to cause a trait/disorder; an individual with one copy of a pathogenic gene variant is a carrier
- sex-linked inheritance: when disease is caused by pathogenic variants in a gene on the X or the Y chromosome. Because the X chromosome contains more genes than the Y chromosome, almost all sex-linked traits are X-linked. X-linked inheritance generally results in a trait/disorder that is seen more commonly or with greater severity in males than females
  - e.g. Hemophilia A, Duchenne muscular dystrophy

Triplet Repeat Expansions
- disorders where the number of trinucleotide repeats in certain genes exceeds the normal number and results in altered gene expression or production of an abnormal protein
  - these disorders can demonstrate genetic anticipation, where signs and symptoms are more severe and appear at an earlier age from one generation to the next due to expansion of the triplet repeat number
  - length of expansion segment is often proportional to severity of clinical phenotype
- e.g. Fragile X syndrome, Huntington disease

Imprinting Disorders
- imprinted genes are expressed entirely from either the maternal or paternal allele, depending on the gene (parent-of-origin gene expression)
- imprinting is determined by allele-specific epigenetic mechanisms (i.e. modifications to DNA other than a change in the underlying sequence, such as DNA methylation and/or histone modifications)
- disorders occur when a pathogenic variant disrupts the normally expressed allele of an imprinted gene or through uniparental disomy of the normally silenced allele
- e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome

Mitochondrial Disorders
- disorders caused by pathogenic variants in mitochondrial DNA or in nuclear genes whose protein products are important for mitochondrial function
- high phenotypic heterogeneity
- mitochondrial disorders caused by pathogenic variants in nuclear genes demonstrate Mendelian inheritance (e.g. Alpers syndrome caused by autosomal recessive pathogenic variants in *POLG*)
- disorders caused by pathogenic variants in mitochondrial DNA are maternally inherited by all offspring as all mitochondria and associated mitochondrial DNA in the embryo comes from the maternal ovum, with no paternal contribution of mitochondria
- e.g. mitochondrial encephalomyopathy and lactic acidosis with stroke-like episodes syndrome (MELAS)

Common Indications for Genetic Referrals
- preconception and prenatal: abnormal prenatal screening test, fetal anomaly, recurrent pregnancy loss, personal or family history of a genetic condition, positive carrier screening test, consanguinity
- pediatric: major and/or multiple minor congenital anomalies, developmental delay, abnormal newborn screen, unusual growth pattern, abnormal pubertal development, connective tissue disorders, congenital hypo- or hypertonia
- adult: family history of adult-onset genetic condition (e.g. Huntington disease), personal or family history of cancer concerning for genetic cause, bleeding or clotting disorder, early onset vision or hearing loss, intellectual disability, leukodystrophies, muscular dystrophy, movement disorders (e.g. ataxia, dystonia, chorea), and metabolic diseases

Pedigrees
- diagrams of a family tree that show the pattern/distribution of phenotypes for a genetic disorder within that family, often across multiple generations
- pedigrees generally indicate sex assigned at birth, with or without genetic confirmation of sex chromosomes; when counselling gender diverse patients (including transgender and non-binary patients), physicians should affirm the patient's gender identity, while clarifying the role of sex assigned at birth or chromosomal sex in determining genetic features for the pedigree

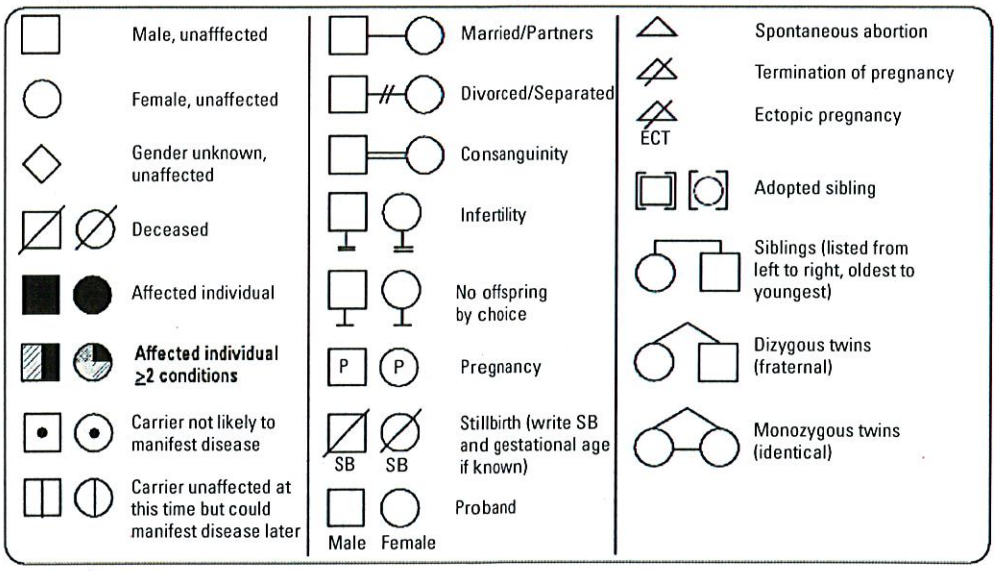


Figure 1. Common pedigree symbols



Meta-analysis of the Diagnostic and Clinical Utility of Genome and Exome Sequencing and Chromosomal Microarray in Children
Genomic Med 2018;3:16
Purpose: To compare the diagnostic and clinical utility of WGS and WES to that of chromosomal microarray.
Methods: A systematic review and meta-analysis of the literature.
Results: 37 studies were included (20068 children). Diagnostic utility of WGS (0.41, 95% CI 0.34-0.48) and WES (0.36, 95% CI 0.33-0.40) were greater than chromosomal microarray (0.10, 95% CI 0.08-0.12). The clinical utility of WGS (0.27, 95% CI 0.17-0.40) and WES (0.17, 95% CI 0.12-0.24) were higher than chromosomal microarray (0.06, 95% CI 0.05-0.07) and this difference was significant for WGS vs. chromosomal microarray ($P<0.0001$).
Conclusion: The diagnostic and clinical utility of WGS and WES is greater than that of chromosomal microarray.

Genetic Testing and Counselling

Common Terms

- presymptomatic genetic testing: used to determine whether individuals without current symptoms, but with a known family history of a genetic disease, carry the familial pathogenic variant associated with the disease
- newborn screening: performed within the first few days of life to detect treatable and potentially fatal disorders before symptoms arise to allow for early therapy
- preconception genetic counselling: pre-pregnancy evaluation to assess the risk of having a child with an inherited condition
- preimplantation genetic diagnosis: genetic testing of in vitro fertilized embryos for specific genetic conditions before uterine transfer

Table 1. Common Genetic Tests

Test	Karyotype	FISH	Microarray Analysis	Sanger Sequencing	NGS	MLPA	Repeat-Primed PCR
Technique	Microscopic analysis of chromosomes with a nucleic acid stain that shows large changes in the number or structure of chromosomes; can detect large CNVs	A fluorescent-tagged DNA probe used to identify a gain, loss, or rearrangement of chromosomal material or specific DNA sequence	A collection of DNA probes attached to a solid surface to which test DNA hybridize in order to determine copy number of DNA regions	A method of DNA sequencing which is based on the selective incorporation of chain-terminating nucleotides during replication	High-throughput method used to sequence multiple genes in parallel; NGS is the technology used for panel sequencing, (W)ES, and (W)GS	High-throughput multiplex PCR assay, which uses probes to evaluate the relative copy number of each DNA sequence	PCR amplification method which uses paired primers to generate different sized amplicons, due to multiple annealing sites on the template
Uses/Indications	Useful in identification of major aneuploidies, structural chromosomal rearrangements, chromosomal changes related to hematological conditions, or other genetic diseases related to chromosome structure	Can confirm the presence or absence of specific DNA sequences and localize them. It has good resolution for microdeletions and small translocations May be used to detect aneuploidies, perform gene mapping, identify oncogenes, and identify circulating tumour cells	Microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome. Commonly indicated when there is developmental delay/ autism or two or more congenital anomalies	The "gold-standard" method for identification of single nucleotide variants in the gene(s) known to cause a suspected syndrome	Limited indications (vary by province) but may include: limit further invasive diagnostics and facilitate early intervention when there is multisystem involvement, or when the differential diagnosis includes ≥2 conditions that would require separate genetic tests	Can detect small copy number variants, at an exon-level resolution Widely used due to low cost, simplicity, and broad availability of commercially developed assays	Used to determine the number of repeats. Used in diagnostic or predictive testing in symptomatic or at-risk individuals

- see Obstetrics, OB7 for information on prenatal screening tests

Differences in Morphology

Congenital Anomalies

Minor and Major Anomalies

- minor anomaly: physical difference that is of no significant medical or cosmetic consequence to the patient (e.g. ear pit/tag, single palmar crease)
- major anomaly: physical difference that creates significant medical, surgical, or cosmetic problems for the patient (e.g. ventricular septal defect, cleft lip)

Mechanisms for Anomalies

- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. skeletal dysplasia)

Multiple Anomalies

- association: non-random occurrence of multiple independent anomalies that appear together more often than would be predicted by chance, but are not known to have a single underlying etiology (e.g. VACTERL association)
- sequence: related anomalies that originate from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence or Pierre-Robin sequence)
- syndrome: a pattern of anomalies that occur together and are known or thought to have a single cause (e.g. CHARGE syndrome)



VACTERL Association
Vertebral dysgenesis
Anal atresia (imperforate anus) ± fistula
Cardiac anomalies
Tracheo**E**sophageal fistula ± esophageal atresia
Renal anomalies
Limb anomalies

Approach to the Patient with Physical Differences



Check the umbilical cord for 2 arteries and 1 vein. The presence of a single umbilical artery may be associated with other congenital anomalies

General Approach

- are the anomalies major or minor?
- what is the mechanism underlying the anomaly?
- do the anomalies fit as part of an association, sequence, or syndrome?
- are the anomalies seen in other family members?

History

- prenatal/obstetrical history (see Obstetrics, OB4) with particular attention to potential teratogenic exposures, developmental history (see Pediatrics, P26), and past medical history
- complete three generation family pedigree: health history, consanguinity, multiple miscarriages/ stillbirths, neonatal deaths, congenital defects, developmental delay/autism, ethnicity

Physical Exam

- compare features with other family members

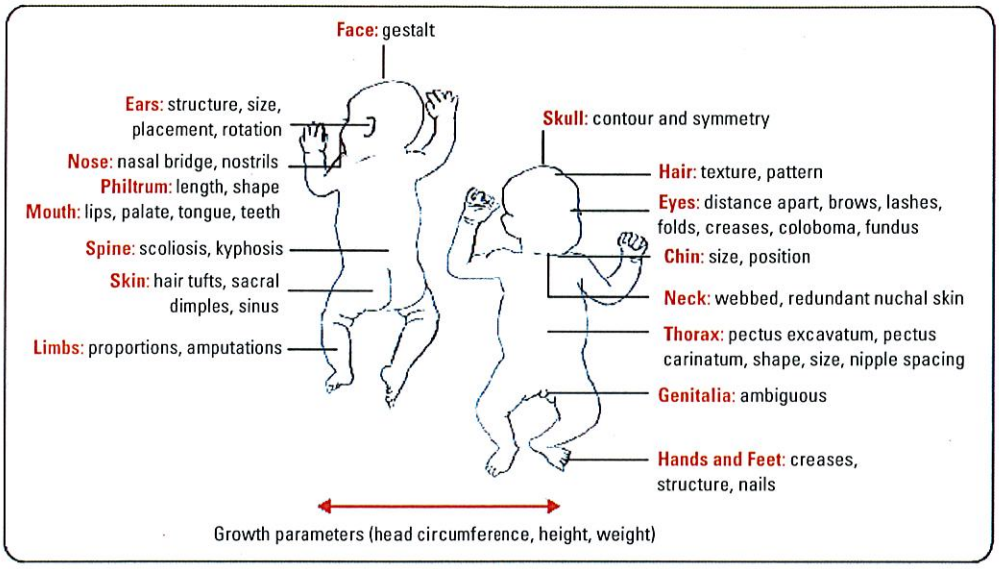


Figure 2. Physical exam in genetic assessment of a child

Investigations

- screening for TORCH infections (toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, herpes infection)
- serial photographs
- x-rays for bony abnormalities
- abdominal U/S and echocardiography to rule out structural abnormalities of organs
- brain imaging, especially if neurodevelopmental/neurological findings
- cytogenetic studies
  - chromosomal microarray analysis (SNP array) if developmental delay/autism or two or more congenital anomalies
  - FISH if aneuploidy syndrome (e.g. trisomy 13, 18, or 21) suspected
  - consider karyotype if a known aneuploidy syndrome is recognized or if there is a family history of a chromosomal rearrangement such as a translocation
- biochemistry: various biochemical tests, specific enzyme assays (e.g. for lysosomal storage diseases)
- single gene testing, gene panel testing, ES, GS
- sensory evaluations including audiology, ophthalmology or optometry

Management

- recurrence risk and prenatal counselling
- referral for specialized medical care or genetic care for symptomatic management
- patient education, connect to social and psychological support services

Genetic Conditions

Table 2. Common Chromosomal Aneuploidy Syndromes

	Trisomy 21	Trisomy 18	Trisomy 13
Disease	Down syndrome	Edwards syndrome	Patau syndrome
Incidence	1 in 600-800 births Most common abnormality of autosomal chromosomes Rises with advanced maternal age from 1 in 1500 at age 20 to 1 in 20 by age 45	1 in 6000 live births F:M=3:1	1 in 10000 live births
Cranium/Brain	Mild microcephaly, flat occiput, third fontanelle, brachycephaly	Microcephaly, prominent occiput	Microcephaly, sloping forehead, scalp defect, holoprosencephaly
Eyes	Upslanting palpebral fissures, epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus	Microphthalmia, hypotelorism, iris coloboma, retinal anomalies	Microphthalmia, corneal abnormalities
Ears	Low-set, small, overfolded upper helix, frequent acute otitis media, hearing loss	Low-set, malformed	Low-set, malformed
Facial Features	Protruding tongue, large cheeks, low flat nasal bridge, small nose	Cleft lip/palate Small mouth, micrognathia	60-80% cleft lip and palate
Musculoskeletal (MSK)	Short stature Excess nuchal skin Joint hyperflexibility (80%) including dysplastic hips, vertebral anomalies, atlantoaxial instability	Intrauterine growth restriction Clenched fist with overlapping digits, hypoplastic nails, clinodactyly	Small head size Polydactyly
Cardiac Defect	50% (particularly atrioventricular septal defect)	60% (ventricular septal defect, patent ductus arteriosus, atrial septal defect)	80% (atrial septal defect, patent ductus arteriosus, ventricular septal defect)
Gastrointestinal (GI)	Duodenal/esophageal/anal atresia, tracheoesophageal fistula, Hirschsprung's disease, chronic constipation	Hernia, tracheoesophageal fistula	None known
Genitourinary (GU)	Cryptorchidism, rarely fertile	Polycystic kidneys, cryptorchidism	Polycystic kidneys
Central Nervous System (CNS)	Hypotonia at birth Low IQ, developmental delay, hearing problems Onset of Alzheimer's disease in 40s	Hypertonia	Hypo- or hypertonia Seizures, deafness
Other Features	Single transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger 1% lifetime risk of leukemia Polycythemia Hypothyroidism	Small for GA Rocker-bottom feet	Single umbilical artery Midline anomalies: scalp, holoprosencephaly, palate, heart, umbilicus, anus
Prognosis/Management	78% 1 yr survival for patients with congenital heart defect, 96% 1yr survival for patients without anomalies Long-term management per AAP Guidelines: Health Supervision of Children with Down Syndrome	13% 1 yr survival, 10% 10 yr survival Profound intellectual disability in survivors	20% 1 yr survival, 13% 10 yr survival Profound intellectual disability in survivors

Table 3. Common Genetic Disorders Involving the Sex Chromosomes

	Fragile X Syndrome	Klinefelter Syndrome	Turner Syndrome
Genotype	CGG trinucleotide repeat expansion in *FMR1* gene on X chromosome; ~55-~200 repeats is considered a premutation, whereas >200 repeats is considered a full mutation	47,XXY (most common) 48,XXXY, 49,XXXXY	45,X0 (50% of cases), 45,X/46,XX mosaic (15% of cases)
Incidence	1 in 3600 males, 1 in 6000 females Most common heritable cause of intellectual disability in males	1 in 1000 live male births Increased risk with advanced maternal age	1 in 2000-2500 live female births No increased risk with advanced maternal age
Phenotype	Overgrowth: macrocephaly, prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macroorchidism, hyperextensibility, and high arched palate Complications: seizures, scoliosis, mitral valve prolapse Premutation carriers (males more often than females) may demonstrate tremor/ataxia syndrome in later life Female permutation carriers have a higher probability of having a child with FXS, because repeats in the permutation range are more likely to expand to pathogenic repeat length	Tall, slim, underweight No features pre-puberty Post-puberty: variable learning/behavioural difficulties, long limbs, gynecomastia, lack of facial hair	Short stature, short webbed neck, low posterior hairline, wide carrying angle Broad chest, widely spaced nipples Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia Coarctation of aorta, bicuspid aortic valve Renal and cardiovascular abnormalities, increased risk of hypertension Less severe spectrum with mosaic
IQ and Behaviour	Mild to moderate intellectual disability, 20% of affected males have normal IQ Attention deficit hyperactivity disorder (ADHD) and/or autism Females with full mutation may show milder intellectual impairment Premutation carriers have a normal IQ	Mild intellectual disability or learning difficulties Behavioural or psychiatric disorders: anxiety, shyness, aggressive, and impulsive behaviour acts	Typically normal intelligence
Gonad and Reproductive Function	Premutation carrier females at risk of developing premature ovarian failure	Infertility due to hypergonadotropic hypogonadism	Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics
Diagnosis	Molecular testing of *FMR1* gene: PCR and/or Southern blot analysis of trinucleotide repeat length, methylation analysis	Karyotype	Karyotype

Table 4. Examples of Other Genetic Syndromes

	22q11.2 Deletion Syndrome (DiGeorge syndrome)	Prader-Willi Syndrome	Angelman Syndrome	Noonan Syndrome	CHARGE Syndrome
Genotype	Autosomal dominant; microdeletions of chromosome region 22q11.2	Lack of gene expression on paternal chromosome 15q11-13 due to deletion, maternal uniparental disomy of chromosome 15, or imprinting defect	Lack of gene expression on maternal chromosome 15q11-13 due to deletion, paternal uniparental disomy of chromosome 15, or an imprinting defect Rarely due to pathogenic variants in *UBE3A*	Autosomal dominant with variable expression, pathogenic variants in RAS/MAPK pathway genes ("RASopathies"); autosomal recessive with pathogenic variants in *LZTR1*	2/3 of children with CHARGE have been found to have a pathogenic variant in *CHD7*
Incidence	1 in 4000; second most common genetic diagnosis (next to Down syndrome)	1 in 15000	1 in 10000	1 in 2000	1 in 10000
Clinical Features	**"CATCH 22"** **C**yanotic suggesting congenital heart disease (CHD) **A**nomalies: craniofacial anomalies, micrognathia, and low set ears **T**hymic hypoplasia: immunodeficiency **C**ognitive impairment **H**ypoparathyroidism, hypocalcemia **22**q11 microdeletions High-risk for schizophrenia and other psychiatric disorders	**"H30"** **H**ypotonia and weakness **H**ypogonadism, obsessive **H**yperphagia **O**besity Short stature, almond-shaped eyes, small hands and feet with tapering of fingers Hypopigmentation, T2DM	Ataxia with severe intellectual disability, seizures, tremulousness, midface hypoplasia, large mouth, fair hair, inappropriately happy demeanour/laughter, fascination with water	Short stature, webbed neck, hypertelorism, low-set ears, epicanthal folds, ptosis, pectus excavatum Right-sided CHD, pulmonary stenosis Increased risk of hematological cancers, cardiomyopathy, moderate intellectual disability, delayed puberty	**"CHARGE"** **C**oloboma **H**eart disease **A**tresia of choanae **R**estriction of growth and mental development **G**U anomalies **E**ar malformations and hearing loss

Table 5. Examples of Familial Cancer Syndromes

Syndrome	Gene	Associated Cancers	Screening and Monitoring
Li-Fraumeni Syndrome	*TP53*	Breast, osteosarcoma, leukemia, soft tissue sarcoma, brain, adrenocortical carcinoma, and numerous other cancers	**Children:** From birth: abdominal/pelvic U/S every 3-4 mo; annual brain MRI and whole-body MRI, if with high-risk TP53 variant **Adults:** Women age 20-75: annual breast MRI Age 18: annual dermatologic examination, abdominal/pelvic U/S, brain MRI, and WBMRI Age 25: colonoscopy and upper endoscopy every 2-5 yr *(Moderate recommendation)*
Lynch Syndrome (HNPCC)	*MSH2, MLH1, MSH6, PMS2, EPCAM*	Colorectal, endometrial, ovarian, renal, pancreatic, liver/biliary duct, stomach, brain, breast	Age 20-25 (or 2-5 yr younger than earliest age of colorectal cancer diagnosis in family): colonoscopy every 1-2 yr Age 30 yr (*MSH6*) and 35 (*PMS2*): colonoscopy every 1-2 yr *(Strong recommendation)*
Familial Adenomatous Polyposis (FAP)	*APC*	Colorectal, small intestine/stomach tumours	Age 10: sigmoidoscopy or colonoscopy every 1-2 yr, colonoscopy once polyps develop *(Strong recommendation)*
Hereditary Breast and Ovarian Cancer Syndrome	*BRCA1, BRCA2*	Female: breast, ovarian, pancreatic Male: prostate, breast, pancreatic	Age 25-65: annual breast MRI Age 30: annual breast MRI and mammograms *(Strong recommendation)*
Von Hippel-Lindau Syndrome	*VHL*	Hemangioblastomas of the brain, spinal cord, and retina; renal cell carcinoma; pheochromocytoma; kidney cysts; pancreatic neuroendocrine tumour; and endolymphatic sac tumour	Age 2: annual physical examination, annual ophthalmologic examination, consider annual catecholamine assessment Consider baseline audiometry at age of school entry Ages 12, 15, and 18: MRI of brain stem, spine, and abdomen, with abdominal U/S in alternating years Age 20: MRI every 2 yr *(Expert opinion)*
Cowden Syndrome	*PTEN*	Breast, thyroid, endometrial	Women: Age 30 (or 5-10 yr before earliest breast cancer in the family): annual mammography Age 30: consider random annual endometrial biopsy and/or U/S Men and Women: At diagnosis: annual thyroid U/S Children: evaluation for neurodevelopmental disorders Age 18: annual comprehensive physical exam Age 30-35: colonoscopy every 5 yr *(Moderate recommendation)*
Neurofibromatosis (NF)			
Type 1	*NF1*	Astrocytoma, optic glioma, neurofibroma, leukemia	Children: evaluation for neurodevelopmental disorders Annual physical exam including evaluation of growth, blood pressure, skin examination, bone examination, neurological examination, and vision screening *(Expert opinion)*
Type 2	*NF2*	Vestibular schwannoma, meningioma, ependymoma, astrocytoma	Annual physical exam including audiology assessment Age 10: annual brain MRI, spinal MRI every 2-3 yr *(Expert opinion)*

Table 6. Examples of Heritable Connective Tissue Disorders

	Loeys-Dietz Syndrome	Classical Ehlers-Danlos Syndrome	Vascular Ehlers-Danlos Syndrome	Marfan Syndrome
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Pathophysiology	Pathogenic variants in *TGFBR1, TGFBR2, SMAD3, TGFB2* genes affecting the TGF-β pathway	Pathogenic variants in *COL5A1* or *COL5A2* genes affecting Type V collagen	Pathogenic variants in *COL3A1* gene that affect Type III collagen, which is most abundant type of collagen in aortic extracellular matrix	Pathogenic variants in *FBN1* gene
Incidence	Unknown	1 in 20000-40000	1 in 100000-250000	1 in 3000-5000
Clinical Features	Vascular findings (aortic aneurysms and dissections, generalized arterial tortuosity), craniofacial features (cleft palate, hypertelorism), skeletal features, easy bruising, allergic/inflammatory disease	Clinical features vary: generalized joint hypermobility, skin hyperextensibility and atrophic scarring, fragile skin, easy bruising, subcutaneous spheroids (fat cysts) on forearms and shins	Arterial fragility and/or rupture, aortic dilatation, intestinal rupture, uterine rupture in pregnancy, characteristic facies (translucent skin, thin lips, pinched nose, prominent ears)	Tall and slender build, disproportionately long limbs and digits, aortic dilatation, lens detachment, pneumothoraces

Table 7. Examples of Intracellular/Extracellular Transport Receptor Disorders

	Hereditary Hemochromatosis	Wilson Disease	CF
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
Pathophysiology	Pathogenic variants in *HFE* gene (rarely *HJV, HAMP, TFR2,* and *SLC40A1* genes), disrupting regulation of iron	Pathogenic variants in *ATP7B* gene, leading to the impairment of cellular copper transport	Pathogenic variants in *CFTR* gene, which predominantly affects the lungs, but also the GI tract
Incidence	1 in 300	1 in 30000	1 in 3200-15000
Clinical Features	Iron overload (elevated transferrin saturation and ferritin), bronze skin, arthralgia, hormone disturbance (DM, hypogonadism), cirrhosis, cardiomyopathy	Liver disease (acute and/or chronic), movement disorders, psychiatric disturbance, Kayser-Fleischer rings	Severe to mild: Malabsorption, failure to thrive, pancreatic insufficiency Bronchiectasis, male infertility More information found in other chapters*
Management	Phlebotomy for elevated serum ferritin and transferrin saturation	Chelating agents (e.g. penicillamine, trientine)	More information found in other chapters*

*See Respirology, R12 and Pediatrics, P92

Other Single Gene Disorders

SICKLE CELL DISEASE

- autosomal recessive disease caused by pathogenic variants in the HBB gene, resulting in the production of an abnormal version of β-globin and subsequently distorted red blood cells
- see Hematology, H21

DUCHENNE MUSCULAR DYSTROPHY

Incidence

- 1 in 4000 males

Etiology

- one type of muscular dystrophy characterized by progressive skeletal and cardiac muscle degeneration
- X-linked recessive: 1/3 de novo pathogenic variants, 2/3 inherited pathogenic variants
- missing structural protein (dystrophin) → muscle fibre fragility → fibre breakdown → necrosis and degeneration

Clinical Features

- proximal muscle weakness by age 3, positive Gowers' sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy

Diagnosis

- molecular genetic studies of dystrophin gene (*DMD*) (first line)
- genotype-phenotype correlations: different variants in the gene will cause some dystrophin production and a milder muscular dystrophy, Becker muscular dystrophy
- family history (pedigree analysis demonstrating X-linked inheritance)
- increased creatine kinase (50-100x normal) and lactate dehydrogenase
- muscle biopsy, EMG



See Landmark Medical Genetics Trials table for more information on the C-type natriuretic peptide analogue therapy (vosoritide) RCT, which assesses the safety and efficacy of vosoritide in the treatment of achondroplasia in children



Gene Therapy for Spinal Muscular Atrophy (SMA): A Review of Current Challenges and Safety Considerations for Onasemnogene Abeparvovec (Zolgensma)
Cureus 2023;15(3):e36197
Purpose: To review the safety, efficacy, and current challenges of the gene therapy onasemnogene abeparvovec (Zolgensma) in the treatment of the autosomal recessive disorder SMA.
Methods: Narrative literature review of PubMed, MEDLINE, and Ovid databases for articles that provided pertinent information about Zolgensma as a gene therapy for SMA.
Results: 10 articles met the inclusion criteria. There is evidence that Zolgensma is an efficacious therapy for SMA type 1 (the most severe form of the disorder), especially when administered to patients under 3 months of age. Hepatotoxicity is a major concern, but can be managed through close monitoring of liver enzyme levels and prophylactic medications. Zolgensma is more cost-effective than comparable therapies.
Conclusion: Due to its effectiveness, safety profile, and cost, Zolgensma is a good treatment option for SMA type 1. More data is needed to evaluate long-term risks and benefits.



See Landmark Medical Genetics Trials table for more information on the FLAURA trial, which compares Osimertinib against other EGFR inhibitors in patients with EGFR positive NSCLC



Corticosteroids for the Treatment of Duchenne Muscular Dystrophy (DMD)
Cochrane DB Syst Rev 2016;5:CD003725
Purpose: To assess the effects of corticosteroids on prolongation of walking ability, muscle strength, functional ability, and quality of life in DMD and address whether benefit is maintained over long term, assess adverse events, and compare efficacy of different regimens.
Methods: Systematic review including RCTs or quasi-RCTs of corticosteroids given to patients with definitive DMD diagnosis for at least 3 mo.
Results: 12 studies with 667 participants included. Meta-analyses showed that corticosteroids improved muscle strength and function vs. placebo over 6 mo. Evidence from single trials showed 0.75 mg/kg/d superior to 0.3 mg/kg/d on most strength and function measures, with little evidence of further benefit at 1.5 mg/kg/d. Improvements were seen in time taken to rise from the floor, timed walk, four-stair climbing time, ability to lift weights, leg function grade, and forced vital capacity. Moderate quality evidence of adverse effects: excessive weight gain, behavioural abnormalities, cushingoid appearance, and excessive hair growth.
Conclusions: Moderate quality evidence from RCTs indicates that corticosteroid therapy in DMD improves muscle strength and function in the short term (12 mo), and strength (up to 2 yr.) Dose of 0.75 mg/kg/d should be enough. Adverse effects were common but not clinically severe.



Gowers' Sign
Child uses hands to "climb up" the legs to move from a sitting to a standing position. Observed in individuals with weakness of the pelvic and proximal lower limb muscles

Management
- supportive (e.g. physiotherapy, wheelchairs, braces); prevent obesity
- cardiac health monitoring and early intervention (annually if male, every 3-5 years if female)
- bone health monitoring and intervention (vitamin D, bisphosphonates), at baseline and annually
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

Complications
- patient usually wheelchair-bound by age 12
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in second-third decade

Metabolic Diseases

- individually rare but collectively occur in 1 in 1500 births
- inherited disorders of metabolism; most are autosomal recessive
- infants and older children may present with failure to thrive or developmental delay
- organelle disorders can present with dysmorphism
- universal newborn screening in Ontario, Canada includes some treatable metabolic disorders

Genetic and Metabolic Investigations for Neurodevelopmental Disorders: Position Statement of the Canadian College of Medical Geneticists (CCMG)
J Med Genet 2023;jmg-2022-108962
Purpose: To provide recommendations for genetic and metabolic investigations for patients with neurodevelopmental disorders (NDD), specifically, patients with global developmental delay (GDD), intellectual disability (ID), and/or autism spectrum disorder (ASD).
Methods: A multidisciplinary group, composed of physicians and clinical scientists, reviewed existing literature and guidelines. Evidence was synthesized and circulated to the CCMG and Canadian Pediatric Society for feedback.
Recommendations:
- chromosomal microarray for patients with GDD, ID, or ASD (first-tier test)
- Fragile X testing for patient with suggestive clinical features or family history (first-tier test)
- metabolic investigations for patients with clinical features suggestive of an inherited metabolic disease
- exome sequencing and comprehensive gene panel for patients with GDD or ID (second-tier test)
- genetic testing is not recommended for patients with NDD in absence of GDD, ID, or ASD, unless accompanied by clinical features suggestive of a syndromic etiology or inherited metabolic disease

Table 8. Metabolic Disorders

	Protein Metabolism Disorders	Carbohydrate Disorders	Fatty Acid Disorders	Organelle Disorders
Examples of Conditions	PKU* Tyrosinemia* Homocystinuria* MSUD* Alkaptonuria Propionic acidemia* Urea cycle defects (Ornithine transcarbamylase deficiency)	Galactosemia* GSDs: von Gierke, Pompe, Cori, Andersen, McArdle	MCADD* VLCAD* LCHAD*	Congenital disorders of glycosylation Lysosomal storage diseases: mucopolysaccharidosis (Hunter, Hurler*), Niemann-Pick, Tay-Sachs, Gaucher, Fabry, Krabbe Peroxisomal defects: Zellweger syndrome, X-linked adrenoleukodystrophy
Clinical Manifestations	Coma, irritability, lethargy, poor feeding Seizures Intellectual disability Vomiting and acidosis after feeding initiation Sweet-smelling urine (MSUD)	Hypoglycemia, hepatomegaly, liver failure, cardiomyopathy Growth retardation, failure to thrive	Lethargy, poor feeding Seizures, coma Symptoms triggered by fasting Liver dysfunction Sudden infant death	Progressive neurological problems Developmental regression Chronic encephalopathy Developmental delay Bone crises (Gaucher) Deafness, blindness
Laboratory Findings	Hyperammonemia with normal anion gap (urea cycle defects), hyperammonemia with high anion gap (organic acidemia)	Elevated liver enzymes (galactosemia) Hypoglycemia lactic acidosis hyperlipidemia (GSD)	Hypoketotic hypoglycemia Elevated free fatty acids Elevated creatine phosphokinase	Elevated urine oligosaccharides (oligosaccharidoses) and glycosaminoglycans (mucopolysaccharidoses), abnormal transferrin isoelectric focusing (congenital disorders of glycosylation), abnormal very long chain fatty acids (peroxisomal defects)
Physical Exam	Hypotonia/hypertonia Microcephaly, musty odour, eczema, hypopigmentation (PKU) Dark urine, pigmented sclerae, arthralgias (alkaptonuria) Lens subluxation, Marfanoid appearance (homocystinuria)	Infantile cataracts (galactosemia) Hepatomegaly Muscle weakness/cramping	Hepatomegaly Hypotonia	Dysmorphic facial features Macrocephaly (Lysosomal storage diseases) Hepatosplenomegaly (Niemann-Pick type A/B/C, not Tay-Sachs) Cherry-red spot on macula (Niemann-Pick type A/B, Tay-Sachs, Gaucher) Corneal clouding (Hurler) Infantile cataract (Fabry) Peripheral neuropathy (Fabry, Krabbe) Spasticity

* Metabolic disorders included in Newborn Screening Ontario

Initial Investigations for a Child with Acute Problems Thought to be Due to an Inborn Error of Metabolism
- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, arterial blood gases (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects, and GSDs)
- lactate, ammonium (hyperammonemia with urea cycle defects or organic acidemias), plasma Ca^{2+} and Mg^{2+}, plasma amino acid screen
- routine U/A: ketonuria must be investigated in a neonate, urinary organic acids
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, CSF glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)

See Landmark Medical Genetics Trials table for more information on the use of Elexacaftor/Tezacaftor/Ivacaftor in children with F508del cystic fibrosis

See Landmark Medical Genetics Trials table for more information on the efficacy and safety of a low-phenylalanine diet in combination with phenylketonuria medical foods or traditional amino acid medical foods in individuals with PKU

Treatment

- varies according to inborn error of metabolism but includes dietary restrictions, toxic metabolite sequestrants, enzyme replacement, etc.
- in the presentation of acute decompensation potentially caused by an inborn error of metabolism, discontinue feeding to prevent further buildup of toxic metabolites



See Landmark Medical Genetics Trials table for more information on the PRISM trial, which evaluates the safety and efficacy of pegvaliase treatment in adults with PKU

Table 9. Presentation and Management of Select Metabolic Disorders

	Phenylketonuria (PKU)	Galactosemia	Maple Syrup Urine Disease (MSUD)	Glycogen Storage Disease (GSD) Type 1 (Von Gierke Disease)	Tay-Sachs Disease	Ornithine Transcarbamylase (OTC) Deficiency
Inheritance and Incidence	1 in 10000; autosomal recessive disease (mutations in *PAH* gene)	1 in 60000; autosomal recessive disease	1 in 185000; autosomal recessive disease (pathogenic variants in *BCKDHA, BCKDHB*, and *DBT* genes), 1 in 25000 in Ashkenazi Jewish, 1 in 400 in Mennonites	1 in 100000; autosomal recessive disease, 1 in 20000 in Ashkenazi Jewish	1 in 320000; autosomal recessive disease, 1 in 3600 in Ashkenazi Jewish	1 in 62000 to 77000; X-linked condition
Pathophysiology	Deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to buildup of phenylalanine and its toxic metabolites Mothers who have PKU may have infants with multiple congenital abnormalities	Most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose	Reduction or elimination of protein complex needed for amino acids leucine, isoleucine, and valine breakdown, leading to toxic build-up	Pathogenic variants in *G6PC* (cause of GSD1a) and *SLC37A4* (cause of GSD1b) genes prevent effective conversion of glucose-6-phosphate to glucose. Glucose-6-phosphate is converted to glycogen and fat which subsequently accumulate in cells, especially in the liver and kidneys	Pathogenic variants in the *HEXA* gene, which encodes alpha subunit of hexosaminidase A; leads to intracellular accumulation of GM2 ganglioside, lysosome dysfunction, and neurodegeneration	Pathogenic variants in the OTC gene, which is localised on the X-chromosome. It encodes an enzyme required for the urea cycle and its dysfunction leads to accumulation of ammonia
Clinical Features	Baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and intellectual disability. Hypopigmentation due to low tyrosine levels (fair hair, blue irises)	Signs of liver and renal failure, jaundice, failure to thrive, and cataracts with ingestion of lactose/galactose Complications: Increased risk of sepsis, especially *E. coli* If the diagnosis is not made at birth, liver and brain damage may become irreversible	Feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odour in urine and cerumen May progress to irreversible intellectual disability, hyperactivity, severe failure to thrive, seizures, coma, cerebral edema, and death if inadequately treated	Typically presents between 3-6 mo of age with hepatomegaly, hypoglycemia, poor fasting tolerance, growth failure, and "doll-like" facies (full cheeks with thin extremities) Complications: Lactic acidosis, hyperuricemia, hyperlipidemia, delayed puberty, renal disease, hypoglycemic seizures, hepatic adenomas, osteoporosis	Various presentations: infantile form (onset at 3-6 mo), juvenile form (onset at 2-6 yr), and adult or chronic form (onset at >10 yr) Psychomotor regression, hypotonia, increased startle response, macular cherry red spot, seizures, and hearing impairment	Neonatal onset (male presentation is typically more severe than female presentation): infants appear well at birth, and develop reduced oral intake and lethargy, progressing into tachypnea, hypothermia, severe encephalopathy and a coma Late onset forms: may present at any time and have precipitating event (fasting, illness, protein overload). Lethargy, episodic vomiting, and headaches Complications: seizures, encephalopathy, acute liver failure and a coma
Diagnosis and Management	PKU screening at birth Life-long dietary restriction of phenylalanine starting within the first 10 d of life; especially important during pregnancy to maintain normal phenylalanine levels to prevent maternal PKU effects on fetus Large neutral amino acid (tyrosine) replacement, BH4 enzyme treatment, phenylalanine lyase treatment are other options	Screened for in many newborn screening programs but generally present with liver failure and E. coli sepsis before screening result reported Elimination of galactose from the diet (e.g. dairy, breast milk) Most infants are fed a soy-based diet	MSUD is screened in most newborn screening programs. Serum amino acid evaluation (leucine, isoleucine, alloisoleucine, and valine) and urine organic acid analysis Protein-restricted, high-carbohydrate diet to limit branched amino acid intake A trial of thiamine therapy in addition may be recommended for some infants	Hypoglycemia when interval between feeds are increased (>3-4 h), lactic acidemia, hypertriglyceridemia, and hepatomegaly Treat with nutrition therapy (small frequent feedings, avoid fructose/sucrose/galactose), continuous overnight feedings, raw cornstarch (for slow, sustained glucose release), vitamin supplementation, frequent blood glucose monitoring	Clinical suspicion β-Hexosaminidase enzyme activity (serum) Ashkenazi Jewish carriers often identified by preconception screening Treatment is supportive	Suspect OTCD in patients with hyperammonemia and high urinary orotic acid. Enzyme analysis and/or genetic testing can confirm. Treat with calories (typically 10% dextrose solution at 1.5x maintenance fluids), IV arginine, IV ammonium scavengers (combination of sodium benzoate and sodium phenylbutyrate). Hemodialysis if ammonia >500 umol/L. Long-term: protein restriction supplemented with essential amino acids, citrulline, and ammonia scavengers



See Landmark Medical Genetics Trials table for more information on the SONIA-2 trial, which investigates the efficacy, safety and clinical benefit of nitisinone in the treatment of alkaptonuria

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Acronyms

ALF	acute liver failure
BE	Barrett's esophagus
BT	biologic therapy
CCK	cholecystokinin
CD	Crohn's disease
CMV	cytomegalovirus
CNS	central nervous system
DGP	deamidated gliadin peptides
DES	diffuse esophageal spasm
EBV	Epstein-Barr virus
EGD	esophagogastroduodenoscopy
EIM	extraintestinal manifestation
EN	enteral nutrition
EPEC	enteropathogenic E. coli
ERCP	endoscopic retrograde cholangiopancreatography
ETEC	enterotoxigenic E. coli
EUS	endoscopic ultrasound
EVL	endoscopic variceal ligation
GE	gastroesophageal
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRS	hepatorenal syndrome
HSV	herpes simplex virus
HUS	hemolytic uremic syndrome
HVPG	hepatic venous pressure gradient
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICP	intracranial pressure
INH	isoniazid
LES	lower esophageal sphincter
LGIB	lower gastrointestinal bleed
MRCP	magnetic resonance cholangiopancreatography
MS	multiple sclerosis
NAC	N-acetylcysteine
NAFLD	non-alcoholic fatty liver disease
NERD	non-erosive reflux disease
NMS	neuroleptic malignant syndrome
O&P	ova and parasites
PBC	primary biliary cirrhosis
PN	parenteral nutrition
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiography
PUD	peptic ulcer disease
RA	rheumatoid arthritis
RLQ	right lower quadrant
RUQ	right upper quadrant
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt
TNF	tumour necrosis factor
TPN	total parenteral nutrition
TTG	tissue transglutaminase
UC	ulcerative colitis
UGIB	upper gastrointestinal bleed

Anatomy Review

Overview of Gastrointestinal Tract

- the GI tract runs from mouth to anus ("gum to bum")

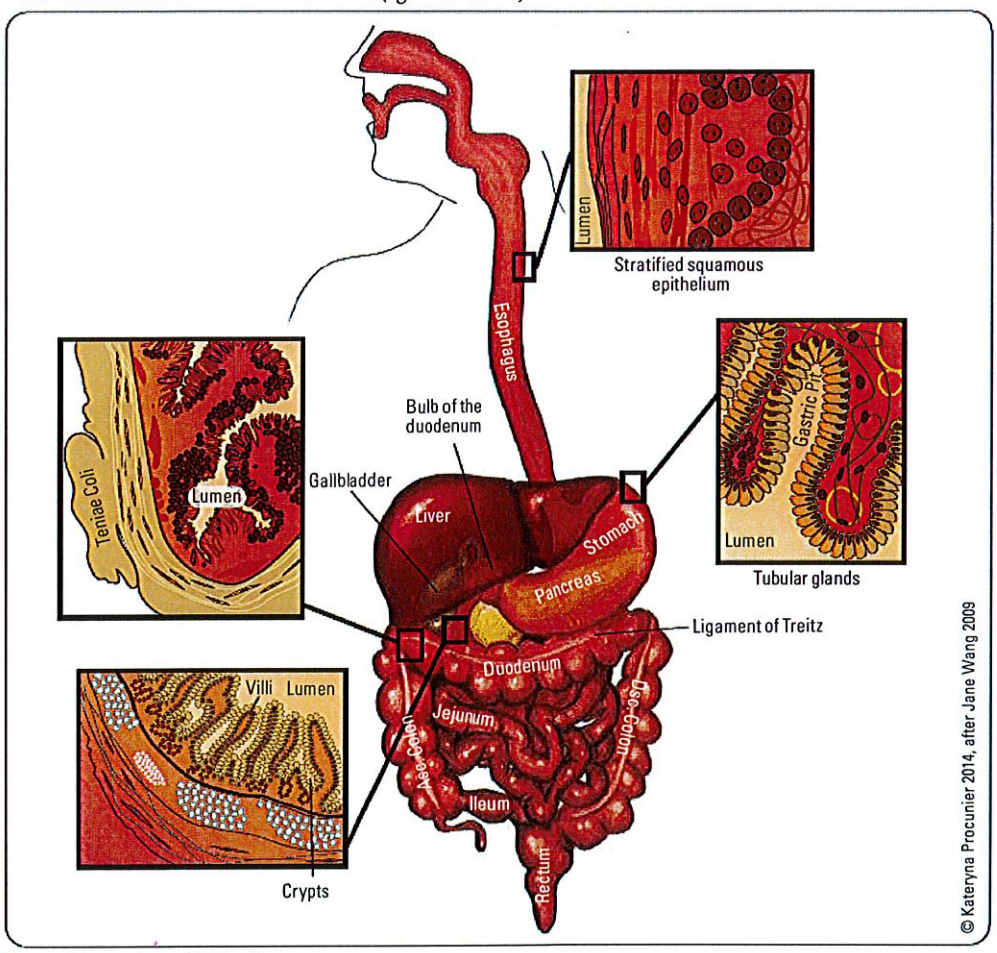


Figure 1. Overview of GI tract

Table 1. Summary of GI Tract Structure and Function

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
Esophagus	Muscular tube approximately 40 cm long with a diameter of 2 cm Extends from the pharynx to the stomach	Arterial: left gastric artery and left inferior phrenic artery Venous: Left gastric vein → portal venous system Esophageal veins → azygos vein → inferior vena cava (systemic)	Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks) Sympathetic innervation via thoracic trunks of the greater splanchnic nerves	Mucosa: stratified squamous epithelium Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle Upper 1/3: striated muscle Middle 1/3: transition zone Lower 1/3: smooth muscle
Stomach	Prepares and delivers food to intestine for digestion and absorption Secretes acid to reduce enteric infections/ pneumonia and facilitate digestion of protein and absorption of iron/B_{12} Secretes intrinsic factor (IF) to facilitate B_{12} absorption Minor contribution to initial protein digestion via pepsin	Lesser curvature Right and left gastric arteries (from celiac trunk) Greater curvature Right and left gastro-omental (gastroepiploic) arteries (from gastroduodenal and splenic arteries respectively) Fundus: short and posterior gastric arteries (from the splenic artery)	Parasympathetic innervation via vagus nerve Sympathetic innervation via celiac plexus (from T6-T9)	5 parts Cardia Fundus Body Antrum Pylorus
Duodenum	Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion Secretes CCK to stimulate gallbladder contraction Site of iron absorption	Branches of celiac artery and superior mesenteric artery	Parasympathetic innervation via vagus nerve Sympathetic innervation via greater and lesser splanchnic nerves	4 parts Superior (5 cm) Descending (7-10 cm) Horizontal (6-8 cm) Ascending (5 cm) 1st part is intraperitoneal; rest is retroperitoneal
Jejunum	Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vitamin A, B, C, D, E, K)	Superior mesenteric artery	Parasympathetic innervation via fibres of the posterior vagal trunk Sympathetic innervation via fibres of T8-T10	Deep red colour 2-4 cm in thickness Thick and heavy wall Plicae circulares are large, tall, and closely packed Has long vasa recta Scant fat in mesentery Scant Peyer's patches
Ileum	Absorption of sodium, water, nutrients, soluble vitamins (only site of vitamin B_{12} absorption), and bile salts (entero-hepatic circulation)	Superior mesenteric artery	Same as jejunum	In comparison to jejunum: Paler pink colour 2-3 cm in thickness Thin and light walls Plicae circulares are small and sparse Contains more mesenteric fat Many Peyer's patches
Large Bowel	Absorption of water (5-10% of total water) Bacteria: provide further digestion of chyme and metabolism of undigested carbohydrate to short chain fatty acids Formation and storage of feces	Branches of superior and inferior mesenteric arteries Rectal blood supply: sigmoid, right pudendal, and rectal arteries	Parasympathetic innervation via vagus nerve Sympathetic innervation via greater and lesser splanchnic nerves	Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal Features include teniae coli, haustra, and omental appendices
Liver	Glucose homeostasis Plasma protein synthesis Lipid and lipoprotein synthesis Bile acid synthesis and secretion Vitamin A, D, E, K, B12 storage Biotransformation, detoxification Excretion of compounds Immune surveillance	2 sources Portal vein (75-80%) Hepatic artery (20-25%)	Parasympathetic innervation via fibres of the anterior and posterior vagal trunks Sympathetic innervation via fibres of the celiac plexus	Largest internal organ Composed of 4 lobes (left, right, caudate, quadrate), and divided into 8 segments
Biliary Tract	Gallbladder stores and releases bile that is produced in the liver Bile emulsifies fat and is composed of cholesterol, lecithin, bile acids, and bilirubin CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release	Cystic artery	Parasympathetic innervation via vagus nerve Sympathetic and visceral innervation via celiac nerve plexus Somatic afferent fibres via right phrenic nerve	Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater
Pancreas	Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the α, β, and δ cells, respectively) Exocrine function: digestive enzymes, including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase, are produced	Anterior superior pancreaticoduodenal artery (from the celiac trunk) Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery) Dorsal pancreatic artery (from the splenic artery) Pancreatic veins drain into the portal, splenic, and superior mesenteric veins	Parasympathetic innervation via vagus nerve Sympathetic innervation via abdominopelvic splanchnic nerves	4 parts of pancreas: head (includes uncinate process), neck, body, and tail (Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater Accessory pancreatic duct connected directly to duodenum

Visualizing the Gastrointestinal Tract

- see Medical Imaging, MI11

Esophagus, Stomach, Duodenum

- EGD: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation for the treatment of esophageal strictures)
  - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation), possibility of fistulae
  - endotracheal intubation first if massive UGIB, acidemia, or inability to protect airway

Small Bowel

- most difficult to visualize, especially if mucosal detail is needed
- CT enterography favoured over small bowel follow-through in view of accuracy, but both have low sensitivity
- MRI small bowel imaging increasingly available, especially useful if radiation exposure is an issue (e.g. young patient, multiple radiological images already done)
  - note: MRI enteroclysis, luminal contrast is administered by nasojejunal (NJ) tube to dilate the small bowel – disliked by both radiologist and patient, but may improve sensitivity
- "double balloon" enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction, known strictures) is also accurate in diagnosis but does not provide any therapeutic intervention

Colon and Terminal Ileum

- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography ("virtual colonoscopy") more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonoscopy is less sensitive
  - most often used when optical endoscopic colonoscopy is risky (e.g. frail elderly) or unsuccessful (e.g. stricture)

Pancreatic/Biliary Duct

- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if therapeutic intervention likely to be required (strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required)
- EUS can provide detailed anatomy of biliary tree and pancreas with potential for sampling/intervention (e.g. cyst drainage)

Acute Upper Abdominal Pain
Remember to rule out thoracic sources (e.g. MI, pneumonia, dissecting aneurysm)

Differential Diagnosis of Common Complaints

- see General Surgery and Thoracic Surgery, GS4

Table 2. Differential Diagnosis of Common Presenting Complaints

CHRONIC/ RECURRENT ABDOMINAL PAIN	Inflammatory	Neoplastic/ Vascular	Toxin	Other
	PUD Biliary colic IBD Chronic pancreatitis	Gastric cancer Recurrent bowel obstruction Mesenteric ischemia Sickle cell anemia	Lead poisoning	Mittelschmerz Endometriosis Porphyria IBS Radiculopathy Diverticular disease Anterior cutaneous nerve entrapment syndrome

ACUTE DIARRHEA	Inflammatory		Non-Inflammatory	
*Causes of bloody diarrhea	**Bacterial** *Shigella** *Salmonella** *Campylobacter** *Yersinia** *E. coli* (EHEC 0157:H7)*	**Protozoal** *E. histolytica** (amoebiasis) *Strongyloides* **Others** NSAIDs IBD* Ischemia*	**Bacterial** *S. aureus* *C. perfringens* *B. cereus* *E. coli* (enterotoxigenic, enteropathogenic) *Salmonella enteritidis* *Vibrio cholera* **Protozoal** *Giardia lamblia*	**Viral** Rotavirus Norwalk CMV **Drugs** ABx Colchicine Laxatives Antacids (magnesium)

Obscure but Treatable Causes of Abdominal Pain
Acute Intermittent Porphyria
Hereditary Angioedema
Familial Mediterranean Fever
Vasculitis (e.g. polyarteritis nodosa)

Inflammatory Diarrhea: Occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Diarrhea may be profuse or very small in volume. Often associated with abdominal pain ± fever and chills. Stool may be positive for white blood cells

Non-Inflammatory Diarrhea: No damage to the mucosal lining. Nausea/vomiting may be present. Fever, chills, blood in the stool, severe abdominal pain, or tenderness are not present. Stool is negative for white blood cells

Table 2. Differential Diagnosis of Common Presenting Complaints

CHRONIC DIARRHEA	**Organic**				**Gastric cancer**
*Causes of bloody diarrhea	**Inflammatory**	**Secretory**	**Steatorrhea**	**Osmotic**	
	IBD* Infectious (TB, CMV, HSV) Ischemic bowel* Radiation colitis Neoplasia *C. difficile* rarely causes bleeding	Stimulant laxatives Post-ileal resection/ cholecystectomy (bile salts) Bacterial toxins Vasculitis Neoplasia* (colon cancer, carcinoid, vasoactive intestinal peptide tumour (i.e. VIPoma)) Addison's disease Congenital syndromes	*Giardia lamblia* Celiac disease Chronic pancreatitis Chronic cholestasis Bacterial overgrowth	Osmotic laxatives Lactose intolerance Chewing gum (sorbitol, mannitol)	IBS Constipation (overflow diarrhea) Anal sphincter dysfunction
CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found (and dysmotility assumed)					
	Colorectal cancer Stricture Extrinsic compression Anal disease Rectocele	Medications (narcotics, antidepressants, calcium channel blockers) Metabolic (DM, thyroid, hypercalcemia)	Neurologic (Parkinson's, MS, stroke) Collagen vascular disease (scleroderma, dermatomyositis)		
NAUSEA/VOMITING	**With Abdominal Pain**		**Without Abdominal Pain**		
	Relieved by Vomiting	**Not Relieved by Vomiting**	**Headache/Dizziness**		**No Other Symptoms**
	Gastric outlet obstruction Small bowel obstruction GERD (regurgitation more common)	Gallbladder disease Pancreatitis MI Hepatitis Infectious Gastroenteritis	Cerebral tumour Migraine Vestibular disease Increased ICP		Drugs Uremia Pregnancy Metabolic (e.g. hypercalcemia) Gastroparesis (e.g. DM) Ketoacidosis
DYSPEPSIA	**Common**		**Uncommon**		**Rare**
	Functional dyspepsia Drug side effect Peptic ulcer GERD (esophagitis)		Angina CD Cancer (stomach, pancreas, liver) Gallstones Aerophagia		*Giardia lamblia* Malabsorption (celiac sprue) Pancreatitis
UPPER GI BLEED	**Common**		**Uncommon**		**Rare**
	Ulcers (*H. pylori*, ASA, NSAIDs) Esophageal varices Mallory-Weiss tears Erosive esophagitis Erosive gastritis		Tumours Arteriovenous malformation Dieulafoy's lesion (arterial) Gastric antral vascular ectasia (GAVE) Portal hypertensive gastropathy		Aorto-enteric fistulae Hemobilia
LOWER GI BLEED	**Common**		**Uncommon**		**Rare**
	Diverticulosis Ischemia Angiodysplasia (elderly) Infectious Anorectal (hemorrhoids, fissure, ulcer)		UGIB (brisk) Post-polypectomy Radiation colitis IBD		Intussusception Vasculitides Stercoral ulcer Coagulopathies
DYSPHAGIA	**Mechanical (Solids)**		**Motility (Solids and Liquids)**		**Other**
	Peptic stricture/cancer Eosinophilic esophagitis Extrinsic compression Schatzki ring/esophageal web Zenker's diverticulum		Achalasia DES Scleroderma		Foreign body Eosinophilic esophagitis
ODYNOPHAGIA	**Infection**	**Inflammation/Ulceration**	**Drugs**		**Other**
	Candida HSV CMV (common in those who are immunosuppressed)	Caustic damage Eosinophilic esophagitis	Quinidine Iron Vitamin C ABx (e.g. tetracycline) Bisphosphonates		Radiation
ABDOMINAL DISTENSION	**Fluid (Ascites)**	**Flatulence**	**Feces**		**Other**
	Portal HTN / **Normal Portal Pressure**				
	Cirrhosis Cardiac failure Hepatic vein thrombosis / Cancer (especially ovarian) Pancreatitis TB	Functional bowel disease (e.g. IBS) Fibre Lactose intolerance Chewing gum (e.g. sorbitol, mannitol)	Constipation Colonic obstruction Dysmotility		Pregnancy (fetus) Pregnancy (fetus) Obesity (fat) Blood Large tumours (fatal growth) Organomegaly



IBD is a common cause of bloody diarrhea but can be diagnosed only if mimickers are excluded; such as infection, ischemia, and medication induced



Commonly Forgotten Causes of Vomiting
Drugs
Uremia
CNS disease
Pregnancy
- Cannabis (cannabinoid hyperemesis)



Differentiating Between Dysphagia and Odynophagia
Dysphagia: Difficulty swallowing due to mechanical obstruction or dysmotility of the esophagus or pharynx
Odynophagia: Pain when swallowing due to ulceration or inflammation (e.g. candida esophagitis) in the esophagus or pharynx



Differential Diagnosis of Abdominal Distension

6 Fs
Fat
Feces
Fetus
Flatus
Fluid
Fatal growth

Table 2. Differential Diagnosis of Common Presenting Complaints

JAUNDICE (UNCONJUGATED BILIRUBIN)	**Overproduction**	**Decreased Hepatic Intake**	**Decreased Conjugation**
	Hemolysis Ineffective erythropoiesis (e.g. megaloblastic anemias)	Gilbert's syndrome Drugs (e.g. rifampin)	Drug inhibition (e.g. chloramphenicol) Crigler-Najjar syndromes type I and II Gilbert's syndrome Neonatal jaundice
JAUNDICE (CONJUGATED BILIRUBIN)	**Hepatocellular Disease**		**Biliary Obstruction**
	Drugs Cirrhosis (any cause) Inflammation (hepatitis, any cause) Infiltrative (e.g. hemochromatosis) Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy) PBC PSC Sepsis Postoperative/TPN		Intraductal obstruction: Gallstones Biliary stricture Parasites Malignancy (cholangiocarcinoma) Sclerosing cholangitis Extraductal obstruction: Malignancy (e.g. pancreatic cancer, lymphoma) Metastases in periportal nodes Inflammation (e.g. pancreatitis)

Esophagus

Gastroesophageal Reflux Disease

Definition

- a condition which develops when the reflux of gastric content causes troublesome symptoms or complications

Etiology

- increased number of transient relaxations of the LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy, acid hypersecretion (rare) from Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery and Thoracic Surgery, GS23)

Clinical Features

- "heartburn" (pyrosis) and regurgitation (together are 80% sensitive and specific for reflux); less sensitive and less specific: water brash, sensation of a lump in the throat (globus sensation), and frequent belching
- non-esophageal symptoms are increasingly recognized as being poor predictors of reflux

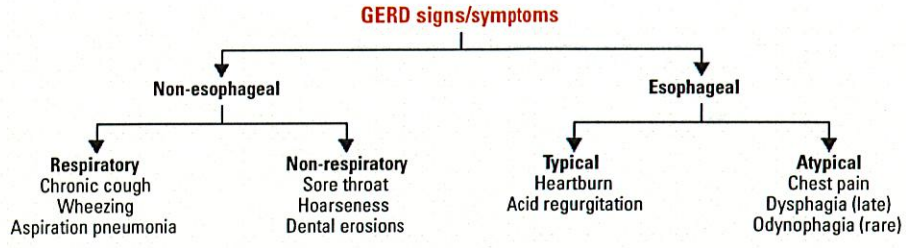


Figure 3. Signs and symptoms of GERD

Investigations

- usually, a clinical diagnosis is sufficient based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
- however, response to anti-secretory agents such as PPI is not a requirement for GERD diagnosis
- gastroscopy indications
  - absolute indications
    - heartburn accompanied by red-flags (bleeding, weight loss, dysphagia, persistent vomiting, family history of GI cancer, etc.)
    - persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI BID
    - history suggests esophageal stricture especially dysphagia
    - high-risk for BE (male, ages >50, obese, white, tobacco use, long history of symptoms)
- repeat endoscopy after 8 wk of PPI therapy/ indicated if severe esophagitis because it can mask BE or symptoms

Ischemic Colitis
The splenic flexure and rectosigmoid junction are watershed areas and are susceptible to ischemia. History and symptoms include acute onset crampy left abdominal pain, rectal bleeding, in addition to possible abdominal tenderness on exam. Risk factors include atherosclerotic risk factors, vasoconstricting medications, and history of low flow state

Dyspepsia = postprandial fullness, early satiety, epigastric pain or burning

Foods/Substances that May Aggravate GERD Symptoms (but diet does not change the underlying disease)

- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

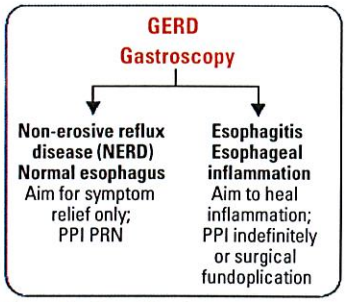


Figure 2. Classification and gastroscopic findings of GERD

Side Effects of Long-Term Use of PPIs

Only some (*C. difficile* diarrhea, hypomagnesemia, vitamin B_{12} deficiency, small bowel bacterial overgrowth) seem to be related to suppressing gastric acid whereas others (pneumonia, fractures, chronic kidney disease, dementia) have no apparent pathophysiological relationship

Stopping PPIs can increase gastric acid above baseline by a "rebound effect" causing heartburn even in healthy volunteers

May increase the risk of IBD with prolonged regular use

These associations do not preclude long term use of PPIs in patients with esophagitis or peptic ulcer, or those needing gastric protection when taking NSAIDs or anti-platelet drugs, but do emphasize the importance of being as definitive as possible when making these diagnoses and accurately assessing risk-benefit ratios (as is true for all drugs)

- esophageal manometry (study of esophageal motility): indicated in patients who have non-cardiac chest pain and/or dysphagia with normal gastroscopy
  - done to diagnose abnormalities of peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure intact esophageal function; exclude alternative diagnoses like scleroderma and achalasia
  - surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to alleviate symptoms if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24 h pH monitoring: most accurate test for reflux, but not required or performed in most cases
  - most useful if PPIs do not improve symptoms



Up to 25% of patients with BE do not report symptoms of GERD

Treatment

- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- empiric 8 wk trial of PPI in patients with classic GERD symptoms; PPIs are the most effective therapy; may need to be continued as maintenance therapy
- discontinuation of PPIs after 8 wk in recovered patients without Barrett's esophagus or erosive esophagitis; symptoms may recur if therapy is discontinued
- on-demand: antacids ($Mg(OH)_2$, $Al(OH)_3$), alginate, H_2-blockers, or PPIs can be used for non-erosive esophagitis (NERD)
- diet helps symptoms, not the disease; avoid EtOH, coffee, spices, tomatoes, and citrus juices
- only beneficial lifestyle changes are weight loss (if obese or significant weight gain) and elevating the head of bed (if nocturnal symptoms)
- symptoms may recur if therapy is discontinued

Complications

- esophageal stricture disease – scarring can lead to dysphagia (solids)
- esophagitis (e.g. ulceration, bleeding)
- BE and esophageal adenocarcinoma – EGD is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)



Screening for Esophageal Adenocarcinoma in Patients with Chronic Gastroesophageal Reflux Disease
CMAJ 2020;192(27):E768-E777
Though Barrett's esophagus increases the incidence of esophageal adenocarcinoma, the Canadian Task Force on Preventive Health Care currently does not recommend routine screening for esophageal adenocarcinoma and precursor conditions, including Barrett's esophagus, in adults with chronic GERD without red flag features (e.g. dysphagia, odynophagia, weight loss, anemia, gastrointestinal bleeding). In this systematic review, no clinically significant survival benefits were identified in patients undergoing screening. This systematic review reported that patients receiving screening may be unnecessarily exposed to harm, ranging from pre-procedural anxiety to endoscopic injury. Strikingly, the presence of risk factors for esophageal adenocarcinoma, including age, male sex, and family history, is not sufficient to warrant screening endoscopy in patients with chronic GERD. On the other hand, patients with known Barrett's esophagus should be referred to a Gastroenterologist for endoscopy.

Barrett's Esophagus

Definition

- metaplasia of normal squamous esophageal epithelium to intestinal columnar epithelium

Etiology

- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Clinical Features

- prominent GERD symptoms

Epidemiology

- in North America and Western Europe, 0.5-20% of adults are thought to have BE
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, ages >50, White individuals, smokers, overweight, hiatus hernia, and long history of reflux symptoms

Pathophysiology

- endoscopy shows salmon pink mucosa in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes the esophageal lining to premalignant changes characterized as low or high-grade dysplasia, which then progresses to adenocarcinoma



Clinical Guidelines Update on the Diagnosis and Management of Barrett's Esophagus
For a report reviewing the US and international guidelines on the diagnosis and management of BE, please refer to: Dig Dis Sci 2018;63:2122-2128

Significance

- rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia
- risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance



Randomized Trial of Medical vs. Surgical Treatment for Refractory Heartburn
NEJM 2019;381:1513-1523
Patients with PPI-refractory and reflux-related heartburn (n=78) were randomly assigned to surgical treatment (laparoscopic Nissen fundoplication), active medical treatment (omeprazole plus baclofen, and desipramine prn), or control medical treatment (omeprazole plus placebo). The incidence of treatment success in the surgical treatment group (67%) was significantly greater than that in the active medical treatment group (28%; P=0.007) or control medical treatment group (12%; P<0.001).

Treatment

- acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication) may reduce the transformation of BE to dysplasia
- surveillance gastroscopy every 3-5 yr if no dysplasia
- high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes
  - however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
- if low grade dysplasia, both surveillance (every 6 mo for 1 yr then annually) and endoscopic ablation/resection are satisfactory options

Dysphagia

Definition
- difficulty swallowing

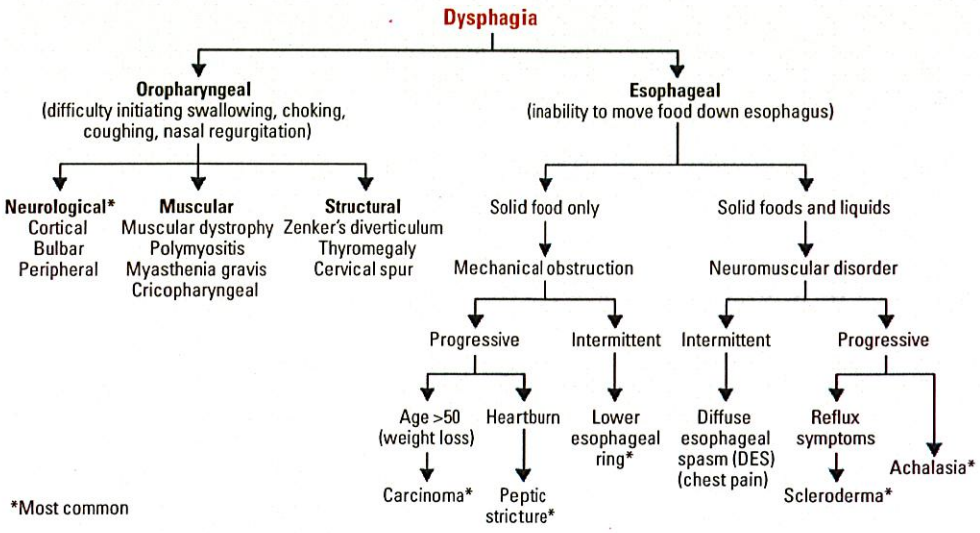


Figure 4. Approach to dysphagia (eosinophilic esophagitis omitted)

Remember:
Dysphagia = Difficulty in swallowing
Odynophagia = Pain on swallowing

Key Questions in Dysphagia

Abnormal features when initiating the act of swallowing?

Associated symptoms? (regurgitation, chest pain, change in voice pitch, weight loss)

Solids, liquids, or both?

Intermittent or progressive?

History of heartburn?

Change in eating habits/diet?

Esophageal Motor Disorders

Clinical Features
- dysphagia with solids and liquids
- chest pain (in some disorders)

Diagnosis
- motility study (esophageal manometry)
- barium swallow sometimes helpful

Causes
- idiopathic
- achalasia
- scleroderma
- DM
- DES: rare and can be difficult to diagnose due to intermittent presentation

Table 3. Esophageal Motor Disorders

Disorder	Achalasia	Scleroderma	Diffuse Esophageal Spasm
Definition	Failure of smooth muscle relaxation at LES Increased LES pressure Progressive loss of peristaltic function	See Rheumatology, RH14 Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)	Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)
Etiology	Usually idiopathic Secondary or pseudo-achalasia e.g. malignancy, Chagas disease (Trypanosoma cruzi)	Involves autoimmune, genetic, hormonal, and environmental factors Dysphagia: caused by reflux, dysmotility, or both	Idiopathic
Pathophysiology	Inflammatory degeneration of Auerbach's plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis	Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia	Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis
Diagnosis	CXR: no air in stomach, dilated esophagus Barium studies: esophagus terminates in narrowing at LES ("bird's beak") Endoscopy: normal mucosa Manometry: definitive diagnosis (signs listed above)	Clinical features of scleroderma Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus	Barium x-ray: "Corkscrew pattern" Manometry: >20% premature contractions Endoscopy: normal mucosa
Treatment	Pneumatic dilation, 5% risk of perforation Injection of botulinum toxin into LES (temporary) Surgical myotomy POEM (peroral endoscopic myotomy)	Medical: aggressive GERD therapy (PPIs BID)	Reassurance that symptoms are not due to cardiac pain Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful), balloon dilatation

Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia
NEJM 2019;381:2219-2229
Purpose: To compare peroral endoscopic myotomy (POEM) to laparoscopic Heller's myotomy (LMH) in the treatment of achalasia.
Methods: Patients with symptomatic achalasia (n=221) were randomly assigned to either POEM or LMH. The primary endpoint was clinical success, while secondary endpoints included adverse events, esophageal function, Gastrointestinal Quality of Life (G QoL) score, and gastroesophageal reflux (GER).
Results: 83.0% of patients in the POEM group and 81.7% of patients in the LHM group achieved clinical success at 2 yr (P=0.007 for noninferiority). There was no difference in improvement of esophageal function or G QoL score between groups. Serious adverse events were observed in 2.7% and 7.3% of patients in the POEM and LHM groups, respectively. At 12 mo, 44% of patients in the POEM group and 29% of patients in the LHM group had reflux esophagitis.
Conclusions: POEM was noninferior to LHM in the treatment of symptomatic achalasia. GER was more common among patients who were treated with POEM than those treated with LHM.

Esophageal Diverticula

Definition
- outpouchings of one or more layers of the esophageal tract

Clinical Features
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

Classification
- pharyngoesophageal (Zenker's) diverticulum
  - most common form of esophageal diverticulum
  - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
  - symptoms: dysphagia, regurgitation of undigested food, halitosis (bad breath)
  - treatment: small and asymptomatic: no treatment required, large and symptomatic: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac

Peptic Stricture (from Esophagitis)

Definition
- a smooth, concentric narrowing most commonly seen in the lower esophagus

Clinical Features
- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops

Diagnosis
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

Treatment
- endoscopic dilatation and indefinite PPI

Esophageal Carcinoma

- see General Surgery and Thoracic Surgery, GS21

Webs and Rings

Definition
- web = partial occlusion by an eccentric, smooth extension of normal esophageal tissue, mucosa and submucosa (upper esophagus)
- ring = circumferential narrowing caused by an abnormal ring of tissue, congenital or acid-reflux induced (lower esophagus)

Clinical Features
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic dilation

Plummer-Vinson Syndrome Triad

Iron deficiency anemia

Dysphagia

Esophageal webs

Rare (prevalence <1 in 1000000) but good prognosis when treated with iron and esophageal dilatation

Infectious Esophagitis

Definition
- severe mucosal inflammation and ulceration as a result of a viral or fungal infection

Risk Factors
- DM
- chemotherapeutic agents
- immunocompromised states

Clinical Features
- characteristically odynophagia, less often dysphagia

Appearance
- *Candida* (most common): whitish-yellow plaques without visible ulceration or inflammation
- HSV (second most common), CMV: focal ulcers

Investigations
- diagnosis via endoscopic visualization and biopsy

Eosinophilic Esophagitis

Eosinophils infiltrate the epithelium of the esophagus

Causes dysphagia, common cause of bolus food impaction

Usually primary, but can be part of the spectrum of eosinophilic gastroenteritis, secondary to drugs, parasites etc.

Often associated with allergies

Most characteristically occurs in young men

Diagnosis established by endoscopic biopsy, suggested by mucosal rings seen in the esophageal mucosa at endoscopy

Treatment: (a) diet (milk, soy, eggs, wheat, peanuts/tree nuts, and seafood), (b) PPI (c) swallowed topical corticosteroid (fluticasone or budesonide), (d) rarely prednisone

Treatment
- *Candida*: nystatin swish and swallow (for simple *Candida* infection), ketoconazole, fluconazole
- HSV: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV ganciclovir, famciclovir, or oral valganciclovir

Stomach and Duodenum

Dyspepsia

Definition
- predominant epigastric pain/burning lasting at least 1 mo
- other symptoms under umbrella of dyspepsia: post-prandial fullness, early satiety
- although the most common cause is functional (investigations show no organic disease but pain persists), sinister disease can present similarly (e.g. pancreatic cancer)

History and Physical Exam
- history: most important risk factors are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett's sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

Investigations
- consider blood tests including CBC, liver enzymes, calcium, *H. pylori* serology (Rome IV), and U/S
- gastroscopy to investigate dyspepsia: most causes of dyspepsia are either functional or diagnosable by either blood tests or PPI trial (for peptic disease); however, gastric cancer should not be missed. Gastroscopy recommended if ages ≥60 (and if ages <60 and under special circumstances such as risk factors for gastric cancer)

The most common cause of dyspepsia is functional (idiopathic) dyspepsia

Red Flags of Dyspepsia
(raise suspicion of gastric malignancy):
- Unintended weight loss
- Persistent vomiting
- Progressive dysphagia
- Odynophagia
- Unexplained anemia or iron deficiency
- Hematemesis
- Jaundice
- Palpable abdominal mass or lymphadenopathy
- Family history of upper GI cancer
- Previous gastric surgery

Stomach

Table 4. Cells of the Gastric Mucosa

Cell Type	Secretory Product	Important Notes
Parietal Cells	Gastric acid (HCl) and IF	Stimulated by histamine, acetylcholine (ACh), gastrin
Chief Cells	Pepsinogen	Stimulated by vagal input and local acid
D-Cells	Somatostatin	Inhibits release of hormones including gastrin
G-Cells	Gastrin	Stimulates H+ production from parietal cells
Superficial Epithelial Cells	Mucus, HCO_3^-	Protect gastric mucosa

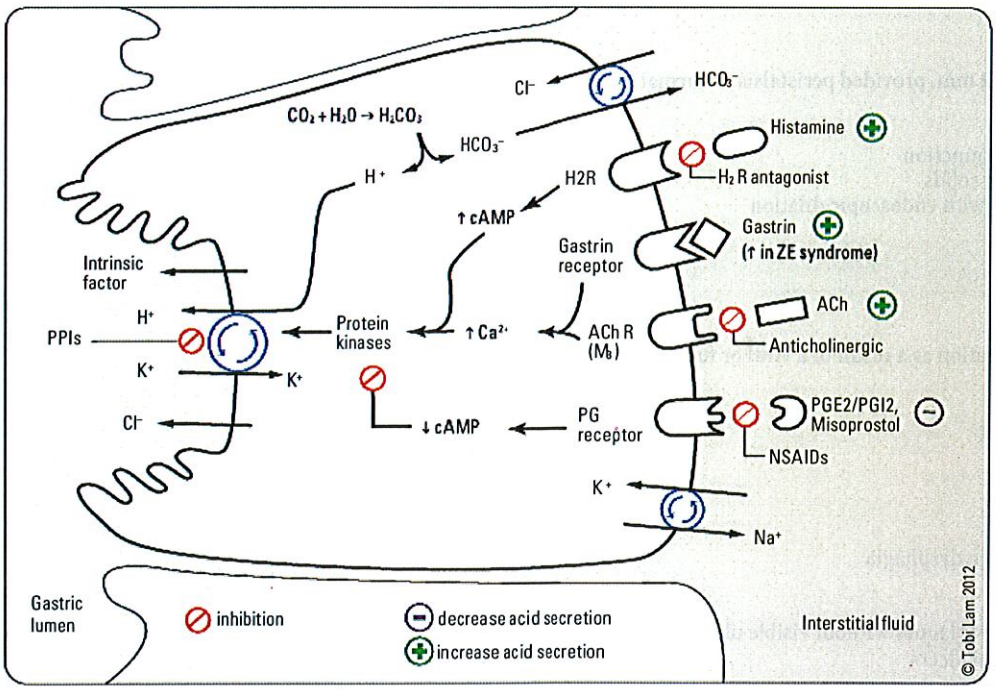


Figure 5. Stimulation of H+ secretion from the parietal cell

Gastritis

Definition

- defined histologically: inflammation of the stomach mucosa

Etiology

- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

Type	Common Etiology
Acute Gastritis	
Hemorrhagic/erosive gastritis	EtOH, Aspirin®/NSAID, shock/physiological stress (seen in ICU patients)
Helicobacter gastritis	*H. pylori*
Chronic Gastritis	
Non-atrophic	*H. pylori*
Atrophic	*H. pylori*, dietary, environmental factors (multi-focal), autoimmunity
Chemical	NSAID, bile
Radiation	Radiation injury
Lymphocytic	Celiac disease, drug
Eosinophilic	Food allergies
Non-infectious granulomatous	CD, sarcoidosis
Other infectious gastritides	Bacteria, viruses, fungi, parasite, TB, syphilis

Clinical Features

- non-erosive gastritis is asymptomatic (except with certain rare causes like CD), does not cause pain; difficult to diagnose clinically or endoscopically – requires biopsy for diagnosis
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Treatment

- determined by etiology (see *H. pylori, G13, NSAID-Induced Ulceration, G13* and *Stress-Induced Ulceration, G14*)
- non-pharmacological: avoidance of mucosal irritants such as EtOH, NSAIDs, and foods that trigger symptoms

Peptic Ulcer Disease



Definition

- focal defects in the mucosa that penetrate the muscularis mucosa layer
- PUD includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

Etiology

Table 6. Etiology of PUD

	Duodenal	Gastric
***H. pylori* Infection**	90%	60%
NSAIDs	7%	35%
Physiologic Stress-Induced	<3%	<5%
Zollinger-Ellison Syndrome	<1%	<1%
Idiopathic	15%	10%

- NSAID negative, *H. pylori* negative ulcers becoming more commonly recognized as *H. pylori* prevalence decreases
- others: CMV (especially immunocompromised patients), ischemic, idiopathic
- EtOH: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with cigarette smoking, cirrhosis of liver, COPD, and chronic renal failure



Cigarette Smoking and PUD
Increased risk of ulcer
Increased risk of complications
Increased chance of death from ulcer
Impaired healing

Clinical Features

- dyspepsia: most common presenting symptom
  - only 5% of patients with dyspepsia have ulcers, while most have functional disease
  - however, 70% of peptic ulcers are asymptomatic
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery), perforation 2% (usually anterior ulcers), gastric outlet obstruction 2%
  - posterior inflammation (penetration) 2%; may also cause pancreatitis

- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters of weeks with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations

- endoscopy (most accurate)
- upper GI series
- *H. pylori* tests (see *Table 7, G13*)
- fasting serum gastrin measurement if Zollinger-Ellison syndrome suspected (but most common cause of elevated serum gastrin level is atrophic gastritis)

Gastric vs. Duodenal Ulcers
Most gastric ulcers require follow-up endoscopy with biopsy to rule out malignancies; duodenal ulcers are rarely malignant and therefore, do not usually warrant follow-up upper endoscopy to reassess ulcer status

Treatment

- specific management depends on etiology; (see *H. pylori, G13, NSAID-Induced Ulceration, G13* and *Stress-Induced Ulceration, G14*)
- treat *H. pylori* infection if present; eradication of infection prevents recurrence of PUD
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H+/K+-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other medications (e.g. histamine H2-antagonists) less effective
- smoking cessation
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, EtOH, and spices

Approach to PUD
Stop NSAIDs
Acid neutralization
H. pylori eradication
Quit smoking

Management of Bleeding Peptic Ulcers

- Gastroscopy (EGD) to explore upper GI tract
- IV pantoprazole
- establish risk of rebleeding/continuous bleed (since most ulcers stop bleeding spontaneously)
  - clinical risk factors: increased ages >60, bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
    - if ulcer possesses high-risk stigmata, then endoscopic therapy (e.g. clip) should be performed, consider ICU admission

Bleeding Peptic Ulcers
Risk Factors for Increased Mortality
Co-existent illness
Hemodynamic instability
Ages >60 yr
Transfusion required

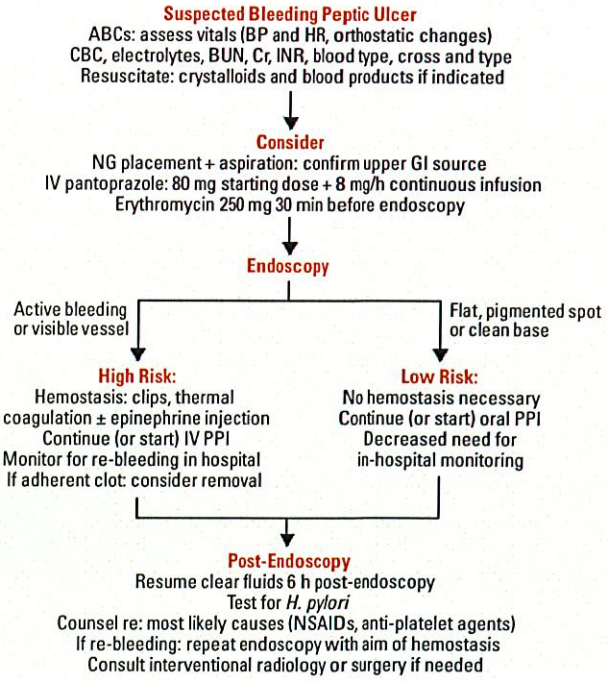


Figure 6. Approach to management of suspected bleeding peptic ulcer
Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937

H. pylori-Induced Peptic Ulceration

Pathophysiology

- *H. pylori*: Gram-negative flagellated rod that resides within the gastric mucosa, causing persistent infection and inflammation
- acid secreted by parietal cells (stimulated by vagal ACh, gastrin, histamine) necessary for most ulcers
- etiology of PUD secondary to *H. pylori* is not well understood; however, the pattern of colonization correlates with outcome
- gastritis only in antrum (15% of patients), high gastric acid, associated with duodenal ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
- gastritis throughout stomach ("pangastritis" – 85% of patients), low gastric acid, associated with stomach ulcer and cancer

Epidemiology

- *H. pylori* is found in about 20% of all Canadians, with increased prevalence in Indigenous populations and immigrants from high prevalence countries
- highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

Outcome

- gastritis (non-erosive) occurs in 100% of patients but is asymptomatic
- peptic ulcer in 15% of patients
- gastric carcinoma and mucosal associated lymphomatous tissue (MALT) lymphoma in 0.5% of patients
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children ages <5)

Diagnosis

Table 7. Diagnosis of H. pylori Infection

Test	Sensitivity	Specificity	Comments
Non-invasive Tests			
Urea breath test	90-100%	89-100%	Affected by PPI therapy (false negatives)
Serology	88-99%	89-95%	Does not distinguish active vs. past infection; therefore, should not be used to assess post eradication status
Can remain positive after treatment			
Fecal antigen			Only rarely used in clinical practice
Invasive Tests (require endoscopy)			
Histology	93-99%	95-99%	Gold standard; affected by PPI therapy (false negatives)
Rapid urease test (on biopsy)	89-98%	93-100%	Rapid
Microbiology culture	98%	95-100%	Not widely available but can be used to determine ABx susceptibility. Research only

Treatment: *H. pylori* Eradication

- bismuth quadruple therapy recommended for 14 d: PPI (e.g. lansoprazole 30 mg BID) + bismuth 525 mg QID + metronidazole 500 mg QID + tetracycline 500 mg QID
- alternatively, concomitant non-bismuth quadruple therapy for 14 d: PPI + amoxicillin + metronidazole + clarithromycin

Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer
NEJM 2018;378:1085-1095
Purpose: To evaluate the role of H. pylori eradication in the prevention of metachronous gastric cancer.
Study: Double-blinded RCT.
Population: 470 patients with a subtotal gastrectomy for gastric cancer and H. pylori infection with or without ABx treatment.
Outcome: Incidence of metachronous gastric cancer.
Results: After almost 6 yr, 7.2% of the ABx-treated group developed another cancer in the gastric remnant vs. 13.4% in the placebo control group.
Conclusions: This provides definitive evidence that H. pylori is worthwhile treating no matter how advanced the gastric carcinogenic process.

Serology for *H. pylori* should not be used to check for eradication

NSAID-Induced Ulceration

Pathophysiology

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (IV NSAID causes ulcers, but not erosions)
  - NSAIDs also inhibit mucosal cyclooxygenase, leading to decreased prostaglandin synthesis
  - this results in ulcers from reduced secretion of protective bicarbonate and mucous, and decreased mucosal blood flow

Risk Factors for NSAID-induced Peptic Ulcer

- previous peptic ulcers/UGIB
- age (≥65 yr)
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

Clinical Features
- erosions may bleed, but usually only ulcers (which represent mucosal/submucosal injury) cause significant clinical problems
- most NSAID-induced ulcers are clinically asymptomatic: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulce
- may exacerbate underlying duodenal ulcer disease

Treatment
- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol (less effective) in one tablet
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration



If at high-risk for development of ulcers, prophylaxis with PPI indicated

Stress-Induced Ulceration

Definition
- ulceration or erosion in the upper GI tract of ill patients, usually in ICU (stress is physiological, not psychiatric)
- lesions most commonly in fundus of stomach

Pathophysiology
- injury to the mucosal barrier secondary to systemic stress resulting in multiple superficial erosions of the stomach
- commonly seen in patients with acute CNS injury (referred to as Cushing's ulcers) than other stress-related diseases (i.e. severe burns) (Curling's ulcers)
- etiology unclear - may involve ischemia / acid hypersecretion
- mechanical ventilation is the most important risk factor



Curling's and Cushing's Ulcers
Curling's Ulcer: acute peptic ulcer of the duodenum resulting as a complication from severe burns when reduced plasma volume leads to ischemia and cell necrosis (sloughing) of the gastric mucosa (think BURN from a CURLING iron)
Cushing's Ulcer: peptic ulcer produced by elevated ICP (may be due to stimulation of vagal nuclei secondary to elevated ICP which leads to increased secretion of gastric acid)

Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

Clinical Features
- UGIB (see *Upper Gastrointestinal Bleeding, G28*)
- painless

Treatment
- prophylaxis with gastric acid suppressants decreases risk of UGIB; PPI most potent but may increase risk of pneumonia; H2 blockers less potent but less likely to cause pneumonia
- treat underlying cause, aggressive fluid resuscitation
- ulcer treatment same as for bleeding peptic ulcer, but often less successful

Gastric Carcinoma

- see General Surgery and Thoracic Surgery, GS26

Small and Large Bowel

Classification of Diarrhea

Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal (i.e. ≥3x/d); physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) vs. large volume (>1/2 cup stool; typical of small bowel diseases)
- watery: secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)
- steatorrhea
- inflammatory/transit or functional

Acute Diarrhea

- see Pediatrics, P43

Definition
- passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

Epidemiology
- one of the leading causes of death worldwide (about 88% of diarrhea associated deaths are caused by unsafe water, inadequate sanitation, and insufficient hygiene)
- significant morbidity in developed countries (over 900000 hospitalizations in the United States each year)

Etiology
- most commonly due to infections
- most infections are self-limiting and resolve within 7 d

Risk Factors
- food (raw or undercooked meat and seafood, unpasteurized dairy products)
- medications: ABx, laxatives
- others: high-risk sexual activity, infectious outbreaks, occupational exposures (daycare workers), family history (IBD)

Approach to Acute Diarrhea
- the most common cause of acute diarrhea is infectious
- in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
- investigations are costly and are necessary only in certain circumstances
  - therefore, evaluation of acute diarrhea involves identifying characteristics of the patient or illness that warrant further investigation and assessing volume status to determine the most appropriate method of rehydration

Physical Exam
- volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
- abdominal exam: pain, guarding, peritoneal signs

Table 8. Classification of Acute Diarrhea

	Inflammatory	Non-Inflammatory
Definition	Disruption of intestinal mucosa	Intestinal mucosa intact
Site	Usually colon	Usually small intestine
Mechanism	Organisms and cytotoxins invade mucosa, resulting in the destruction of mucosal cells, and perpetuation of the diarrhea	Stimulation of intestinal water secretion and inhibition of water absorption (i.e. net secretion)
Sigmoidoscopy	Usually abnormal mucosa seen	Usually normal mucosa seen
Symptoms	Bloody (not always) Small volume, high frequency Often lower abdominal cramping with urgency ± tenesmus May have fever ± shock	Watery, little or no blood Large volume, low frequency Upper/periumbilical pain/cramping ± shock
Investigations	Fecal WBC and RBC positive	Fecal WBC negative
Etiology	See *Differential Diagnosis of Common Complaints, G4*	See *Differential Diagnosis of Common Complaints, G4*
Differential Diagnosis	Acute presentation of idiopathic IBD	Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)
Significance	Higher yield with stool C&S Can progress to life-threatening megacolon, perforation, hemorrhage ABx may be helpful	Lower yield with stool C&S Chief life-threatening problem is electrolyte disturbances/ fluid depletion ABx unlikely to be helpful

Investigations
- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (daycare worker, nursing home resident, community outbreaks, e.g. Walkerton, etc.)
  - O&P takes up to three weeks to obtain the results
  - C&S only tests *Campylobacter, Salmonella, Shigella, E. coli, Yersinia*
    - other organisms must be ordered separately
- flexible sigmoidoscopy (without bowel preparation): useful if inflammatory diarrhea suspected
  - histology (i.e. biopsies of mucosa) helps to distinguish idiopathic IBD (CD and UC) from infectious colitis or acute self-limited colitis
- *C. difficile* toxin: indicated in cases with recent/remote antibiotic use, hospitalization, nursing home living, or recent chemotherapy

Useful Questions in Acute Diarrhea

Those Fads Wilt
Travel
High-risk sexual activity (increased risk of fecal-oral exposure)
Outbreaks
Seafood
Extra intestinal signs of IBD
Family history
ABx
Diet
Steatorrhea
Weight loss
Immunosuppression
Laxatives
Tumour history

Infectious Causes of Inflammatory Diarrhea

Your Stool Smells Extremely Crappy
Yersinia
Shigella
Salmonella
E. coli (EHEC 0157:H7), *E. histolytica*
Campylobacter, *C. difficile*

An Update on the Role for Bacteriotherapy SER-109, an Oral Microbiome Therapy for Recurrent Clostridiodes difficile Infection
NEJM 2022;386:220-229
Building on the success of prior work demonstrating the efficacy of donor fecal transplant in patients with recurrent C. difficile infections, this randomized controlled trial shows that oral microbiome therapy (SER-109) effectively reduces the recurrence of C. difficile infection to 12% compared to 40% in cohorts receiving placebo. This trial along with similar prospective and retrospective work may standardize the use of medical probiotic therapy in patients with gastrointestinal disorders, including recurrent C. difficile infection.

Treatment

- fluid and electrolyte replacement orally in most cases, intravenously if severe extremes of age/coma
- antidiarrheals
  - antimotility agents: diphenoxylate, loperamide (Imodium®) should be used with caution; contraindicated in patients with mucosal inflammation, bloody diarrhea
  - side effects: abdominal cramps, toxic megacolon
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful (but should not be used in the presence of bloody diarrhea or fever)
- ABx: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially *Salmonella*)
    - drug side effects (including *C. difficile* infection)
    - development of resistant strains
    - renal failure/hemolysis (enterohemorrhagic *E. coli* O157:H7)
  - indications for antimicrobial agents in acute diarrhea
    - septicemia
    - prolonged fever with fecal blood (bloody diarrhea) or WBCs seen on O&P
    - clearly indicated: *Shigella, V. cholerae, C. difficile*, traveller's diarrhea (*E. coli* (ETEC)), *Giardia, Entamoeba histolytica, Cyclospora*
    - situational: *Salmonella, Campylobacter, Yersinia*, non-enterotoxigenic *E. coli*
    - *Salmonella*: always treat *Salmonella typhi* (typhoid or enteric fever); treat other *Salmonella* only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease
- report diarrheal illness to public health if appropriate

Causes of Acute Bloody Diarrhea

CHESS
Campylobacter
Hemorrhagic E. coli (e.g. O157:H7)
Entamoeba histolytica
Salmonella
Shigella

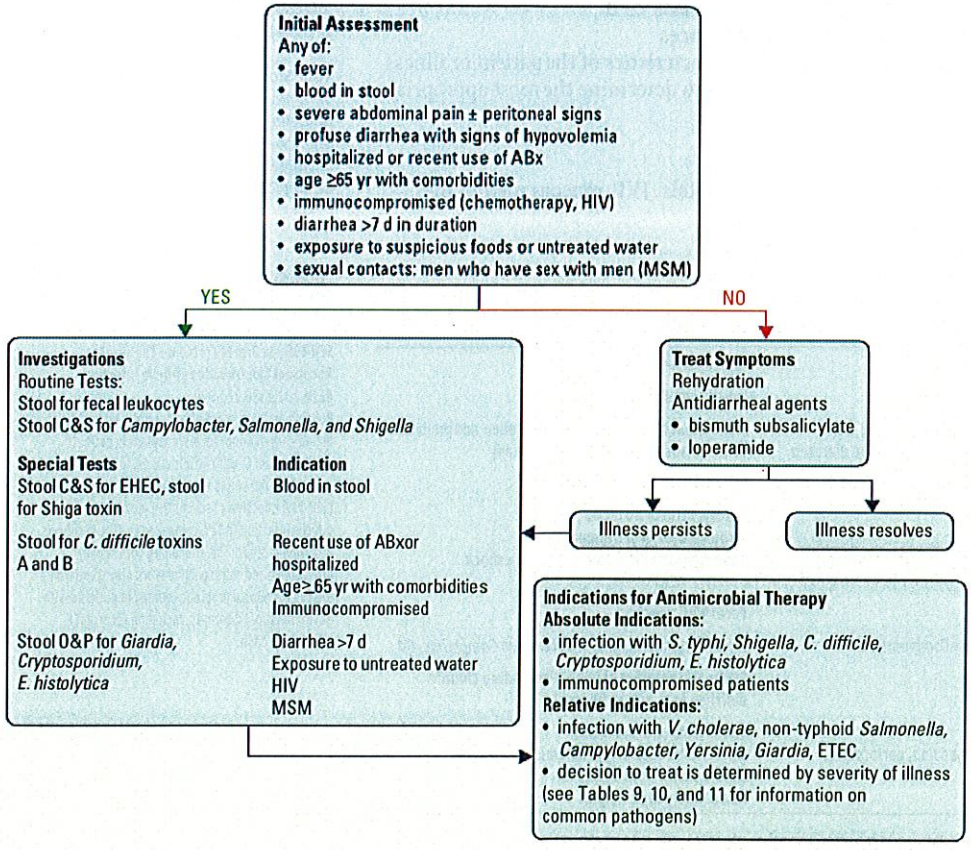


Figure 7. Approach to acute diarrhea
Note: S. typhi has a rose spot rash (transient maculopapular rash on anterior thorax, upper abdomen), and a prodrome of high fever, bradycardia, headache, and abdominal pain. Diarrhea is not the initial presentation

Table 9. Bacteria in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	Nausea/ Vomiting			
***B. cereus* – Type A (emetic)**	Rice dishes	1-6 h	–	–	–	+	<12 h	None	Preformed exotoxin
***B. cereus* – Type B (diarrheal)**	Meats, vegetables, dried beans, cereals	8-16 h	–	–	–	–	<24 h	None	Secondary endotoxin
Campylobacter jejuni	Uncooked meat, especially poultry	2-10 d	+	±	+	±	<1 wk	Macrolide or fluoroquinolone if diarrhea >1 wk, bloody diarrhea, or immunocompromised	Most common bacterial cause of diarrhea in Canada Associated with Guillain-Barré syndrome
Clostridium difficile	Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials)	Unclear	±	±	±	–	Variable	Stop culprit antibiotic therapy if possible Supportive therapy (IV fluids) Empiric treatment with either vancomycin or fidaxomicin If access to empiric treatment is limited, then metronidazole may be used For fulminant *C. difficile* infection (previously called severe), oral vancomycin is used. IV metronidazole added to regimen if ileus present	Usually follows antibiotic treatment (especially clindamycin, fluoroquinolones, penicillins, cephalosporins) Can develop pseudomembranous colitis
Clostridium perfringens	Contaminated food, especially meat and poultry	8-12 h	±	–	+	–	<24 h	None	*Clostridium* spores are heat resistant Secondary enterotoxin Enteroinvasive
E. coli (EIEC)	Contaminated food/ water	1-3 d	+	±	+	–	7-10 d	None	Relatively uncommon Enterotoxigenic
E. coli (ETEC)	Contaminated food/ water	1-3 d	–	–	+	–	3 d	Fluoroquinolone or azithromycin for moderate to severe symptoms	Most common cause of traveller's diarrhea Heat-labile and heat-stable toxins
Enterohemorrhagic E. coli (EHEC/STEC) i.e. O157:H7	Contamination of hamburger, raw milk, drinking, and recreational water	3-8 d	–	+	+	±	5-10 d	None: ABx increase risk of HUS	Shiga toxin production Monitor renal function: 10% develop HUS Antidiarrheals increase risk of HUS
***Salmonella Typhi* *S. Paratyphi* (i.e. Enteric Fever, Typhoid)**	Fecal-oral Contaminated food/ water Travel to endemic area	10-14 d	+	±	+	±	<5-7 d	Empiric treatment with ceftriaxone, ciprofloxacin, or azithromycin Fluoroquinolone resistance is increasing	*Salmonella typhi*: "Rose spot" rash (on anterior thorax, upper abdomen), fever, and abdominal pain precedes diarrhea
Non-typhoidal Salmonellosis *S. Typhimurium*, *S. Enteritidis*	Contaminated animal food products, especially eggs, poultry, meat, milk	12-72 h	+	±	+	+	3-7 d	Ciprofloxacin only in severe illness, extremes of age, joint prostheses, valvular heart disease, severe atherosclerosis, cancer, uremia	
Shigella dysenteriae	Fecal-oral Contaminated food/ water	1-4 d	+	±	+	+	<1 wk	Fluoroquinolone	Very small inoculum needed for infection Complications include toxic megacolon, HUS Antidiarrheals may increase risk of toxic megacolon
Staphylococcus aureus	Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)	2-4 h	–	–	+	+	1-2 d	None	Heat-stable preformed exotoxin
Vibrio cholerae	Contaminated food/ water, especially shellfish	1-3 d	–	–	–	+	3-7 d	Tetracycline or fluoroquinolones (ciprofloxacin)	Massive watery diarrhea (1-3 L/d) Mortality <1% with treatment
Yersinia	Contaminated food Unpasteurized milk	5 d	+	±	+	±	Up to 3 wk	Fluoroquinolone only for severe illness	Majority of cases in children 1-4 yr Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis Can also mimic CD of terminal ileum

Table 10. Parasites in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	Nausea/ Vomiting			
Cryptosporidium	Fecal-oral	7 d	±	–	–	+	1-20 d	Paromomycin + nitazoxanide	Immune reconstitution if immunosuppressed
Entamoeba histolytica	Worldwide endemic areas Fecal-oral	2-4 wk	±	+	–	+	Variable	Metronidazole + iodoquinol or paromomycin if symptomatic infection Only iodoquinol or paromomycin for asymptomatic cyst passage	If untreated, potential for liver abscess Sigmoidoscopy may show flat ulcers with yellow exudates
Giardia lamblia	Fecal-oral Contaminated food/ water	1-4 wk	–	–	+	+	Variable	Metronidazole or nitazoxanide Treatment of asymptomatic carriers NOT recommended	Higher risk in: daycare children, intake of untreated water ("beaver fever"), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy

Table 11. Viruses in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	Nausea/ Vomiting			
Norovirus	Fecal-oral	24 h	–	–	+	+	24 h	None	Noroviruses include Norwalk virus
Rotavirus	Fecal-oral	2-4 d	±	–	–	±	3-8 d	None	Can cause severe dehydration Virtually all children are infected by 3 yr Oral vaccine given at 2 and 4 mo

Traveller's Diarrhea



Epidemiology

- most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

Etiology

- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter, Shigella, Salmonella, Vibrio* (non-cholera); wide regional variation (e.g. *Campylobacter* more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia, Entamoeba histolytica, Cryptosporidium*, and *Cyclospora* for ~10% in long-term travellers
- pathogen-negative traveller's diarrhea common despite exhaustive microbiological workup

Treatment

- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss, use oral rehydration solutions (1 package in 1 L boiled or treated water)
- treat symptoms: antidiarrheal agents (e.g. rifamycin ABx, bismuth subsalicylate, loperamide)
- empiric ABx in moderate or severe illness: ciprofloxacin, azithromycin, or rifaximin

note: there is increasing fluoroquinolone resistance in causative agents, especially in South and Southeast Asia

Prevention

- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
- bismuth subsalicylate (Pepto-Bismol®): 60% effective (2 tablets QID)
- antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
  - high-risk groups (e.g. immunocompromised individuals) likely to be infected with pathogen not covered by standard antimicrobial agents

- Dukoral®: oral vaccine that offers protection against *V. cholerae* (efficacy ~80%) and ETEC (efficacy ~50-67%)
  - 2 doses should be taken 2 wk prior to traveling and the effect may last up to 3 mo
  - Public Health Agency of Canada recommends that it may be considered for the following situations (not recommended for routine use in travellers):
    - increased risk of acquiring traveller's diarrhea (gastric hypochlorhydria or young children >2 yr)
    - short-term travellers who are high-risk (e.g. chronic illness) and have an increased risk of serious consequences of traveller's diarrhea (e.g. chronic renal failure, CHF, T1DM, IBD)
    - immunosuppression
    - history of repeat traveller's diarrhea
    - travellers to cholera endemic countries at increased risk of exposure
- two vaccines against *Salmonella typhi* are available and their effectiveness is estimated to be 50-70%

Chronic Diarrhea



Definition
- passage of frequent unformed stool for >4 wk (compared to persistent diarrhea lasting 14-30 d)

Etiology/Classification
- majority of cases are non-infectious
- see *Differential Diagnosis of Common Complaints, G5*

Investigations
- guided by history
- stool analysis for: *C. difficile* toxin, C&S, O&P ± fecal fat, WBC, fecal calprotectin
- blood for: CBC, electrolytes, C-reactive protein (CRP) , TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency, which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease

Treatment
- approach is similar to that of acute diarrhea
- dependent on underlying etiology

Maldigestion and Malabsorption

Definition
- maldigestion: inability to break down large molecules in the lumen of the intestine into their component small molecules
- malabsorption: inability to transport molecules across the intestinal mucosa into circulation

Etiology
- maldigestion
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis (CF) (remember CF can result in pancreatic exocrine insufficiency as well), pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impaired enterohepatic recycling in view of loss greater than synthesis), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic, e.g. PBC)
  - specific enzyme deficiencies (e.g. lactase)
- malabsorption
  - inadequate absorptive surface
    - infections/infestations (e.g. Whipple's disease, *Giardia*)
    - immunologic (e.g. celiac disease)
    - infiltration (e.g. lymphoma, amyloidosis)
    - fibrosis (e.g. systemic sclerosis, radiation enteritis): can lead to loss of surface area but also areas of stricture formation resulting in stasis with small bowel overgrowth
    - small bowel resection (length, site, location, presence/absence of ileocecal valve, and integrity of colon are important)
    - congenital (e.g. short bowel syndrome)
    - inflammatory: extensive ileal CD (pivotal number is 100 cm as <100 cm = bile salt or choleretic diarrhea, >100 cm = fatty diarrhea or steatorrhea)

- drug-induced
  - cholestyramine, ethanol, neomycin, tetracycline, and other ABx
- endocrine
  - DM (complex pathogenesis)



Fat Soluble Vitamins: ADEK
vitamin **A**, vitamin **D**, vitamin **E**, vitamin **K**

Clinical Features

- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency

Table 12. Absorption of Nutrients and Fat Soluble Vitamins

Deficiency	Absorption	Clinical Disease and/or Features	Investigations
Iron	Duodenum, upper jejunum	Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica	↓ Hb, ↓ serum Fe, ↓ serum ferritin
Calcium	Duodenum, upper jejunum (binds to Ca^{2+} binding-protein in cells; levels increased by vitamin D)	Metabolic bone disease, may get tetany and paresthesias if serum calcium falls* (see Endocrinology, E42)	↓ Serum Ca^{2+}, ↓ serum Mg^{2+}, and ↑ ALP Evaluate for ↓ bone mineralization radiographically (dual energy x-ray absorptiometry, DEXA)
Folic Acid	Jejunum	Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)	↓ Serum folic acid
Vitamin B_{12}	B_{12} ingested and bound to R proteins mainly from salivary glands; stomach secretes IF in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B_{12}-IF complex forms, protecting B_{12} from further protease attack; B12 absorbed in ileum and binds to transcobalamin (TC)	Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis	Differentiate causes by nuclear Schilling test (when available) Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H25)
Carbohydrate	Complex polysaccharides hydrolyzed to oligosaccharides and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum	Generalized malnutrition, weight loss, flatus, and diarrhea	Hydrogen breath test Trial of carbohydrate-restricted diet D-xylose test
Protein	Digestion begins in stomach, then brush border, and inside cell Absorption occurs primarily in the jejunum	General malnutrition and weight loss, amenorrhea, and ↓ libido if severe	↓ Serum albumin (low sensitivity)
Fat	Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Absorption occurs primarily in the jejunum Fatty acids diffuse into cell cytoplasm	Generalized malnutrition, weight loss, and diarrhea Foul-smelling feces + gas Steatorrhea	Small bowel biopsy MRCP, ERCP, pancreatic function tests (not routinely available) Quantitative stool fat test (72 h) May start with qualitative stool fat test (Sudan stain of stool) C-triolein breath test (not routinely available)
Vitamin A	Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)	Night blindness Dry skin Keratomalacia	
Vitamin D	Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)	Osteomalacia in adults Rickets in children	
Vitamin E	Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)	Retinopathy, neurological problems	
Vitamin K	Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum ABx and/or starvation	Prolonged INR may cause bleeding	

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone

Investigations

- tTG-IgA antibody serology/immunoglobulin A quantitation and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- fecal elastase to screen for pancreatic insufficiency and/or consider empiric trial of pancreatic enzymes based on clinical context
- serum carotene (precursor to vitamin A), folate, Ca^{2+}, Mg^{2+}, vitamin B_{12}, albumin, ferritin, serum iron solution, international normalized ratio/partial thromboplastin time (INR/PTT)
- stool fat globules on fecal smear stained with Sudan (used as an initial qualitative screening tool)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)

Treatment

- dependent on underlying etiology

Celiac Disease (Gluten Enteropathy/Sprue)

Definition

- abnormal small intestine mucosa due to intestinal reaction to gluten, a protein found in wheat, barley, rye, and possibly oats (certified gluten-free oats may be acceptable in a subgroup of patients)

Etiology

- unique autoimmune disease because the genetics (HLA-DQ2/8), the auto-antigen (tTG), and the environmental trigger (gluten) are all known
- associated with other autoimmune diseases, especially Sjögren's, T1DM, thyroid disease
- gluten is broken down to gliadin, which is the toxic protein
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared to 20% of the general population; celiac also associated with HLA-DQ8
- HLA-DQ2/Q8 are necessary permissive genes, but their presence does not confer a diagnosis of celiac disease (note: up to 40% of White individuals carry the HLA alleles, but will never develop celiac disease)

Epidemiology

- more common in women
- prevalence: 1 first degree relative: 10%; 2 first degree relatives: 20%
- may present any time in life, with peak presentation in infancy (when cereals introduced)

Clinical Features

- classic presentation: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; more common current presentation: bloating, gas, iron deficiency, or asymptomatic (patient at risk)
- improves with gluten-free diet, disease exacerbation when gluten reintroduced
- disease is usually most severe in proximal bowel
  - iron, calcium, and folic acid deficiency (absorbed in proximal small bowel) more common than vitamin B12 deficiency (absorbed in distal small bowel or ileum)
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations

- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - patients with selective IgA deficiency have false-negative anti-tTG
    - therefore, measure serum IgA concomitantly (via serum immunoglobulin quantitation)
- incorporate serum testing tTG and/or DGP IgG in IgA deficiencies
- small bowel mucosal biopsy (usually duodenum) is diagnostic:
  - increased intraepithelial lymphocytes (earliest pathologic finding)
  - crypt hyperplasia (next stage of pathophysiology)
  - villous atrophy (last stage of pathophysiology)
  - note: there is a wide differential diagnosis for villous atrophy, including, but not limited to, small bowel overgrowth, CD, lymphoma, Giardia, HIV
- improvement with a gluten-free diet, but should not be started before serological tests and biopsy
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca^{2+}, Fe, albumin, cholesterol, carotene, B12 absorption
- quantitative fecal fat >7%

Treatment

- dietary counselling
  - gluten free diet; avoid barley, rye, wheat (as these grains are related and have toxic proteins, similar to gliadin)
  - oats allowed if not contaminated by other grains (grown in soil without cross-contamination)
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
- if poor response to diet change, consider
  - alternate diagnosis
  - non-adherence to gluten-free diet (advertent or inadvertent)
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
  - development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
  - development of diffuse jejunal ileal intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)



Early Gluten Introduction and Celiac Disease in the EAT Study: A Prespecified Analysis of the EAT Randomized Clinical Trial
JAMA Pediatr 2020;174:1-7
Purpose: Determine whether introduction of high-dose gluten lowers celiac disease prevalence at 3 yr of age
Methods: Infants were randomized to consume 6 allergenic foods in addition to breast milk from age 4 mo (early introduction), or to avoid allergenic foods and follow exclusive breastfeeding guidelines (standard introduction). Evaluation of celiac disease was an a priori secondary outcome of the EAT trial, tested at age 3 with anti transglutaminase 2 antibodies.
Results: 1.4% of infants in the standard introduction group had a celiac disease diagnosis confirmed, versus 0% of infants in the early introduction group.
Conclusion: Introduction of gluten from age 4 mo was associated with a reduction in the prevalence of celiac disease.



Gluten Found in BROW

Barley
Rye
Oats (controversial)
Wheat

Prognosis
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon; slight increase compared with general population), autoimmune diseases
- risk of lymphoma may be lowered by dietary gluten restriction

Inflammatory Bowel Disease

Definition
- group of disorders characterized by inflammation, and potentially ulceration, of the gastrointestinal tract; two main forms include CD and UC

Etiology
- complex, multifactorial etiology
- most likely a sustained response of the immune system, perhaps to enteric flora
- lack of appropriate down-regulation of immune responsiveness after an infection in a genetically predisposed individual

Genetics
- increased risk of both UC and CD in relatives of patients with either disease, especially siblings; early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 200+ associated gene loci
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially in Ashkenazi Jews, early onset disease, ileal involvement, and fistulizing, fibrostenotic, or stricturing disease
  - *CARD15* gene product modulates NFκβ, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

Clinical Features

Table 13. Clinical Differentiation of Ulcerative Colitis from Crohn's Disease

	Crohn's Disease	Ulcerative Colitis
Location	Any part of GI tract ("gum to bum") Small bowel + colon: 50% Small bowel only: 30% Colon only: 20%	Isolated to large bowel Always involves rectum, may progress proximally
Rectal Bleeding	Uncommon; possible if colonic disease	Very common (90%)
Diarrhea	Usually non-bloody (may be bloody, particularly if distal colon is involved)	Frequent, mucous, bloody, small volume stools
Abdominal Pain	Post-prandial/colicky	Predefecation/colicky
Fever	Common	Uncommon
Urgency/Tenesmus	Uncommon (unless rectum involved)	Common
Palpable Mass	Frequent (25%), RLQ	Rare (if present, often related to cecum full of stool)
Recurrence After Surgery	Common	None post-colectomy (with permanent ileostomy)
Endoscopic Features	Segmental inflammation, ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning	Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps
Histologic Features	Transmural distribution with skip lesions Focal inflammation ± Noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures Glands intact	Mucosal distribution, continuous disease (no skip lesions) Architectural distortion, gland disruption, crypt abscess Granulomas absent
Radiologic Features	Cobblestone mucosa Frequent strictures and fistulae Abdominal x-ray: bowel wall thickening, "string sign"	Lack of haustra Strictures rare; if present, need to rule out complicating cancer
Complications	Strictures, fistulae, perianal disease	Toxic megacolon
Colon Cancer Risk	Increased if >30% of colon involved	Increased except in proctitis

Table 14. Extraintestinal Manifestations of IBD

System	Crohn's Disease	Ulcerative Colitis
Dermatologic		
Erythema nodosum	15%	10%
Pyoderma gangrenosum	10%	Less common
Perianal skin tags	75-80%	Rare
Oral mucosal lesions, stomatitis	Common	Rare
Psoriasis	Present in 5-10% of those with IBD but not an EIM	
Rheumatologic		
Peripheral arthritis	15-20% of those with IBD (CD>UC)	
Ankylosing spondylitis	10% of those with IBD (CD>UC)	
Sacroiliitis	Occurs equally in CD and UC	
Ocular (~10% of IBD)		
Uveitis (vision threatening)		
Episcleritis (benign)	3-4% of IBD patients (CD>UC)	
Hepatobiliary		
Cholelithiasis	15-35% of patients with ileal CD	
PSC	1-5% of IBD cases with colonic involvement	
Fatty liver		
Gallstones	Pigment stones in CD	
Urologic		
Calculi	Most common in CD, especially following ileal resection or extensive terminal ileal disease (oxalate stones), in context of an intact colon	
Ureteric obstruction		
Fistulae	Characteristic of CD	
Others		
Thromboembolism		
Vasculitis		
Osteoporosis	Increased in CD with/without prior steroids, in UC only after steroids usage	
Vitamin deficiencies (B_{12}, ADEK)		
Cardiopulmonary disorders		
Pancreatitis (rare)		
Phlebitis		

Crohn's Disease

Definition

- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region ("gum to bum")

Epidemiology

- worldwide incidence 3-15 to 10-20/100000; 135000 Canadians living with CD
- bimodal: onset before age 30, second smaller peak at age 60; M=F
- incidence of CD increasing (relative to UC) especially in young females
- more common in White people, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in CD patients is higher than general population

Pathology

- most common location: ileum + right colon
- linear ulcers leading, when in clusters, connect and form mucosal islands or a "cobblestone" appearance
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

Clinical Features

- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- commonly presents as recurrent episodes of abdominal cramps, diarrhea (with or without bleeding), fatigue, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- EIMs are more common with colonic involvement
- fistulae, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina, and other parts of bowel

Effect of Tight Control Management on Crohn's Disease (CALM): A Multi-Centre, Randomized Controlled Phase 3 Trial
Lancet 2017; 390:2779-2789
Purpose: To define the role of incorporating laboratory biomarkers in the management algorithm of active CD.
Study: RCT
Population: 224 adult patients (22 countries at 74 hospitals) with active CD were randomized to intensify treatment based on either laboratory biomarkers (serum CRP, fecal calprotectin) plus clinical evaluation (CD activity index and prednisone use) or treatment based on clinical evaluation alone.
Outcomes: Mucosal healing via the absence of deep ulcers.
Results: At 2 yr, more patients receiving treatment criteria that included laboratory tests had complete mucosal healing (i.e. no ulcers) than the group treated on the basis of symptoms alone (46% vs. 30%). Admittedly, the endpoint of mucosal healing is not a strong clinically relevant result, but other studies have shown that the greater the mucosal ulceration, the higher the rate of complications (i.e. strictures, fistulae, abscesses, hospitalizations, and surgery).
Conclusions: This is not definitive data but adds to other evidence showing that the traditional management paradigm needs revising, so in most patients it is worthwhile aiming for endoscopic healing of CD irrespective of symptoms.

Investigations

- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response (especially acutely in UC)
- bacterial cultures, O&P, *C. difficile* toxin to exclude other causes of inflammatory diarrhea

Management (see Figure 8)

Table 15. Management of Crohn's Disease

Management	Notes
Lifestyle/Diet	Smoking cessation Fluids only during acute exacerbation Enteral diets may aid in remission only for Crohn's ileitis, not colitis No evidence for any non-enteral diet changing the natural history of CD, but may affect symptoms Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vitamin D, Ca^{2+}, Mg^{2+}, Zn, Fe, B_{12})
Antidiarrheal Agents*	Loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive) All work by decreasing small bowel motility, used only for symptom relief CAUTION: if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups
5-ASA**	Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine Hydrolysis by intestinal bacteria releases 5-ASA (active component) Dose-dependent efficacy Mesalamine (Pentasa®, Salofalk®, Mezavant®, Olsalazine®): used for the treatment of mild ileitis (CD) and mild UC, when inflammation is mild
Antibiotics	E.g. metronidazole (20 mg/kg/d, BID or TID dosing) or ciprofloxacin Best described for perianal CD, although characteristically relapse when discontinued
Corticosteroids	Prednisone: starting dose 40 mg once daily for acute exacerbations of colon-only CD; Budesonide: (first pass metabolism corticosteroid) 9 mg once daily for acute exacerbations of terminal ileum ± right colon CD; IV methylprednisolone if severe No proven role for steroids in maintaining remission; masks intra-abdominal sepsis
Immunosuppressives	6-mercaptopurine (6-MP), azathioprine (Imuran®); MTX (used less often) More often used to maintain remission than to treat active inflammation Most commonly used as steroid-sparing agents i.e. to lower risk of relapse as corticosteroids are withdrawn Usually requires >3 mo to have beneficial effect; usually continued for several years May help to heal fistulae, decrease disease activity Increases efficacy of biologics, plus lowers chances of biologic dosing efficacy (tolerance) - may be used in combination (dual therapy) with biologics Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy (i.e. lymphoma)
Biologics	Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α Proven effective for treatment of fistulae and medically refractory CD First-line immunosuppressive therapy with infliximab + azathioprine (dual therapy) more effective than using either alone (monotherapy) Ustekinumab, monoclonal antibody against P40 subunit of interleukin 12 and 23 Vedolizumab, monoclonal antibody directed against integrin α4β7 thereby reducing lymphocyte traffic to gut – now indicated for UC and CD
Immunotherapy (Small molecules)	JAK (Janus Kinase) inhibitors (e.g. tofacitinib). Efficacy demonstrated in UC
Surgical/ Experimental	Surgical treatment (see General and Thoracic Surgery, GS36) Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding, and for medically refractory disease If <50% or <200 cm of functional small intestine, risk of short bowel syndrome At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher 40% likelihood of second bowel resection, 30% likelihood of third bowel resection Complications of ileal resection <100 cm resected → watery diarrhea or cholorrhea (impaired bile salt absorption) Treatment: cholestyramine or antidiarrheals, e.g. loperamide >100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency) Treatment: fat restriction, medium chain triglycerides

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific antidiarrheals are more convenient and often more potent
**5-ASA use in CD is controversial; however, initial trial for mild ileitis only is warranted (induction and maintenance if clinical response)

Traditional Medical Management of Crohn's Disease

	Induction of Remission	Maintenance
5-ASA*	?	?
Steroids	+	
Immuno-modulators (e.g. azathioprine, methotrexate (MTX))	-	+
Antibiotics	+	
Biologics	+	+

*5-aminosalicylic acid (5-ASA) use in CD is controversial. However, initial trial for mild ileitis only is warranted (induction and maintenance if clinical response)

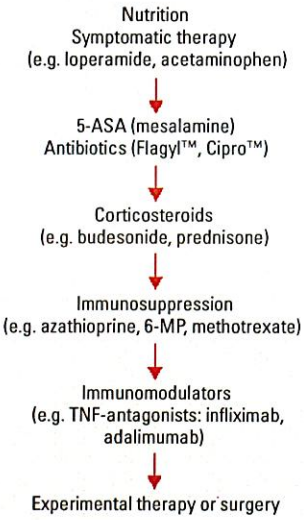


Figure 8. Traditional graded approach to induction therapy in Crohn's disease
Note: immunosuppressants and immunomodulators are increasingly used initially ("top-down management strategy"), 5-ASA drugs have limited role in Crohn's disease

Prognosis

- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as UC (see *Ulcerative Colitis, G25*) if more than 1/3 of colon involved

Ulcerative Colitis

Definition
- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

Epidemiology
- worldwide incidence 3-15 to 10-20/100000; 120000 Canadians living with UC (less common than CD)
- 2/3 onset by age 30 (with second peak after 50 yr); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- reduced risk in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

Pathology
- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation is diffuse, continuous, and confined to mucosa

Clinical Features
- rectal bleeding is the hallmark feature; diarrhea present if more than the rectum is involved
  - can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- EIMs (see *Table 14, G23*)
- characteristic exacerbations and remissions; 5% of cases are fulminant

Investigations
- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel preparation often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- occasionally CT colonography (formerly barium enema) to complete evaluation of colon if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, *C. difficile* toxin assay necessary to exclude infection
- no single confirmatory test

Treatment
- mainstays of treatment: 5-ASA derivatives (only in mild to moderate disease) and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- there is no specific diet to decrease inflammation; however, during a flare-up, elimination of dairy products may alleviate symptoms
- antidiarrheal medications generally not indicated in UC
- 5-ASA
  - topical (suppository or enema): effective for distal disease (rectum to splenic flexure) if inflammation is mild, preferable to corticosteroids
  - oral: effective for mild to moderate, but not severe colitis (e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d)
  - commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  - may decrease rate of colorectal cancer
- corticosteroids
  - to remit acute disease, especially if severe or first attack; may need IV steroids initially (e.g. methylprednisolone 20 to 30 mg IV q12 h)
  - limited role as maintenance therapy for mild to moderate disease
  - for mild to moderate disease, may use oral Budesonide -CR (colonic extended release formulation)
  - use suppositories (predominantly available in compound pharmacies) for proctitis
  - use enemas and topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants / immunobiologics / immunotherapy(steroid-sparing)
  - in hospitalized patients with severe UC – add IV infliximab if no response to IV methylprednisolone within 3 d; then consider colectomy if inadequate response
  - immunosuppressant: azathioprine and 6-MP: too slow to rapidly resolve acute relapse
    - most commonly used to maintain remission as corticosteroids withdrawn
    - given with biologics: increase efficacy of infliximab and decrease likelihood of developing tolerance to infliximab (~10% chance/yr)
  - biologics (infliximab, adalimumab, golimumab, vedolizumab) can be used for outpatients with moderate-severe disease, particularly those that are steroid-unresponsive or steroid-dependent, some evidence that they are best used early in course of disease
- immunotherapy:
  - tofacitinib, upadacitinib: JAK-inhibitors, non-selective and gut selective respectively, can also be used for outpatients with moderate-severe disease, with failure to other biologic agents, steroid-unresponsive or steroid-dependent
  - ozanimod: an oral sphingosine-1-phosphate receptor modulator used for treating moderate-to severe UC
    - does not require previous failure of immunosuppressants, glucocorticoids, biologics, or other small molecules
    - increases clinical remission rates compared to placebo

In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea

Medical Management of Ulcerative Colitis

	Induction of Remission	Maintenance
5-ASA	+	+
Steroids	+	
Immuno-suppressive	±	+

- surgical treatment (restorative)
  - aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis (IPAA)
  - indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy

Complications
- similar to CD, except:
  - more liver problems (especially PSC in men)
  - greater risk of colorectal cancer
    - risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
    - risk is increased in patients with chronic, active mucosal inflammation
    - thus, regular colonoscopy with surveillance biopsies and or chromoendoscopy is indicated in pancolitis of ≥8 yr is indicated
    - patients with coincident liver disease, PSC have a 5-fold risk of colon cancer versus those with UC alone. Patients with UC and PSC require annual surveillance colonoscopy with biopsy and or chromoendoscopy annually
    - patients with proctitis alone have the same risk for colon cancer as the general population
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery and Thoracic Surgery, GS45)

When Considering Complications of IBD, Think:

ULCERATIVE COLITIS
Urinary calculi
Liver problems
Cholelithiasis
Epithelial problems
Retardation of growth/sexual maturation
Arthralgias
Thrombophlebitis
Iatrogenic complications
Vitamin deficiencies
Eyes
Colorectal cancer
Obstruction
Leakage (perforation)
Iron deficiency
Toxic megacolon
Inanition (wasting)
Strictures

Prognosis
- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course, lifetime risk of extension is 15%
- fecal calprotein is a useful stool surrogate marker of bowel mucosal inflammation, that can be utilized as a follow-up marker for disease activity

Irritable Bowel Syndrome

Definition
- a form of functional bowel disease, now also known as disorder of gut-brain interaction; more than just a label for GI symptoms unexplained after normal investigations

Epidemiology
- 11% worldwide prevalence
- onset of symptoms usually in young adulthood
- F>M

Clinical Features
- Rome IV Criteria are used for diagnosis
- diagnosis is based chiefly on history; no specific diagnostic test available

Pathophysiology
- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associated or causative
- psychological: stress may increase IBS symptoms but probably does not cause IBS
- 4 main types of IBS
  - IBS-D: IBS with predominant diarrhea
  - IBS-C: IBS with predominant constipation
  - IBS-M: IBS-mixed with both diarrhea and constipation (each >25% of all abnormal bowel movements)
  - IBS untyped: insufficient abnormalities to be IBS-C, D, or M

Emerging Biologic Treatments for Ulcerative Colitis

Generic Name	Brand Name	Major Study
Ustekinumab	Stelara™	NEJM 2019; 381:1201-1214
Vedolizumab	Entyvio™	NEJM 2019; 381:1215-1226
Adalimumab	Humira™	NEJM 2019; 381:1215-1226

Diagnosis

Table 16. Rome IV Criteria for Diagnosing Irritable Bowel Syndrome

IBS Rome IV Criteria	
Recurrent abdominal pain for more than 6 mo, at least 1 d/wk in the last 3 mo, associated with 2 or more of the following: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool	
Symptom onset at least 6 mo before diagnosis and criteria present during the last 3 mo	
The following are supportive, but not essential to the diagnosis: Abnormal stool frequency (>3/d or <3/wk) Abnormal stool form (lumpy/hard/loose/watery) >1/4 of defecations Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) >1/4 of defecations Passage of mucus >1/4 of defecations Bloating	
Diagnosis of IBS Less Likely in Presence of "Red Flag" Features	
Weight loss Fever Nocturnal defecation	Anemia Blood or pus in stool Abnormal gross findings on flexible sigmoidoscopy
Normal Physical Exam	

Investigations
- if history consistent with Rome IV criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS, particularly celiac disease and IBD
- investigations can be limited to CBC and celiac serology
- if available, fecal calprotectin is likely more reliable test to rule out IBD
- consider TSH, stool cultures depending on clinical circumstances
- consider colonoscopy (e.g. if alarm features present, family history of IBD, or age >50)

IBS Mimickers
Enteric infections e.g. Giardia
Lactose intolerance/other disaccharidase deficiency
CD
Celiac sprue
Drug-induced diarrhea
Diet-induced (excess tea, coffee, colas)

Treatment
- education: reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction, cognitive behavioural therapy, probably exercise
- dietary: low FODMAP (Fermentable Oligo-, Di-, Monosaccharides And Polyols) diet for pain, bloating, gas, irregular bowel movements (BMs)
- no therapeutic agent consistently effective, pain most difficult to control, no drug changes natural history so the drug should be "wanted, since it is not needed"
- symptom-guided treatment
  - pain predominant
    - antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine - low level of evidence)
    - tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) - moderate level of evidence
  - IBS-D
    - increase fibre (bran or psyllium) to increase stool consistency but may worsen abdominal gas (controversial)
    - loperamide (Imodium®) (continuous use not recommended)
    - diphenoxylate (Lomotil®)
    - eluxadoline
    - rifaximin
  - IBS-C
    - increase fibre in diet
    - linaclotide, plecanatide, tenapanor
    - osmotic or other laxatives (help more with the constipation than the pain)

Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation
NEJM 2011;364:22-32
Purpose: Previous evidence suggests that gut flora may play an important role in the pathophysiology of IBS. This study evaluated rifaximin, a minimally absorbed antibiotic, in treating IBS without constipation.
Methods: Two phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2). 1260 patients who had IBS without constipation were randomly assigned to rifaximin (550 mg dose) or placebo, TID for 2 wk, with a follow-up of 10 wk. The primary endpoint was adequate self-reported relief of global IBS symptoms.
Results: Significantly more patients in the rifaximin group had adequate self-reported relief of global IBS symptoms compared to the placebo group during the first 4 wk after treatment (40.8% vs. 31.2%, respectively). Also, more patients in the rifaximin group had adequate relief of bloating compared to the placebo group (39.5% vs. 28.7%, respectively).
Conclusions: Rifaximin therapy for 2 wk provided significant relief of symptoms, bloating, abdominal pain, and stool consistency associated with IBS without constipation.

Prognosis
- 80% improve over time
- most have intermittent episodes
- normal life expectancy

Constipation

Definition
- passage of infrequent/hard stools and/or difficult stool evacuation (e.g. straining, sensation of anorectal blockage)

Epidemiology
- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries

Etiology
- most common: functional, idiopathic attributed to colon dysmotility but this is difficult to measure
- organic causes: likely only if there are symptoms other than constipation
  - medication side effects (e.g. narcotics, antidepressants) are the most common

Causes of Constipation

DOPED
Drugs
Obstruction
Pain
Endocrine dysfunction
Depression

- intestinal obstruction, left sided colon cancer (consider in older patients), and fecal impaction
- metabolic
  - DM
  - hypothyroidism
  - hypercalcemia, hypokalemia, uremia
- neurologic
  - intestinal pseudo-obstruction
  - Parkinson's disease
  - MS
- collagen vascular disease (e.g. scleroderma)
- painful anal conditions (e.g. fissures)

Clinical Features
- overlaps with IBS with constipation (IBS-C) but labeled as IBS-C when pain is a predominant feature
- stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

Investigations
- underlying disease rarely found if constipation is the only presenting symptom
  - only test indicated in this situation is a CBC (2013 recommendation of American Gastroenterology Association), but also consider TSH, calcium, glucose, and abdominal x-ray
- colon visualization (colonoscopy, CT colonography) if concomitant symptoms such as rectal bleeding, weight loss, anemia or age >50
- if refractory to treatment, consider classification based on colon transit time; can measure colonic transit time with radio-opaque (Sitz) markers that are ingested and followed with a series of plain film abdominal x-rays (normal: elimination of markers within 70 h)
  1. normal = misperception of normal defecation (IBS)
  2. prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of 1 and 3 common

Treatment (in order of increasing potency)
- dietary fibre
  - useful if mild or moderate constipation, but not if severe
  - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
  - docusate salts (likely limited efficacy based on evidence), mineral oils
- osmotic agents (effective in 2-3 d)
  - polyethylene glycol 3350, lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia), lactitol (β-galactosido-sorbitol)
- cathartics/stimulants (effective in 24 h)
  - senna, bisacodyl
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)
- prokinetic agents (e.g. prucalopride, HT4 inhibitor)
- secretagogues: linaclotide, plecanatide (increases water secretion into the intestinal lumen)
- NHE3 (sodium-proton) inhibitors: tenapanor

Upper Gastrointestinal Bleeding

Definition
- bleeding proximal to the ligament of Treitz, see *Overview of Gastrointestinal Tract, G2* (75% of GI bleeds)
  - ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Etiology
- above the GE junction
  - epistaxis
  - esophageal varices (10-30%)
  - esophagitis
  - esophageal cancer
  - Mallory-Weiss tear (10%)
- stomach
  - gastric ulcer (20%) (see *Peptic Ulcer Disease, G11*)
  - erosive gastritis (e.g. from EtOH or post-surgery) (20%)
  - gastric cancer
  - gastric antral vascular ectasia (rare, associated with cirrhosis and connective tissue disease)
  - Dieulafoy's lesion (very rare)
- duodenum
  - ulcer in bulb (25%)
  - aortoenteric fistula: usually only if previous aortic graft (see sidebar)



Always ask about NSAID/Aspirin® or anticoagulant therapy in GI bleed



Aortoenteric Fistula is a rare and lethal cause of GI bleed, most common in patients with a history of aortic graft surgery. Therefore, perform emergency endoscopy if suspected, emergency surgery if diagnosed
Note: The window of opportunity is narrow. Suspect if history of aortic graft, abdominal pain associated with bleeding



Transfusion Strategies for Acute Upper Gastrointestinal Bleeding
NEJM 2013;368:11-21
Study: Prospective, unblinded, RCT, follow-up up to 45 d.
Population: 921 patients with hematemesis, bloody nasogastric aspirate, melena, or both. Exclusion criteria included massive bleed, acute coronary syndrome, stroke/ transient ischemic attack or transfusion within previous 90 d; recent trauma/ surgery; lower GI bleed.
Intervention: Patients randomized to restrictive (<70 g/L) or liberal (<90 g/L) transfusion.
Outcome: Mortality, further bleeding, adverse events.
Results: Fewer patients in the restrictive group required transfusion (51% vs. 15%; P <0.001). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI 0.33-0.92; P=0.02. Further bleeding occurred in 10% vs. 16% (P=0.01) of patients, while adverse effects occurred in 40% vs. 48% (P=0.02) of patients in the restrictive and liberal strategies, respectively. The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI 0.11-0.85), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI 0.45-2.37) or a peptic ulcer (HR: 0.70; 95% CI 0.26-1.25).
Conclusions: Transfusing patients with an acute UGIB at Hb of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.

- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy's lesion, arteriovenous malformation)

Clinical Features
- in order of decreasing severity of the bleed: hematochezia (brisk UGIB) > hematemesis > melena > coffee ground emesis > occult blood in stool

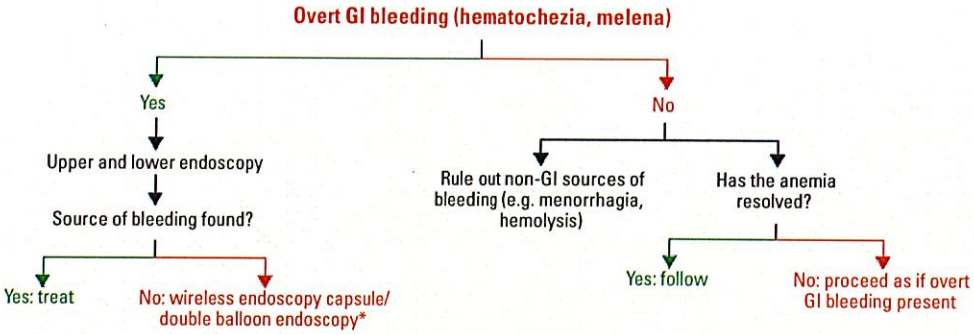
Treatment
- stabilize patient (1-2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider nasogastric (NG) tube to determine upper vs. lower GI bleeding in some cases
- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  - given to stabilize clot, not to accelerate ulcer healing
  - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h and ABx for those with cirrhosis (reduces risk of infections)
- consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach
- H2-antagonists should not be used since they have minimal impact on rebleeding rates and need for surgery
- endoscopy (EGD): establish bleeding site + treat lesion
  - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  - endoclips
  - Hemospray™
  - dual therapy (more than one therapeutic intervention method) is standard of care and has greater efficacy than single therapy

Forrest Prognostic Classification of Bleeding Peptic Ulcers

Forrest Class	Type of Lesion	Risk of Rebleed (%)
I	Arterial bleeding (oozing/spurting)	55-100
IIa	Visible vessel	43
IIb	Sentinel clot	22
IIc	Hematin covered flat spot	10
III	No stigmata of hemorrhage	5

Lancet 1974;2:394-397

Prognosis
- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding (Forrest classification): spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no high-risk predictors of rebleeding
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)



* Wireless endoscopy capsule results help double balloon endoscopy localize source of bleeding
- Angiography if overt bleeding hemodynamically significant, estimated >0.5 cc/min
- CT enterography if wireless endoscopy capsule/double balloon endoscopy not available

Figure 9. Approach to iron deficiency anemia

Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations from the International Consensus Group
Ann Intern Med 2019;171:805-822

Pre-Endoscopic Management: In patients without cardiovascular disease, the suggested Hb threshold for blood transfusion is <80 g/L. The threshold is higher for patients with cardiovascular disease.

Endoscopic Management: Patients with acute UGIB should undergo endoscopy within 24 h of presentation. In patients with high-risk stigmata, thermocoagulation and sclerosant injection are recommended. TC-325, a hemostatic powder, can be used as a temporizing agent for actively bleeding ulcers.

Pharmacologic Management: High-dose PPI should be given for 3 d to patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy. Continued oral PPI therapy is recommended twice daily for 14 d, then once daily for a duration that depends on the nature of the bleeding lesion.

Esophageal Varices

Definition
- dilated esophageal veins connecting portal and systemic circulation

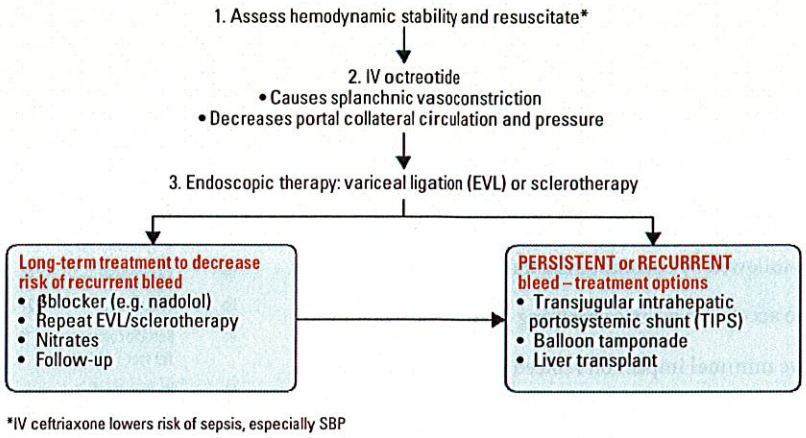
Etiology
- almost always due to portal hypertension

Clinical Features
- characteristically massive upper GI bleeding

Prognosis
- risk of bleeding: 30% in 1st yr
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

Investigations
- endoscopy

Management
- empirical treatment with broad-spectrum antibiotics (such as ceftriaxone) reduces mortality in variceal bleeding and should be initiated as soon as variceal bleeding is suspected, as early administration is associated with a lower rebleeding rate and lower mortality



If varices isolated to stomach, think of splenic vein thrombosis

Gastric varices best treated by endoscopic injection of cyanoacetate ("crazy glue")

Figure 10. Management of bleeding esophageal varices

Mallory-Weiss Tear

Definition
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

Etiology
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia often present

Clinical Features
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

Management
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

Lower Gastrointestinal Bleeding

Definition
- bleeding distal to ligament of Treitz

Etiology
- **anatomic**
  - diverticular
- **vascular**
  - angiodysplasia (small vascular malformations of the gut)
  - anorectal (hemorrhoids, fissures)
- **inflammatory**
  - infection
  - inflammatory bowel disease
  - colitis (ulcerative, infectious, radiation, ischemic) (see *Ulcerative Colitis, G25*)
- **neoplasm**
- polyp(s)
- post-polypectomy
- cancer

Lower GI Bleed

CHAND
Colitis (radiation, infectious, ischemic, IBD (UC > CD))
Hemorrhoids/fissure
Angiodysplasia
Neoplasm
Diverticular disease

Clinical Features
- hematochezia
- anemia
- occult blood in stool (no visible blood, detected via FIT)
- occasionally melena due to slow small bowel or right-colonic course

Treatment
- if blood per rectum with hemodynamic instability, stabilize patient (1-2 large bore IVs, IV fluids, monitor) and rule out upper GI source with endoscopy (EGD)
- send blood for CBC, cross and type, INR/PTT, electrolytes, BUN, Cr, LFTs
- initial examination of choice is colonoscopy to determine source of the bleeding

- if bleeding is severe or ongoing, consider radionuclide imaging or angiography (see Medical Imaging, MI16)
- treat underlying cause
  - majority of cases will stop bleeding spontaneously

Always exclude upper GI lesion before localizing the site of the bleeding to the lower GI tract

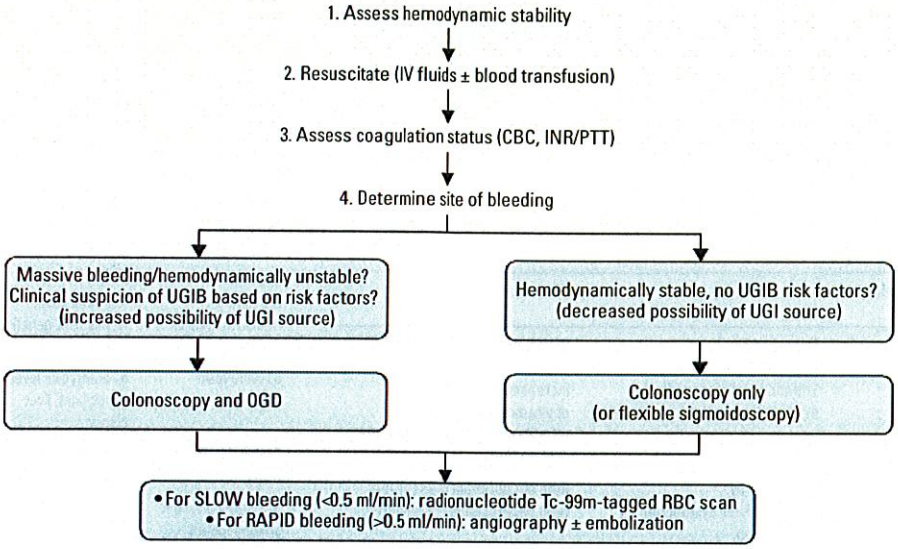


Figure 11. Approach to hematochezia

Diverticular Bleeding

Etiology
- herniation of diverticula exposes vasa recta, increasing susceptibility to disruption
- bleeding most common from the right colon (thinner walled), although diverticula often develop throughout colon

Clinical Features
- painless hematochezia, acute onset
- stool can range from bright red to dark maroon; gelatinous clots often mixed in
- 80% of diverticular bleeding resolves spontaneously without intervention

Management
- if colonoscopy identifies source (rare), hemostatic therapy can be applied
- if ongoing, can consider embolization or surgery

Infectious Colitis

Etiology
- variety of pathogens; often due to *Campylobacter, Entamoeba histolytica, Salmonella, E. coli, Shigella*
- consider travel history, food exposures

Clinical Features
- bloody diarrhea, fever, abdominal pain

Management
- stool cultures to determine pathogen and guide management
- see *Acute Diarrhea, G15*

Colorectal Carcinoma

- see General Surgery and Thoracic Surgery, GS43

Colorectal Polyps

- see General Surgery and Thoracic Surgery, GS41

Familial Colon Cancer Syndromes

- see General Surgery and Thoracic Surgery, GS42

Benign Anorectal Disease

- see General Surgery and Thoracic Surgery, GS47

Liver

Investigations of Hepatobiliary Disease

A. Tests of Liver Function

Table 17. Liver Function Tests

Test	What Do Levels Correlate With?	Increased by	How to Interpret
Prothrombin Time (PT or INR)	Hepatic protein synthesis All coagulation factors except VIII	Increased by: Hepatocellular dysfunction Vitamin K deficiency (due to malnutrition, malabsorption, etc.)	PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction
Serum Albumin	Hepatic protein synthesis (and other causes listed in next column)	Decreased by: Hepatocellular dysfunction Malnutrition Renal or GI losses Significant inflammation Malignancy	Rule out potential causes other than hepatocellular dysfunction
Serum Direct Bilirubin*	Hepatic excretion from hepatocyte to biliary system	Increased by: Liver dysfunction	Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction

*Serum Bilirubin
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect bilirubin = unconjugated

B. Tests of Liver Injury

Table 18. Liver Enzyme Profile

Profile	Liver Enzyme Change	Notes
Hepatocellular	↑ AST ↑ ALT	AST from multiple sources (especially muscle) ALT more specific to liver Elevation of both highly suggestive of liver injury
Cholestatic	↑ ALP ↑ GGT	Cholestasis = stasis of bile flow If ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT If ALP elevation out of proportion to ALT/AST elevation, consider: • Obstruction of common bile duct (e.g. extraluminal = pancreatic cancer, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths) • Predominant rise in hepatocellular enzyme possible in acute biliary obstruction secondary to a stone due to the sudden impairment in bile flow and because ALP is an inducible enzyme which takes time to rise • Destruction of microscopic ducts (e.g. PBC) • Bile acid transporter defects (e.g. drugs, intrahepatic cholestasis of pregnancy) • Infiltration of the liver (e.g. liver metastases, lymphoma, granulomas, amyloid)

Acute Viral Hepatitis (General)

Definition
- viral hepatitis lasting <6 mo

Clinical Features
- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - N/V, anorexia, headaches, fatigue, myalgia, low-grade fever, arthralgia, and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

Quick Reference Diagnostic Tests for Common Liver Conditions

Disease	Diagnostic Tests
Viral Hepatitis	Anti-HAV IgM, HBsAg, anti-HCV
Autoimmune Hepatitis	ANA, SMA, LKM, IgG levels
Wilson's Disease	Ceruloplasmin, liver biopsy
Hereditary Hemochromatosis	Iron saturation, ferritin, HFE genetic testing
α1-Antitrypsin Deficiency	α1-antitrypsin levels/ genotyping, liver biopsy
Drug-induced Liver Injury	Careful medication history, liver biopsy
NAFLD/Nonalcoholic Steatohepatitis (NASH)	U/S, metabolic testing, liver biopsy

ANA = anti-nuclear antibody; SMA = smooth muscle antibody; LKM = liver-kidney microsomal-1 antibody; HFE = hemochromatosis gene

DDx for Hepatomegaly
- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
- Malignant (primary, secondary, lymphoproliferative, leukemia)
- Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
- Infectious (viral, tuberculosis, abscess, echinococcus)
- Inflammatory (granulomas (sarcoid), histiocytosis X)

All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver. Factor VIII is also produced in the endothelium. In cirrhosis, risk of bleeding does not correlate closely with elevations in INR/ PTT since so many of the proteins in the coagulation cascade are affected

ALT > AST = most causes of hepatitis
AST > ALT = alcoholic liver disease or other causes of hepatitis (i.e. non-alcoholic liver disease) that have progressed to advanced cirrhosis

Serum Transaminases >1000 due to
- Viral hepatitis
- Drugs/toxins
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone

Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly IgM antibody directed to the virus

Treatment
- supportive (hydration, diet)
- usually resolves spontaneously, but if severe HBV infection, treatment with antiviral agent such as tenofovir or entecavir can be considered; in acute hepatitis C, antiviral treatment should be considered (see *Hepatitis C Virus, G34*)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia

Complications
- cholestasis (most commonly associated with HAV infection)
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Hepatitis A Virus

- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice, hepatomegaly
- can cause ALF and subsequent death (<1-5%)
- can relapse (rarely), but never becomes chronic
- treatment is supportive (no specific treatments available, disease is often self-limiting)
- preventable by vaccination

Hepatitis B Virus

Table 19. Hepatitis B Serology

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	Liver Enzymes
Acute HBV	+	–	+	–	IgM	
Chronic (HBe-Ag positive) HBV (generally high HBV-DNA)	+	–	+	–	IgG	ALT, AST may or may not be elevated
Chronic (HBe-Ag negative) HBV (generally low HBV-DNA)	+	–	–	+	IgG	ALT, AST may or may not be elevated
Resolved Infection	–	±	–	±	IgG	
Immunization	–	+	–	–	–	

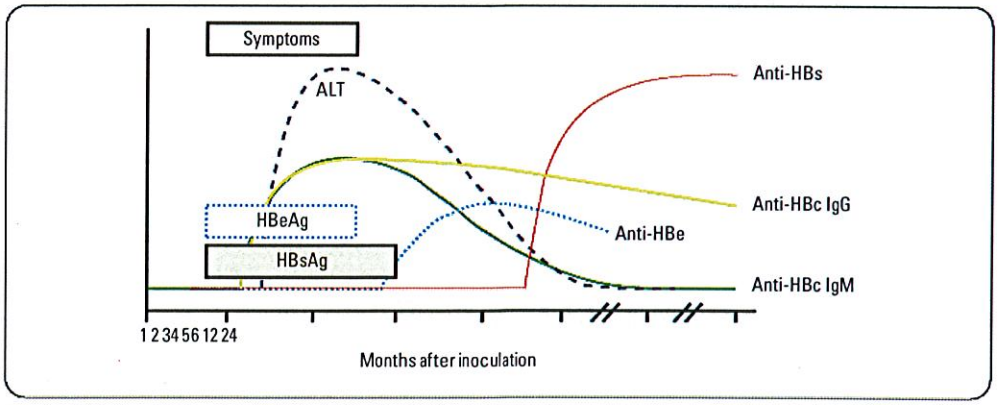


Figure 12. Time course of acute hepatitis B infection

Alcoholic Hepatitis: history of chronic EtOH use (possibly with recent increased consumption, although often patient may have stopped drinking in the days-weeks prior to presentation due to symptoms), RUQ abdominal pain, AST/ALT >2, AST usually <300, low grade fever, mildly elevated WBC

Major Sources of ALP
Hepatobiliary tree
Bone
Placenta
Intestine

DDx for Hepatitis
Viral infection
Alcohol
Drugs
Immune-mediated
Toxins

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury

Risk of HCC in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis, and serum HBV-DNA
Risk of HCC in HCV increases only after cirrhosis develops

HCV (and HBV) treatment lowers the risk of HCC

Risk Factors for Progression
EtOH
HIV coinfection
Old age at diagnosis

Epidemiology

- 4 phases of chronic hepatitis B: not all carriers will go through all 4 phases, but all carriers will have positive HBsAg
    1. **immune tolerance**: extremely high HBV-DNA (>20000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or 'incubation period' in adult with newly-acquired HBV)
    2. **immune clearance (or immunoactive):** HBV-DNA levels (>20000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or HCC); likely to benefit from treatment
    3. **inactive carrier (immune control):** lower HBV-DNA (<2000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
    4. **HBeAg-negative chronic hepatitis (immune escape) ("core or precore mutant"):** elevated HBV-DNA (>2000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or HCC); likely to benefit from treatment

Treatment

- counselling: 40% of men and 10% of women with perinatal infection without treatment will die from HBV-related complications
- HCC screening with U/S q6 mo, especially if high serum HBV-DNA levels, cirrhosis, men, (ages >40 in Asian men, >50 in Asian women, and >20 in African descent)
- contexts to consider pharmacological therapy:
    1. HBeAg positive and HBV-DNA >20000 IU/mL and elevated ALT
    2. HBeAg negative and HBV-DNA >2000 IU/mL and elevated ALT with or without stage ≥2 fibrosis on liver biopsy
    3. to prevent flare when placed on immunosuppressive therapy such as prednisone, chemotherapy, biologics, etc.
- treatment goal: reduce serum HBV-DNA to undetectable level
    - prolonged immune-mediated damage leads to higher risk of liver fibrosis
- treatment options: tenofovir, entecavir, lamivudine (not preferred due to high rate of developing resistance)
- vaccinate against HAV if serology negative (to prevent further liver damage)
- follow blood and sexual precautions
- vaccinate household contacts

Hepatitis D Virus

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with HBV; causes more aggressive disease than HBV alone
- coinfection: acquire HDV and HBV at the same time
- superinfection: new acquisition of HDV on a background of chronic HBV infection (e.g. injection drug users)
- HDV can present as ALF and/or accelerate progression to cirrhosis
- treatment: low-dose interferon (20% response) and liver transplant for end-stage disease

Hepatitis C Virus

- RNA virus (7 genotypes; genotype 1 is most common in North America)
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- acute hepatitis C occurs 2-6 mo after transmission
    - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage
    - almost 30% of cases of acute hepatitis C are cleared spontaneously without therapy

Diagnosis

- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- normal hepatocellular enzymes does not rule out active disease or presence of advanced fibrosis
- abdominal U/S and transient elastography (FibroScan®) to assess the staging of the disease and the degree of fibrosis



In acute hepatitis B, HDV coinfection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis



Causes of Elevated Serum Transaminases in Chronic Hepatitis B
Active hepatitis (either immune clearance phase in HBeAg-positive individuals or HBeAg-negative active hepatitis)
Reactivation (e.g. due to immunosuppression)
Hepatitis D
Other liver insult (fatty liver, EtOH, drugs, hepatitis A)



Risk Factors for Contracting Hepatitis B
Infants born to a hepatitis B-infected parent (maternal or paternal)
Unprotected sexual intercourse (especially if multiple partners)
Needle sharing (e.g. injection drug users)
Travel to endemic regions
Exposure to human blood, semen, and other bodily fluids



Clinical Features of Hepatitis B
Many patients are asymptomatic, both in the acute and chronic phases
Acute hepatitis can manifest as jaundice, nausea, arthritis, or constitutional symptoms
Patients with chronic hepatitis can be asymptomatic, experience exacerbations, develop extrahepatic complications (e.g. glomerular disease), or develop cirrhosis

Treatment

- blood-borne precautions; vaccinate for hepatitis A and B if serology negative; avoid EtOH
- clearest indication for treatment is in subgroups likely to develop clinically significant liver disease, i.e. persistently elevated transaminases, liver biopsy showing moderate-advanced fibrosis/cirrhosis, and at least moderately severe necrosis/inflammation
  - now that a safe, effective cure is available, the risk/benefit ratio favours treating everyone with chronic hepatitis C
- choice and duration of treatment depends mostly on whether patient is cirrhotic (and if so, whether decompensated or not), prior treatment history, and possibly genotype (but less so with availability of pan-genotypic therapies)
- direct acting antiviral (DAA) tablets (Maviret®, a combination of glecaprevir and pibrentasvir, and Epclusa®, a combination of velpatasvir and sofosbuvir) are the most commonly used
- other oral interferon-free regimens (for all genotypes) (e.g. sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir+dasabuvir, or elbasvir/grazoprevir, and sofosbuvir/velpatasvir) are also available but used less frequently
- it is important to check for hepatitis B prior to therapy as direct acting antivirals may lead to reactivation of hepatitis

Prognosis

- 80% of acute hepatitis C cases become chronic (of these, 20% evolve to cirrhosis within 20 years of exposure)
- risk of HCC increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

Table 20. Characteristics of the Viral Hepatitides

	HAV	HBV	HCV	HDV	HEV	CMV	EBV	Yellow Fever
Virus Family	*Picomaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Deltaviridae*	*Caliciviridae*	*Herpesviridae*	*Herpesviridae*	*Flavivirus*
Genome	RNA	DNA	RNA	RNA	RNA	DNA	RNA	RNA
Envelope	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Transmission	Fecal-oral	Parenteral/sexual or equivalent Vertical	Parenteral/sexual (transfusion, IV drug user, sexual (<HBV)) 40% have no known risk factors	Non-parenteral (close contact in endemic areas) Parenteral (blood products, IV drug user) —sexual transmission is inefficient	Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)	Close contacts, most body fluids	Saliva-oral	Vector (mosquito)
Incubation	4-6 wk	6 wk-6 mo	2-26 wk	3-13 wk	2-8 wk	20-60 d	30-50 d	3-6 d
Onset	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt	Variable	Variable	Usually abrupt
Communicability	2-3 wk in late incubation to early clinical phase Acute hepatitis in most adults, 10% of children	HBsAg+ state highly communicable Increased during third trimester or early post-partum	Communicable prior to overt symptoms and throughout chronic illness	Infectious only in presence of HBV (HBsAg required for replication)	Unknown	Variable – dormant or persistent	Highly communicable during year after primary infection but never zero	Variable, vector-dependent
Chronicity	None, although can relapse	5% adults, 90% infants	80%, 20% of which develop cirrhosis	5%	None	Common; latent	Common; latent	Infection confers lifelong immunity
Serology	Anti-HAV (IgM)	See *Table 19, G33*	HCV-RNA Anti-HCV (IgG/IgM)	HBsAg Anti-HDV (IgG/IgM)	Anti-HEV (IgG/IgM)	Anti- CMV (IgM/IgG)	Monospot; anti-EBV IgM/IgG, EBV-DNA quantitation	Anti-YF (IgM/IgG)
Vaccine	Havrix®, 2 doses q6 mo, combined with Twinrix® at 0, 7, and 21 d	Recombivax® HBTM, ages 11-15, 2 doses q6 mo	No	No	No	No	No	YF-VAX®, 1 dose booster q10 yr
Management	General hygiene Treat close contacts (anti-HAV Ig) Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune	Prevention: HBV vaccine and/or hepatitis B Ig (HBIg) for needlestick, sexual contact, infants of infected mothers (unless already immune) Rx: oral antivirals vs. interferon if indications met	Prevention: no vaccine Rx: interferon + ribavirin ± protease inhibitor; although all oral antiviral (IFN-free) therapies now available are highly efficacious	Prevention: HBV vaccine	Prevention: general hygiene, no vaccine	In high-risk transplant patients: CMV Ig and antivirals (ganciclovir, valganciclovir)	Supportive treatment post-infection	Prevention: vaccine Supportive treatment post infection
Acute Mortality	0.1-0.3%	0.5-2%	1%	2-20% coinfection with HBV, 30% superinfection Predisposes HBV carriers to more severe hepatitis and faster progression to cirrhosis	1-2% overall, 10-20% in pregnancy	Rare in immunocompetent adults	Rare	20-60% in developing countries
Oncogenicity	No	Yes	Yes	Yes	No	No	Yes	No
Complications	Can cause ALF and subsequent death (<1-5%)	HCC secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda	HCC in 2-5% of cirrhosis per yr, cryoglobulinemia, B-cell non-Hodgkin lymphoma	Leukocytoclastic vasculitis, membranous glomerulonephropathy	Mild, except in third trimester (10-20% ALF)	5% of newborns with multiple handicaps Immunocompromised patients at risk of CMV-induced hepatitis, retinitis, colitis, esophagitis, pneumonitis	Associated with Burkitt's lymphoma and nasopharyngeal carcinoma (rare in Western world)	Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates

Autoimmune Liver Disease

- diagnosis of exclusion: rule out viruses, drugs/EtOH, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
  - hypergammaglobulinemia (particularly elevated IgG)
  - typical auto-antibodies: ANA and/or anti-smooth muscle antibody
  - infrequently may see anti-LKM elevation (liver kidney microsome), especially in children
  - can have false positive viral serology (especially anti-HCV)
  - biopsy – periportal (zone 1) and interface inflammation and necrosis
- treatment: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

Drug-Induced Liver Disease

Table 21. Classification of Hepatotoxins

	Predictable	Idiosyncratic
Example	Acetaminophen, CCl4	Phenytoin, INH
Dose-Dependence	Usual	Unusual
Latent Period	Hours-days	Weeks-months
Host Factors	Not important	Very important



Hy's Law: drug-induced hepatocellular jaundice indicates a mortality of at least 10%

- many different patterns of liver injury (i.e. hepatocellular, cholestatic, mixed, granulomatous, ALF) can be seen in drug-induced liver injury and thus this requires a high index of suspicion
- see: LiverTox for Information regarding drug-specific risks and patterns of hepatotoxicity (http://livertox.nih.gov)

Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause ALF (transaminases >1000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy individuals, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite (NAPQI (n-acetyl-p-benzoquinone imine)) is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: nausea and vomiting (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with ALF or resolution
    - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emesis (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC – Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given regardless of time of ingestion)
      - promotes hepatic glutathione regeneration
    - no recorded fatal outcomes if NAC given before increase in transaminases
    - NAC use should be determined by the Rumack-Matthew nomogram or if unclear, time of ingestion
- antimicrobials are the most common class of causative agent (e.g. amoxicillin-clavulanate, isoniazid, nitrofurantoin, sulfamethoxazole-trimethoprim)
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia
- Isoniazid (INH)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- Methotrexate (MTX)
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methyldopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: khat, chaparral, Chinese herbs (e.g. germander, comfrey, bush tea). Weight loss supplements (containing green tea extract) have been associated with cases of acute liver failure. Body-building supplements have been associated with prolonged cholestatic jaundice)

Wilson's Disease

Definition
- autosomal recessive defect in copper elimination (gene *ATP7B*)

Etiology
- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin
- worldwide incidence: 1 in 40000

Clinical Features
- liver: acute hepatitis, ALF, chronic active hepatitis, cirrhosis, low-risk of HCC
- eyes: Kayser-Fleischer rings (copper deposits in Descemet's membrane); more common in patients with CNS involvement, present in only 50% of isolated liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi's syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications

Investigations
- suspect if increased liver enzymes with clinical manifestations at young age (<40); especially combination of liver disease with dystonia, psychiatric symptoms
- screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion (measure 24-hour urine copper)
- gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible
- first-degree relatives should also be considered for screening

Treatment
- 4 drugs available
  1. penicillamine: chelates copper, but poorly tolerated
  2. trientine: chelates copper
  3. zinc: impairs copper excretion in stool and decreases copper absorption from gut. Often used as maintenance therapy or in neurologic presentations
  4. tetrathiomolybdate: preferred if neurological involvement
- hepatic presentations are best treated with a trientine + zinc combination
- liver transplant in severe cases of liver failure

Clinical Manifestations of Wilson's Disease

ABCD
Asterixis
Basal ganglia degeneration: suspect if parkinsonian features in the young
Ceruloplasmin decreases
Cirrhosis
Corneal deposits (Kayser-Fleischer ring)
Copper
Dementia

Hemochromatosis

Definition
- excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body iron stores increased to 20-40 g (normal 1 g)

Etiology
- primary (hereditary) hemochromatosis
  - usually related to HFE mutation (see Epidemiology below)
  - decreased hepcidin production results in increased GI absorption and tissue iron deposition despite adequate iron stores
- secondary hemochromatosis
  - parenteral iron overload (e.g. transfusions, hemodialysis, parenteral iron injections)
  - excessive oral iron intake (e.g. dietary iron overload)
  - other liver diseases (e.g. EtOH, NAFLD, viral hepatitis)
  - iron-loading anemias (hemolytic, sideroblastic, aplastic, thalassemia major)
  - ineffective erythropoiesis

Epidemiology
- classic hereditary hemochromatosis most common in Northern European descent
- mainly caused by mutations in the *HFE* gene (e.g. C282Y/C282Y, C282Y/H63D), which has a homozygous genetic prevalence of 1/400
  - C282Y/H63D only potentially causative as compound heterozygote
- very rare non-HFE mutations also exist (e.g. ferroportin, hemojuvelin, hepcidin, aceruloplasminemia)

Hemochromatosis Clinical Features

ABCDH
Arthralgia
Bronze skin
Cardiomyopathy, cirrhosis of liver
Diabetes (pancreatic damage)
Hypogonadism (anterior pituitary damage)

Clinical Features
- usually presents with trivial elevation in serum transaminases although often picked up incidentally when iron studies noted to be elevated
- liver: cirrhosis (less common nowadays due to earlier detection), HCC (200x increased risk)
- pancreas: DM, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: diastolic dysfunction and arrhythmias in early stages with dilated cardiomyopathy in later stages
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially metacarpophalangeal joints), chondrocalcinosis

Ferritin may never normalize if other causes of high ferritin present (e.g. fatty liver from metabolic syndrome or EtOH)

Investigations
- screening for individuals with clinical features and/or family history (25% chance of sibling having the disease)
  - transferrin saturation (free Fe^{2+}/total iron binding capacity (TIBC)) >45%
  - serum ferritin >400 ng/mL
  - *HFE* gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- MRI (often used instead of a liver biopsy)
  - non-invasive approach to assess iron overload
  - most sensitive and specific modality in the diagnosis of hemochromatosis
  - serum ferritin >1000 ng/mL or symptoms of organ injury (e.g. elevated LFTs, symptoms of heart failure)
  - can be used to follow treatment by phlebotomies
- liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
  - markers of advanced fibrosis: if any of the following are present at the time of diagnosis → ages >40, elevated liver enzymes, or ferritin >1000 ng/mL
  - considered if compound heterozygote and potential other cause of liver injury (e.g. NAFLD, excess EtOH, hepatitis)
  - if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
- HCC screening if cirrhosis

Treatment
- phlebotomy: weekly or q2 wk then lifelong maintenance phlebotomies q2-6 mo, generally aiming for ferritin of 50-100 ng/mL
- chelation therapy such as deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

Prognosis
- normal life expectancy if treated before the development of cirrhosis or DM

Alcoholic Liver Disease

Definition
- spectrum of diseases, ranging from:
  - fatty liver (common amongst individuals with EtOH use disorder): reversible if EtOH stopped
  - alcoholic hepatitis (35% of individuals with EtOH use disorder): usually reversible if EtOH stopped
  - cirrhosis (10-15% of individuals with EtOH use disorder): irreversible

Standard Drink Equivalent
1 standard drink = 14 g EtOH
= 12 oz beer (5% alcohol)
= 5 oz wine (12-17%)
= 3 oz fortified wine (17-22%)
= 1.5 oz liquor (40%)
Tip: percentage EtOH multiplied by oz in 1 standard drink roughly equals 60

Pathophysiology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde
  - reduces NAD+ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- EtOH increases gut permeability leading to increased bacterial translocation
- EtOH metabolism causes:
  - relative hypoxia in liver zone III (near central veins; poorly oxygenated) > zone I (around portal tracts, where oxygenated blood enters)
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

Biopsy + Histology of Alcoholic Hepatitis (triad)

Hepatocyte necrosis with surrounding inflammation in zone III

Mallory bodies (intracellular eosinophilic aggregates of cytokeratins)

Chicken-wire fibrosis (network of intralobular connective tissue surrounding cells and venules)

Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10-20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of EtOH consumed above threshold
- clinical findings do not accurately predict type of liver involvement
- fatty liver
  - mildly tender hepatomegaly; jaundice rare
  - mildly increased transaminases <5x normal
- alcoholic hepatitis
  - variable severity: mild to fatal liver failure
  - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice, and mildly elevated INR)
  - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased WBC count – mimics right lower lobe pneumonia and cholecystitis

Investigations
- blood tests are non-specific, but in general
  - AST:ALT >2:1 (both usually <300)
  - CBC: increased mean corpuscular volume (MCV), increased WBC often seen with alcoholic hepatitis but not necessarily in other alcohol-related liver injury
  - increased GGT

Treatment
- alcohol cessation (see Psychiatry, PS28)
  - Alcoholics Anonymous (or similar programs), disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
- prednisolone if severe alcoholic hepatitis based on Maddrey's discriminant function or Model for End-Stage Liver Disease (MELD) score as described in Prognosis
  - pentoxifylline less used since most definitive trial did not demonstrate efficacy

Prognosis
- Maddrey's discriminant function (based on PT and bilirubin) and MELD predict mortality and guide treatment (consideration of corticosteroids for severe disease based on Maddrey ≥32 or MELD ≥21)
- bilirubin response at day 7 of corticosteroids (Lille model) also factors into prognosis and decision on whether to continue full course of corticosteroids if started
- fatty liver: complete resolution with cessation of EtOH intake
- alcoholic hepatitis mortality
  - immediate: 30%-60% in the first 6 mo if severe
  - with continued EtOH: 70% in 5 yr
  - with cessation: 30% in 5 yr

Non-Alcoholic Fatty Liver Disease

Definition
- spectrum of disorders characterized by macrovesicular hepatic steatosis, sometimes with inflammation and/or fibrosis
- most common cause of liver disease in North America

Etiology
- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- histological changes indistinguishable from those of alcoholic hepatitis despite negligible history of EtOH consumption

Risk Factors
- component of the metabolic syndrome along with obesity, T2DM, HTN, hypertriglyceridemia
- other less common causes such as medications (e.g. tamoxifen, corticosteroids, MTX), Wilson's, TPN, rapid weight loss, and others

Clinical Features
- often asymptomatic
- may present with fatigue, malaise, and vague RUQ discomfort

Investigations
- elevated serum AST, ALT ± ALP; AST/ALT <1
- presents as echogenic liver texture on U/S
- non-invasive testing of fibrosis: FIB4, NAFLD fibrosis score, FibroTest™, FibroScan®
- liver biopsy cannot distinguish fatty liver from alcoholic vs. non-alcoholic, but considered when investigating alternative etiologies or assessing for level of fibrosis



GI Complications of Alcohol Use

Esophagus
Mallory-Weiss tear
Esophageal varices (secondary to portal hypertension)

Stomach
Alcoholic gastritis

Pancreas
Acute pancreatitis
Chronic pancreatitis

Liver
Alcoholic hepatitis
Fatty liver
Cirrhosis
Hepatic encephalopathy
Portal hypertension
Ascites
HCC

Treatment
- mainstay is gradual weight loss (0.5-1 kg/wk) as rapid weight loss can worsen liver disease
  - ideally, aim to lose at least 7-10% of body weight
- evidence for the use of pharmacologic agents such as pioglitazone and liraglutide, but potential benefits must be balanced with associated adverse effects (e.g. weight gain and CHF with pioglitazone)
- some evidence for vitamin E (800 IU daily) if there is hepatic inflammation in non-diabetic, non-cirrhotic patients
- some evidence for benefits of coffee drinking (3 cups/d) and vitamin D
- consideration for bariatric surgery
- GLP-1 analogues (e.g. semaglutide) do not appear to directly improve liver inflammation in NAFLD, but may indirectly help through promotion of weight loss

Prognosis
- main causes of death, particularly in non-cirrhotic group, are cardiovascular disease and malignancy
- better prognosis than alcoholic hepatitis
  - <25% progress to cirrhosis over a 7-10 yr period
- risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: obesity, T2DM, age, metabolic syndrome, higher levels of fibrosis

Acute Liver Failure (formerly Fulminant Hepatic Failure)

Definition
- severe decline in liver function characterized by coagulation abnormality (INR >1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)



Figure 13. Progression of liver dysfunction based on liver function tests – the "W"

Etiology
- drugs (especially acetaminophen), hepatitis B (measure anti-HBc, IgM fraction because sometimes HBV-DNA and even HBsAg rapidly become negative), hepatitis A, hepatitis C (rare), ischemic, autoimmune hepatitis, Wilson disease, idiopathic

Treatment
- correct hypoglycemia, monitor level of consciousness, prevent GI bleed with PPI, monitor for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value of biopsy is to exclude chronic disease, less helpful for prognosis
- liver transplant (King's College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), ages <10 or >40, cause is drug or unknown, bilirubin >300 µmol/L, INR >3.5, creatinine >200 µmol/L

Cirrhosis

Definition
- liver damage characterized by diffuse distortion of the basic architecture with fibrosis and formation of regenerative nodules
- biopsy gold standard for diagnosis
- compensated cirrhosis = absence of complications, can last for 10-20 yr with almost normal life expectancy
- decompensated cirrhosis = development of complications such as ascites (most common), variceal bleeding, encephalopathy

Etiology
- fatty liver (alcoholic or NAFLD)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- drugs (e.g. chronic MTX or amiodarone use)
- hereditary hemochromatosis
- PBC
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent "burnt-out non-alcoholic steatohepatitis (NASH)")
- rare: Wilson's disease, Gaucher's disease, α1-antitrypsin deficiency

MELD-Na (Model for End-Stage Liver Disease)
Predicts 3 mo survival and used to stratify patients on transplant list
Based on creatinine, INR, total bilirubin, and serum sodium concentration

MELD 3.0
Updated score that includes new variables such as female sex and serum albumin

Investigations

- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive
- blood work
  - fall in platelet count <150 is the earliest finding
  - in late stages of cirrhosis, rise in INR, fall in albumin, rise in bilirubin
  - elevated bilirubin is usually seen in more advanced disease or in the setting of a concurrent insult
  - in very advanced cirrhosis (pre-terminal event), may also see hypoglycemia but this is more often a feature seen in severe ALF
- FibroTest™: combination of various clinical and biochemical markers that can predict degree of fibrosis
- imaging
  - U/S is the primary imaging modality but only finds advanced cirrhosis
  - CT to look for varices, nodular liver texture, splenomegaly, ascites
  - transient elastography (FibroScan®): non-invasive tool using elastography for measuring liver compliance (variable availability)
    - rapidly replacing liver biopsy to determine extent of liver fibrosis and make the diagnosis of cirrhosis
- gastroscopy: varices or portal hypertensive gastropathy

Treatment

- treat underlying disorder
- decrease insults (e.g. EtOH cessation, hepatotoxic drugs, immunize for hepatitis A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease; use MELD score (e.g. MELD ≥15)

Table 22. Child-Pugh Score and Interpretation

Classification	1	2	3
Serum bilirubin (μmol/L)	<34	34-51	>51
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Presence of ascites	Absent	Controllable	Refractory
Encephalopathy	Absent	Minimal	Severe
Interpretation			
Points	**Class**	**Life Expectancy**	**Perioperative Mortality**
5-6	A	15-50 yr	10%
7-9	B	Candidate for transplant	30%
10-15	C	1-3 mo	82%

Score: 5-6 (Child's A), 7-9 (Child's B), 10-15 (Child's C)
*Note: Child's classification is rarely used for shunting (TIPS or other surgical shunts), but is still useful to quantitate the severity of cirrhosis

Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds
  - 1/2 of patients with cirrhosis have gastroesophageal varices and 1/3 of these develop hemorrhage with an overall mortality of >30%
  - HVPG ≥10 mmHg is the strongest predictor of variceal development
  - treatment: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to overdiuresis)
    - acute tubular necrosis
    - HRS
      - type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
    - HRS can occur at any time in severe liver disease, especially after:
      - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
      - GI bleed
      - sepsis



Cirrhosis Complications

VARICES
Varices
Ascites/Anemia
Renal failure (HRS)
Infection
Coagulopathy
Encephalopathy
Sepsis



Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC



Hepatorenal Syndrome vs. Pre-Renal Failure – Difficult to Differentiate
Similar blood and urine findings
Urine sodium: very low in hepatorenal; low in pre-renal
IV fluid challenge: giving volume expanders improves pre-renal failure, but not HRS



Hepatopulmonary Syndrome

Clinical Triad
Liver disease
Increased alveolar-arterial gradient while breathing room air
Evidence for intrapulmonary vascular abnormalities



Fibrosis may regress and disappear if cause of liver injury is treated or resolves

- treatment for HRS (generally unsuccessful at improving long-term survival)
  - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
  - definitive treatment is liver transplant

- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though may be due to other chronic liver diseases, such as non-cirrhotic portal HTN
  - thought to arise from:
    - ventilation-perfusion mismatch (intrapulmonary shunting and limitation of oxygen diffusion)
    - failure of damaged liver to clear circulating pulmonary vasodilators and/or increased production of vasodilators by liver
  - clinical features
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency), and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

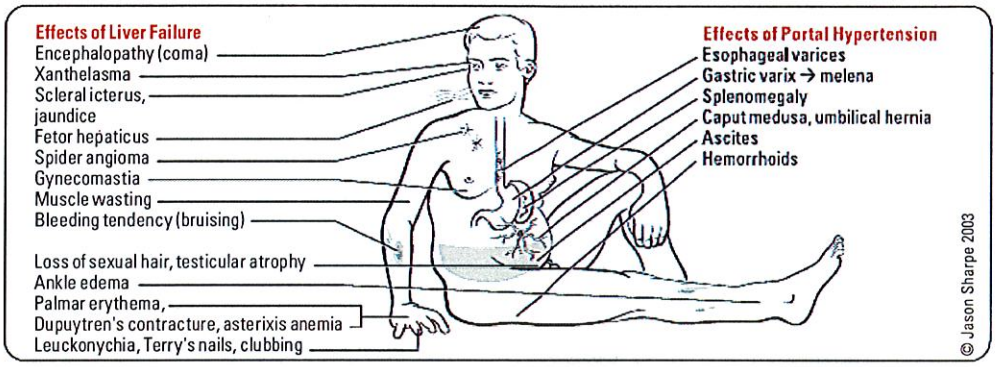


Figure 14. Clinical features of liver disease

Hepatocellular Carcinoma

- see General Surgery and Thoracic Surgery, GS53

Liver Transplantation

- see General Surgery and Thoracic Surgery, GS54

Portal Hypertension

Definition

- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology

- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

Complications

- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Portal Hypertension

Signs
- Esophageal varices
- Melena
- Splenomegaly
- Ascites
- Hemorrhoids

Management
- β-blockers
- Nitrates
- Shunts (e.g. TIPS)

Treatment
- non-selective β-blockers (propranolol, nadolol, carvedilol) decrease risk of bleeding from varices; PREDESCI trial (Lancet 2019;393:1597-1608) showed that non-selective β-blockers in cirrhotic patients with portal hypertension lowers risk of decompensation (particularly ascites)
- TIPS: to decrease portal venous pressure
  - radiologically inserted stent between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute variceal bleeding or prevent rebleeding or treat ascites
  - complications: hepatic encephalopathy, right sided heart failure, deterioration of hepatic function
  - contraindicated with severe liver dysfunction, uncontrolled hepatic encephalopathy, and congestive heart failure

Hepatic Encephalopathy

Definition
- spectrum of potentially reversible neuropsychiatric syndromes secondary to hepatic insufficiency and/or portosystemic shunting, diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

Pathophysiology
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (SBP)
- deterioration in hepatic function or superimposed liver disease
- spontaneous portosystemic shunts (e.g. splenorenal shunts) or intentional portosystemic shunts (e.g. TIPS)

Stages
A. minimal hepatic encephalopathy (diagnosed with specialized cognitive testing)
B. overt hepatic encephalopathy (stages I to IV)
  - I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
  - II: asterixis, lethargy, drowsiness, disorientation
  - III: stupor (rousable), hyperactive reflexes, extensor plantar response (positive Babinski sign)
  - IV: coma (response to painful stimuli only)

Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out:
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. EtOH withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves
- serum ammonia levels increased, but not often necessary to measure in routine clinical use

Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - routine protein restriction is no longer recommended given patients generally have concurrent malnutrition and muscle wasting; however, vegetable protein (as opposed to animal protein) may help reduce risk of encephalopathy
  - lactulose or lactitol: titrated to achieve 2-3 soft stools/d
    - prevents diffusion of NH_3 (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH_4^+ (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
- oral rifaximin for both acute treatment and maintenance therapy has high level evidence for efficacy
- best acute treatment in patients who cannot take medication orally is lactulose or lactitol enemas





Precipitating Factors for Hepatic Encephalopathy

HEPATICS
Hemorrhage in GI tract/Hypokalemia
Excess dietary protein
Paracentesis
Alkalosis/Anemia
Trauma
Infection
Colon surgery
Sedatives



A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin plus Lactulose with Lactulose Alone in Treatment of Overt Hepatic Encephalopathy
American J Gastroenterol 2013;108:1458-1463
Study: Prospective double-blinded RCT.
Purpose: Efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of overt HE.
Results: Of the patients, 48 (76%) in group A (lactulose plus rifaximin 1200 mg/d, n=63) compared with 29 (50.8%) in group B (lactulose plus placebo, n=57) had complete reversal of HE (P<0.004). There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose plus placebo (23.8% vs. 49.1%, P<0.05). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, P=0.01), whereas there were no differences because of GI bleed (group A vs. group B: 4:4, P=nonsignificant (NS)) and HRS (group A vs. group B: 4:7, P=NS). Patients in the lactulose plus rifaximin group had shorter hospital stay (5.8±3.4 vs. 8.2±4.6 d, P=0.001).
Conclusion: Combination of lactulose plus rifaximin is more effective than lactulose alone in the treatment of overt HE.

Ascites

Definition
- accumulation of excess fluid in the peritoneal cavity

Etiology

Table 23. Serum-Ascites Albumin Gradient in the Evaluation of Ascites

Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL) Portal Hypertension Related	Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL) Non-Portal Hypertension Related
Cirrhosis/severe hepatitis	Peritoneal carcinomatosis
Chronic hepatic congestion (right heart failure, Budd-Chiari)	Peritoneal TB
Massive liver metastases	Pancreatic disease
Portal vein thrombosis	Serositis
Idiopathic portal fibrosis	Nephrotic syndrome*

* In nephrotic syndrome: decreased serum [Alb] to begin with, therefore gradient not helpful

Pathophysiology
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis
  - overfill hypothesis
  - peripheral arterial vasodilation theory (most popular): as portal hypertension develops in cirrhosis, production of local mediators such as nitric oxide leads to splanchnic arterial vasodilation, ultimately pulling blood away from the systemic circulation and resulting in reduced effective arterial volume, which causes compensatory sodium and fluid retention by the kidneys (i.e. circulatory volume is increased, as per the overfill hypothesis, but effective volume is decreased as per the underfill hypothesis)

Underfill Hypothesis
First step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney

Overfill Hypothesis
Cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily

Diagnosis
- abdominal U/S
- physical exam (clinically detectable when >500 mL)
  - bulging flanks, flank dullness, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

Investigations
- diagnostic paracentesis
  - 1st aliquot: cell count and differential
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

Serum Ascites Albumin Gradient (SAAG) = serum albumin – ascites albumin
>11 g/L portal HTN
Ascitic fluid total protein >25 g/L, suggests cardiac portal hypertension
Ascitic fluid total protein <25 g/L, suggests cirrhosis portal hypertension
<11 g/L unrelated to portal HTN

Treatment
- diuretic-sensitive ascites
  - Na^+ restriction (daily sodium intake <2 g)
  - no need for fluid restriction unless significant hyponatremia (e.g. Na^+ <120-125 mmol/L)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - if target weight loss is not achieved and there are no complications, increase dose to achieve target while monitoring for complications
- refractory ascites (diuretics are inadequate or not tolerated)
  - therapeutic paracentesis with IV albumin
  - TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
  - liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis is associated with a high 2 yr mortality

Complication: Primary/Spontaneous Bacterial Peritonitis
- primary/SBP
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: *E. coli* (most common), *Streptococcus, Klebsiella*

- diagnosis
  - absolute neutrophil count in peritoneal fluid >0.25x10^9 cells/L (250 cells/mm ^{3})
  - Gram stain positive in only 10-50% of patients
  - culture positive in <80% of patients (not needed for diagnosis)
- prophylaxis: consider in patients with:
  - cirrhotic with GI bleed: ceftriaxone IV daily or norfloxacin BID x 7 d
  - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
- treatment
  - IV ABx (cefotaxime 2 g IV q8h or ceftriaxone 2 g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
  - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

Biliary Tract

Jaundice

- see *Table 2, G6* and *Figures 15 and 16*

Definition

- yellowing of the skin, sclera, and/or mucous membranes due to abnormal deposition of pigmented bilirubin

Signs and Symptoms

- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic/biliary tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer
- kernicterus: rarely seen in adults due to maturation of blood brain barrier

Investigations

- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), ± amylase/lipase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- more detailed evaluation of bile duct ± surrounding structures like pancreas:
  - MRCP: non-invasive
  - EUS: sensitive for stones and pancreatic tumours
  - ERCP: invasive, most accurate, allows for therapeutic intervention
  - PTC: if ERCP fails (endoscopic access not possible)

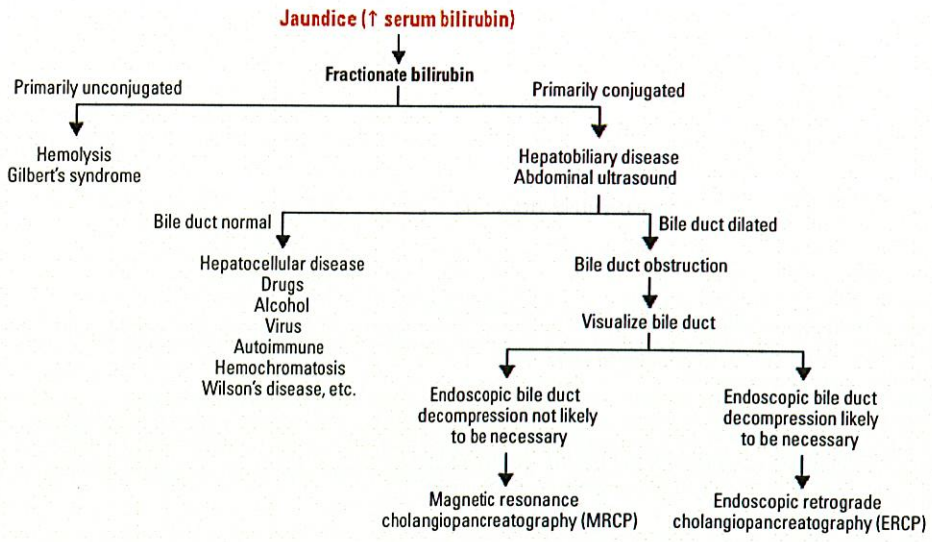


Figure 15. Approach to jaundice

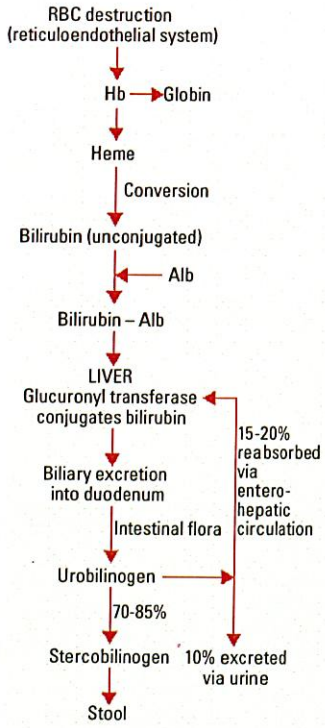


Figure 16. Production and excretion of bilirubin

Gilbert's Syndrome

Definition
- hereditary hyperbilirubinemia due to a deficiency of glucuronyl transferase characterized by repeat episodes of mild asymptomatic jaundice



Gilbert's Syndrome vs. Crigler-Najjar Syndrome
Gilbert's Syndrome: mild decrease in glucuronyltransferase activity
Crigler-Najjar Syndrome: complete deficiency of glucuronyltransferase

Etiology/Epidemiology
- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

Clinical Features
- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications

Treatment
- reassurance (entirely benign)

Primary Sclerosing Cholangitis

Definition
- inflammation, fibrosis, and stricturing of biliary tree (intra- and/or extrahepatic bile ducts) from scarring

Etiology
- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70-80% of patients (usually male) with PSC
- secondary sclerosing cholangitis (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS ("HIV cholangiopathy")
  - IgG4-related disease
  - critical illness

Signs and Symptoms
- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction
- may present with jaundice, hepatomegaly, splenomegaly, excoriations secondary to pruritus

Investigations
- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- MRCP and ERCP shows narrowing and dilatations of bile ducts that may result in "beading," both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC
- consider livery biopsy if suspecting small duct variant (accounts for approximately 10% of cases of PSC)

Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat
- increased incidence of colon cancer in those with concurrent IBD

Treatment
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
- endoscopic sphincterotomy, biliary stent in selected cases of dominant common bile duct stricture
- ABx for cholangitis
- suppurative cholangitis requires emergency drainage of pus in common bile duct
- liver transplantation appears to be the best treatment for advanced sclerosing cholangitis (>90% 1 yr survival; mean follow-up time from diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that it increases mortality if taken in high doses

Prognosis
- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

Primary Biliary Cholangitis (formerly Primary Biliary Cirrhosis)

Definition
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology
- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia), RA, thyroiditis)
- affects mainly middle-aged women (M:F=1:9)

Signs and Symptoms
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal HTN, ascites
- high incidence of osteoporosis

Investigations
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- elevated IgM
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity but is usually not required - elevated ALP for >6 mo and positive AMA are diagnostic
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- "overlap" syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis are possible

Treatment
- drugs that treat the underlying disease:
  - ursodeoxycholic acid (UDCA ; first line treatment)
  - obeticholic acid (if inadequate response to ursodiol)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- repeated monitoring of liver enzymes and LFTs (q 3-6 mo), TSH (annually), and BMD (q 2-4 yr)
- ensure vaccines are updated (notably HAV & HBV); avoid EtOH, smoking
- liver transplant if disease severe, progressive

Prognosis
- can be fatal, although not all asymptomatic patients show progression
- treatment improves prognosis - response to treatment with UDCA (normalization or near-normalization of ALP) is associated with survival comparable to age- and sex-matched controls

Table 24. Primary Sclerosing Cholangitis vs. Primary Biliary Cholangitis

	Primary Sclerosing Cholangitis	Primary Biliary Cholangitis
Predominant Gender	Male	Female
Associated Comorbidities	IBD, especially UC	Other autoimmune disorders (Sjögren's, CREST, RA)
Affected Ducts	Both intra- and extrahepatic	Intrahepatic only
Investigations	ERCP/MRCP (narrowing and dilatations of ducts visualized)	Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)

MRCP/ERCP
Absence of narrowing in PBC
Narrowing of intra- and extrahepatic ducts in PSC

Endoscopic or Surgical Step-Up Approach for Infected Necrotising Pancreatitis: A Multicentre Randomised Trial
Lancet 2018;391:51-58
Purpose: To compare the outcomes of endoscopic vs. the standard surgical removal of infected necrotising pancreatitis.
Study: RCT.
Population: 98 patients with pancreatic or extrapancreatic necrosis were randomized to either endoscopic removal or surgical removal of the infected necrosis.
Outcomes: Major complications and death at 6 mo follow-up.
Results: The primary endpoints of mortality and major complications were the same in the two groups, but the endoscopic group had shortened hospital stays and less pancreatic fistulae.
Conclusions: Three points are worth emphasizing: (1) necrotising pancreatitis is a severe disease: about 15% in each group died; (2) it is best to wait at least 4 wk after the necrosis has developed to allow it to be encapsulated; (3) the management of severe acute pancreatitis should include experts skilled in therapeutic endoscopy.

Biliary Colic, Cholecystitis

- see General Surgery and Thoracic Surgery, GS56

Ascending Cholangitis

- see General Surgery and Thoracic Surgery, *Acute Cholangitis*, GS58

Definition
- infection of the biliary tree

Etiology
- stasis in the biliary tract due to obstruction or stricture
- bacteria
  - *E. coli, Klebsiella, Enterobacter, Enterococcus*
  - coinfection with *Bacteroides* and *Clostridia* can occur

Charcot's Triad
RUQ pain
Fever
Jaundice

Reynolds' Pentad
Charcot's triad
Hypotension
Altered mental status

Signs and Symptoms
- Charcot's triad: fever, RUQ pain, jaundice (50-70%)
- Reynolds' pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

Investigations
- evidence of systemic inflammation (increased WBC, increased CRP)
- usually increased ALP and bilirubin, ALT variably elevated (can be markedly increased if acute obstruction from common bile duct (CBD) stone)
- blood culture
- abdominal U/S: CBD dilation, stricture, stones

Treatment
- most important is drainage, ideally via ERCP; perform by percutaneous biliary or by surgical routes (least often) if ERCP not possible
- antibiotic therapy: broad spectrum to cover Gram-negatives, Enterococcus, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

Prognosis
- good with effective drainage and ABx in mild to moderate cases
- high mortality (~50%) in patients with Reynolds' pentad

Pancreas

Pancreatic Enzyme Abnormalities

Causes of Increased Serum Amylase
- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

Causes of Increased Serum Lipase
- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure



Pancreatic Enzymes

TALC
Trypsin
Amylase
Lipase
Chymotrypsin



When serum amylase >5x normal, the cause is almost always pancreatitis or renal disease

Acute Pancreatitis



Etiology (most common are alcohol and gallstones)
- Idiopathic: thought to be hypertensive sphincter or microlithiasis
- Gallstones (45%)
- Ethanol (35%)
- Tumours: pancreas, ampulla, choledochocele
- Scorpion stings
- Microbiological
  - bacterial: *Mycoplasma, Campylobacter,* TB, *M. avium intracellulare, Legionella, Leptospira*
  - viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
  - parasites: ascariasis, clonorchiasis, echinococcosis
- Autoimmune: IgG4-related disease, SLE, *polyarteritis nodosa* (PAN), CD
- Surgery/trauma
  - manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer
- Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), hypercalcemia, hypothermia
- Emboli or ischemia
- Drugs/toxins
  - azathioprine, mercaptopurine, furosemide, estrogens, methyldopa, H_2-blockers, valproic acid, ABx, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)



When thinking about the causes of acute pancreatitis remember: **I GET SMASHED,** but vast majority due to gallstones or ethanol

Pathophysiology
- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in *SPINK1* gene, which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

Pathology
- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage → infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology
- 3 phases
  - local inflammation + necrosis → hypovolemia
  - systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  - local complications >2 wk after presentation → fluid collection (pseudocyst) or tissue collection (necrosis), sterile or infected

Signs and Symptoms
- pain: epigastric, noncolicky, constant
- can radiate to back
- may improve when leaning forward (Inglefinger's sign)
- tender rigid abdomen; guarding
- N/V
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen's/Grey-Turner's signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma



Cullen's Sign
Sensitive, not specific for acute pancreatitis

Grey-Turner's Sign
Flank ecchymosis



Increased Amylase
- Sensitive, not specific for acute pancreatitis

Increased Lipase
Higher sensitivity and specificity
Stays elevated longer

Investigations
- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- increased WBC, glucose, low calcium
- imaging: CT most useful for diagnosis and prognosis
  - x-ray: "sentinel loop" (dilated proximal jejunum), calcification, and "colon cut-off sign" (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: most useful when done >1 d after presentation, helpful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

Classification
- interstitial edematous vs. necrotizing
- mild, moderate, severe

Prognosis
- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to:
  - shock
  - pulmonary edema
  - multi-organ dysfunction syndrome
  - GI ulceration due to stress
  - death
    - numerous scales to describe severity: probably most useful is proportion of pancreas not taking up contrast on CT done 48 h after presentation (necrotic pancreas does not take up the contrast dye)
    - presence of organ failure, particularly organ failure that persists >48 h, is associated with worse outcomes

Table 25. Collections in Pancreatitis (Revised 2012 Atlanta Classification)

	Liquid	Solid
Acute	Acute peripancreatic fluid collection (APFC)	Acute necrotic collection (ANC)
Chronic	Pancreatic pseudocyst	Walled-off necrosis (WON)

Treatment
- goals (only supportive therapy available)
  1. hemodynamic stability
  2. analgesia
  3. oxygen
  4. stop progression of damage (difficult)
  5. treat local and systemic complications
- antibiotic use in infection (cephalosporins, imipenem), not indicated to prevent infection, although without aspiration/biopsy can be difficult to distinguish infection from non-infected inflammation
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
  - beware third spacing of fluid, monitor urine output carefully
- NG suction (lets pancreas rest) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: NJ feeding tube or TPN if cannot tolerate enteric feeds
  - recent evidence supports NG enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H_2-blockers, peritoneal lavage
- follow clinically and CT or U/S to exclude complications
- chief role of invasive intervention is to drain fluid collection, excise necrotic tissue (necrosectomy), especially indicated if pseudocyst or walled-off necrosis is infected
  - try to delay for >2 wk to allow demarcation between viable and necrotic tissue, better done endoscopically or radiologically, rather than surgically if technically possible

Late Complications
- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain preferably: endoscopic, percutaneous under radiological guidance, surgical if less invasive methods fail
- infected necrosis/abscesses: ABx + percutaneous drainage, endoscopic preferable to surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: DM, pancreatic duct damage

Chronic Pancreatitis

Definition
- irreversible damage to pancreas characterized by
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology
- Toxic-metabolic
  - EtOH (most common)
    - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
    - changes composition of pancreatic juice (e.g. increase viscosity)
    - decreases pancreatic secretion of pancreatic stone protein (lithostathine), which normally solubilizes calcium salts
      - precipitation of calcium within pancreatic duct results in duct and gland destruction
    - toxic effect on acinar and duct cells - directly or via increasing free radicals
    - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
    - varying degrees of ductular dilatation, strictures, protein plugs, calcification
    - no satisfactory theory to explain why only a minority of individuals with EtOH use disorder develop pancreatitis
  - smoking
  - hypercalcemia
  - hypertriglyceridemia
  - medications
- Idiopathic
- Genetic
- Autoimmune pancreatitis/steroid-responsive pancreatitis (e.g. IgG4-related disease)
- Recurrent acute pancreatitis/severe acute pancreatitis
- Obstructive (e.g. pancreas divisum, ampullary stenosis)

Signs and Symptoms
- early stages
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - steatorrhea (maldigestion) when >90% of function is lost
  - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed



Gallstones only cause acute pancreatitis (not chronic pancreatitis)



Symptoms of Chronic Pancreatitis
- Abdominal pain
- Diabetes
- Steatorrhea

Etiology = Almost Always Alcohol

Treatment
- EtOH abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage



When to Call the Surgeon in Acute Pancreatitis?

Endoscopic Transgastric vs. Surgical Necrosectomy for Infected Necrotizing Pancreatitis: A Randomized Trial
JAMA 2012;307:1053-1061

Once it was recognized that severe acute (necrotizing) pancreatitis had a terrible prognosis because of an exuberant inflammatory response leading to multiorgan failure, pancreatectomy was attempted. However, contrary to the expected favourable results, clinical experience has shown that surgical pancreatectomy is usually not helpful, perhaps because once the inflammatory cascade starts, it persists as a self-perpetuating cycle. The problems caused by acute pancreatitis can be thought of as widespread burn initiated by inflammation in the pancreas, but having little to do with ongoing problems within the pancreas itself. Studies suggest that the only compelling indication for surgery is infected necrotizing pancreatitis not responding to ABx. As predicted, without removal of such infected pancreatic tissue, death is likely from sepsis.

In this recent randomized trial, transgastric necrosectomy, an endoscopic technique that also removes infected necrotic pancreatic tissue, reduced both a composite endpoint of major pancreatitis complications (especially new onset organ failure) and the pro-inflammatory response (as measured by serum IL-6 levels) to a greater extent than surgical necrosectomy. Of course, not all necrotic collections are in areas amenable to endoscopic intervention, and the advice of an experienced surgeon should always be welcomed in severe acute pancreatitis, but the role of surgery in this previously considered surgical disease is rapidly diminishing.

Investigations
- laboratory
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
  - stool elastase is low in steatorrhea
- abdominal x-ray: pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts, most sensitive test
- 72 h fecal fat test: measures exocrine function, fecal elastase preferable
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive

Treatment
- most common problem is pain, difficult to control
- general management
  - complete abstinence from EtOH
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas "burns out"
- endoscopy: sphincterotomy, stent if duct is dilated, remove stones from pancreatic duct
- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct is dilated (more effective than endoscopy); resect pancreas if duct is contracted
- steatorrhea
  - pancreatic enzyme replacement
  - neither endoscopy nor surgery can improve pancreatic function

Autoimmune Pancreatitis

- most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

Investigations
- histology: lymphocyte and plasma cell infiltration of pancreas
- imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage-shaped, low density rim around pancreas
- serology: increased serum IgG4 in type 1
- other organ involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

Treatment
- responds to prednisone
- for refractory patients, consider immunomodulators (azathioprine, mycophenolate mofetil, methotrexate) or rituximab

Clinical Nutrition

Determination of Nutritional Status

Challenging to Differentiate Markers of Malnutrition from Markers of Disease
- most important feature in assessing the need for nutritional support is weight loss (expressed as change in body mass index (kg/m^2))
- Subjective Global Assessment divides nutritional status into A) adequately nourished, B) mild or moderate malnutrition, and C) severe malnutrition in order to identify those who will benefit from nutritional support
- includes weight change in past 6 mo, weight change in past 2 wk, dietary intake change, current dietary intake, GI symptoms, functional capacity, effect of disease on nutritional requirements and physical examination, including loss of subcutaneous fat/muscles wasting/edema/ascites

Table 26. Small Bowel Nutrient Absorption

	Fe^{3+}	CHO	Proteins, Lipids Na^+, H_2O	Bile Acids	Vitamin B_{12}
Duodenum	+++	+++	+++	+	
Jejunum	+	+	++	+	+
Ileum	+	+	++	+++	+++

Determining Nutritional Requirements
- calories: total energy expenditure (TEE) = resting energy expenditure (REE) x stress factor (e.g. 1.7 for burns) usually works out to be 25-35 kcal/kg depending on how disease affects metabolism, with IV nutrition delivered as about 60% carbohydrate, 40% fat. Current trend is to provide fewer calories ("permissive underfeeding"), especially in ICU, to prevent hyperglycemia
- protein: 1-2 g/kg/d, depending on effect of disease on protein metabolism. In disease, a greater proportion of energy expenditure comes from protein than in health
- electrolytes, minerals, and vitamins also required

Indications for Aggressive Nutritional Support:
- inability to meet nutritional needs; logical, but convincing evidence from literature not available for ICU and other acute illnesses
- evidence that nutritional support improves outcome available for (1) short bowel syndrome (home TPN), (2) before major abdominal or thoracic surgery if there is substantial malnutrition, (3) before therapy for cancer of esophagus, head, and neck, (4) decompensated alcoholic liver disease, (5) pancreatitis (acute and chronic). May be helpful for other indications also, but insufficient data
- nutritional support at best prevents protein loss but usually no gain

Enteral Nutrition

Definition
- EN (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
  - nasogastric (NG), or nasojejunal (NJ) if nutritional support required for brief time; percutaneous endoscopic gastrostomy ("G-tube" or "PEG tube")/percutaneous endoscopic jejunostomy (J-tube) if nutritional support required for more than 1 mo
- tubes can be placed endoscopically, radiologically, or surgically



Most Common Indications for Artificial Nutrition Support
- Preexisting nutritional deprivation
- Anticipated or actual inadequate energy intake by mouth
- Significant multiorgan system disease

Indications
- oral feeding inadequate or contraindicated

Feeds
- polymeric feeds contain whole protein, carbohydrates, fat as a liquid, and may or may not have fibre added
- elemental feeds contain protein (as amino acids), carbohydrates (as simple sugars), and are low in fat content (are therefore high in osmolarity)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

Relative Contraindications
- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding



Whenever possible, EN is ALWAYS preferable over PN

Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnia, azotemia (from excess protein)

Parenteral Nutrition

Definition
- PN is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications
- short-term (<1 mo)
  - use whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult-to-control sepsis
  - preoperative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)

- some evidence for efficacy, but convincing data not available for:
  - radiation/chemotherapy-induced enteritis
  - AIDS with wasting diarrhea
  - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of small bowel (e.g. small bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)



Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection

Relative Contraindications

- functional GI tract available for EN
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem



Enteral vs. Parenteral Nutrition for Acute Pancreatitis
Cochrane DB Syst Rev 2010;1:CD002837
Purpose: Compare EN vs. TPN on mortality, morbidity, and hospital stay in patients with pancreatitis.
Study Selection: RCTs of TPN vs. EN in pancreatitis.
Results: Eight trials (n=348) were included. EN decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39), and other local complications (0.70). It also decreased hospital stay by 2.37 d.
Conclusion: EN reduces mortality, organ failure, infections, and length of hospital stay in patients with pancreatitis.

Complications of PN

- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: congestive heart failure, hyperglycemia, gallstones, cholestasis, electrolyte abnormalities, micronutrient deficiency

Enteral Nutrition Preferable to Parenteral Nutrition

- fewer serious complications (especially sepsis)
- nutritional requirements better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids with EN
- nutrients in the intestinal lumen have a trophic effect (prevent atrophy of the gut and pancreas)
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Common Medications

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Proton Pump Inhibitors (H^+K^+-ATPase inhibitors)	omeprazole	Losec®/ Prilosec®	20 mg PO once daily	Inhibits gastric enzymes H^+/K^+-ATPase (proton pump)	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of *H. pylori* (combined with ABx)	Hypersensitivity to drug	Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)
	lansoprazole or dexlansoprazole	Prevacid® Dexilant®	Oral therapy: lansoprazole 15-30 mg once daily (before breakfast), dexlansoprazole 30-60 mg once daily (does not need to be taken before breakfast)	Same as above	Same as above	Same as above	Same as above
	pantoprazole	Pantoloc® Protonix®	40 mg PO once daily for UGIB: 80 mg IV bolus then 8 mg/h infusion	Same as above	Same as above and UGIB	Same as above	Same as above
	rabeprazole	Pariet®/ Aciphex®	40 mg PO once daily	Same as above	Same as above	Same as above	Same as above
	esomeprazole	Nexium®	20-40 mg PO once daily	Same as above	Same as above	Same as above	Same as above
Histamine H_2 Receptor Antagonists	ranitidine* *ranitidine drugs recalled in 2019 due to impurity concerns	Zantac®*	300 mg PO once daily or 150 mg BID IV therapy: 50 mg q8 h (but tachyphylaxis a problem)	Inhibits gastric histamine H_2 receptors	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD; not useful for acute GI bleeds	Hypersensitivity to drug	Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression
	famotidine	Pepcid®	Oral therapy: duodenal/ gastric ulcers: 40 mg qhs GERD: 20 mg BID IV therapy: 20 mg BID	Same as above	Same as above	Same as above	Same as above
Stool Softener	docusate sodium	Colace®	100-400 mg PO once daily, divided in 1-4 doses	Promotes incorporation of water into stool	Relief of constipation	Presence of abdominal pain, fever, N/V	Throat irritation, abdominal cramps, rashes

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Osmotic Laxatives	lactulose	Lactulose Constulose®	Constipation: 15-30 mL PO once daily to BID Encephalopathy: 15-30 mL BID to QID	Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid in the colon, increases osmotic colonic contents, increases stool volume	Chronic constipation, prevention, and treatment of portal-systemic encephalopathy	Patients who require a low galactose diet	Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage
	PEG3350	Lax-a-day® RestoraLAX® Golytely®	Constipation: 17 g powder dissolved in 4-8 oz liquid PO once daily	Osmotic agent causes water retention in stool and promotes frequency of stool	Relief of constipation Colonoscopy prep	Hypersensitivity to drug	Abdominal distension, pain, anal pain, thirst, nausea, rigor, tonic-clonic seizures (rare)
	magnesium hydroxide	Milk of Magnesia/ Pedia-Lax®	Constipation (adult): 400 mg/5 mL: 30-60 mL PO qhs	Osmotic retention of fluid which distends the colon and increases peristaltic activity	Relief of constipation	Patients with myasthenia gravis or other neuromuscular disease	Renal impairment Abdominal pain, vomiting, diarrhea
Stimulant Laxatives	senna	Senokot®	Tablets: 1-4 PO qhs Syrup: 10-15 mL PO qhs	Induce peristalsis in lower colon	Constipation	Patients with acute abdomen	Abdominal cramps, discolouration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial)
	bisacodyl	Bisacodyl®	5-30 mg PO once daily (start at 10 mg for bowel preparation)	Enteric nerve stimulation and local contact-induced secretory effects Colonic movements	Constipation Preparation of bowel for procedure	GI obstruction Gastroenteritis	Abdominal colic, abdominal discomfort, proctitis (with suppository use), diarrhea
Bulk Laxatives	psyllium	Metamucil®	Start at one heaping tablespoon daily	Increases stool bulk → water retention in stool	Constipation	Hypersensitivity to drug GI obstruction	GI obstruction, diarrhea, constipation, abdominal cramps
Guanylate Cyclase C Agonist	linaclotide	Constella®	75-145 µg once daily	Opens water channels in bowel epithelial cells to add water to stool	Chronic constipation IBS-constipation	Children	Diarrhea
Antidiarrheal Agents	loperamide	Imodium®	Acute diarrhea: 4 mg PO initially, followed by 2 mg after each unformed stool	Acts as antidiarrheal via cholinergic, noncholingeric, opiate, and non-opiate receptor-medicated mechanisms; decreases activity of myenteric plexus	Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections	Children <2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute UC or pseudomembranous colitis associated with broad-spectrum ABx	Abdominal pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, N/V, hypersensitivity reaction
	diphenoxylate/ atropine	Lomotil®	5 mg PO TID to QID	Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time	Adjunctive therapy for diarrhea, as above	Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria	Dizziness, drowsiness, insomnia, headache, N/V, cramps, allergic reaction
	eluxadoline	Viberzil®	75-100 mg BID	Bowel opioid modulator	IBS Diarrhea	Pancreatic disease, excess EtOH, gallstones or other biliary disease	Pancreaticobiliary pain including sphincter of Oddi dysfunction
Antiemetics	dimenhydrinate	Gravol®	25-50 mg PO/IV/IM q4-6 h PRN	Competitive H_1 receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoreceptor trigger zone. Diminishes vestibular simulation and disrupts labyrinthine function through central anticholinergic action	Motion sickness, radiation sickness, postoperative vomiting, and drug-induced N/V	Hypersensitivity to drug	Xerostomia, sedation
	prochlorperazine	Stemetil®	5-10 mg PO/IV/IM BID-TID PRN	D_1, D_2receptor antagonist in chemoreceptor trigger zone and α-adrenergic and anticholinergic effects Depresses reticular activating system (RAS) affecting emesis	Postoperative N/V, antipsychotic, anxiety	Hypersensitivity to drug	Dystonia, extrapyramidal symptoms (EPS), seizure, NMS (rarely)
	metoclopramide	Maxeran®	10 mg IV/IM q2-3 h prn, 10-15 mg PO QID (30 min before meals and qhs)	Dopamine and 5-HT receptor antagonist in chemoreceptor trigger zone. Enhances response to ACh in upper GI tract, enhancing motility and gastric emptying. Increases LES tone	GERD, diabetic gastroparesis, postoperative and chemotherapy induced N/V, migraines, constipation	Hypersensitivity to drug, GI obstruction, perforation, hemorrhage, pheochromocytoma, seizures, and EPS	Restlessness, drowsiness, dizziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
	ondansetron	Zofran®	Depends on procedure, generally 8-16 mg PO	Selective 5-HT3 receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve	N/V caused by cancer chemotherapy and radiation therapy; multiple off label uses, including gastroenteritis N/V	Morphine, hypersensitivity to drug	Constipation, diarrhea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia
	granisetron	Kytril®	1 mg PO BID (for nausea from chemotherapy/ radiation)	Same as above	N/V caused by cancer chemotherapy and radiation therapy	Same as above	Constipation, prolonged QT interval (rarely)
Prokinetic Agents	domperidone	Motilium®	GI motility disorder (e.g. gastroparesis): 10 mg TID	peripherally acting D2 receptor blocker, main effect in the upper GI tract (i.e. increased esophageal peristalsis, gastric motility), antiemetic properties	upper GI motility disorders (e.g. gastroparesis, subacute gastritis), prevention of nausea associated with dopamine-agonists	hypersensitivity to domperidone, prolonged QT interval, prolactinoma, electrolyte disturbances, CYP3A4 inhibitors, mechanical GI obstruction or perforation, GI hemorrhage, severe hepatic dysfunction, children <2 yr	cardiac arrhythmia (use lowest dose for shortest duration) and hyperprolactinemia causing hypogonadism, breast engorgement, and galactorrhea
	prucalopride	Resotran® Motegrity®	2 mg PO QD	high affinity 5-HT4 agonist, main effect in the lower GI tract (i.e. increased colonic peristalsis, ameliorates gastroparesis)	chronic idiopathic constipation	hypersensitivity to prucalopride, GI obstruction or perforation, severe inflammation co-morbidity (e.g. Crohn's disease, UC, toxic megacolon)	headache, fatigue, dizziness, abdominal pain, N/V, diarrhea, abdominal distention
Aminosalicylates (5-ASAs)	mesalamine	Pentasa® Salofalk® Asacol® Mesasal®	CD: 1 g PO TID/QID Active UC: 1 g PO QID Maintenance UC: 1.6 g PO divided doses daily also as suppositories and enemas	5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes	Mild to moderate UC	Hypersensitivity to mesalamine salicylates; Asacol® contains phthalate, potential urogenital teratogenicity for male fetus	Abdominal pain, constipation, arthralgia, headache
	sulfasalazine	Salazopyrin®	3-4 g/d PO in divided doses	Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component	Mild to moderate UC	Hypersensitivity to sulfasalazine, sulfa drugs, salicylates; intestinal or urinary obstruction, porphyria	Rash, loss of appetite, N/V, headache, oligospermia (reversible)
Immuno-suppressive Agents	6-mercaptopurine (6-MP)	Purinethol®	CD: 1.5 mg/kg/d PO	Immunosuppressive	IBD: active inflammation and to maintain remission	Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy	Pancreatitis, bone marrow suppression, increased risk of cancer
	azathioprine	Azasan® Imuran®	IBD: 2-3 mg/kg/d PO	Same as above	Same as above	Same as above	Same as above
	prednisone		Induction of remission for acute exacerbations: 20-40 mg PO once daily; taper 2.5-5 mg/wk until discontinued	Anti-inflammatory	Symptomatic moderate to severe CD and UC	Hypersensitivity to prednisone, systemic fungal infections	Hyperglycemia, insomnia, osteoporosis, weight gain, increased risk of infections
Biologics	infliximab	Remicade®	5-10 mg/kg IV over 2 h	Monoclonal antibody to TNFα	Medically refractory CD	Heart failure, moderate to severe, doses >5 mg/kg	Reported cases of reactivated TB, PCP, lymphoma, other infections Other TNFα share similar serious side effects
	adalimumab	Humira®	CD induction: four 40 mg SC on day 1, then 80 mg 2 wk later (day 15) CD maintenance: 40 mg every other wk beginning day 29	Monoclonal antibody to TNFα	Medically refractory CD or poor response to infliximab	Hypersensitivity to adalimumab Severe infection Moderate-to-severe heart failure	Headaches, skin rashes, upper respiratory tract infection
	golimumab	Simponi®	RA: 2 mg/kg at wk 0, 4, and then every 8 wk thereafter (use with methotrexate) UC induction: 200 mg SC at wk 0, then 100 mg at wk 2 UC maintenance: 50 mg every 4 wk	Monoclonal antibody to TNFα	Active ankylosing spondylitis Psoriatic arthritis Moderate-to-severe active RA (combined with methotrexate) UC: medically refractory UC	Hypersensitivity to golimumab or latex Severe infection Moderate-to-severe heart failure	
	vedolizumab	Entyvio®	CD/UC: 300 mg at 0, 2, 6 wk and then every 8 wk thereafter	Monoclonal antibody to α4β7 integrin	Medically refractory CD/UC, including other TNFα inhibitors and corticosteroids	Hypersensitivity to vedolizumab	Infections, liver injury, and progressive multifocal leukoencephalopathy
	ustekinumab	Stelara®	Induction: single IV weight-based dose on day 1 Maintenance: 90 mg subcutaneous injection every 8 wk	Monoclonal antibody to IgG1K, inhibits signals by IL-12 and IL-23	Moderate to severe CD and UC	Hypersensitivity to ustekinumab	Infections, headaches, joint pain, fever, N/V

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Small Molecules	tofacitinib	Xeljanz®	5-10 mg BID	JAK inhibitor	UC	TB, hepatitis B	Infections, macro-cardiac events, thrombosis (e.g. PE, DVT)
Antibiotics	rifaximin	Zaxine®	550 mg BID or TID	Non-absorbable antibiotic, affects dysbiosis of microbiome	Hepatic encephalopathy Non-constipation IBS Traveller's diarrhea	Nil	Nil

Landmark Gastroenterology Trials

Trial Name	Reference	Clinical Trial Details
PEPTIC ULCER DISEASE		
FAMOUS	Lancet 2009;374:119-25	**Title:** Famotidine for the Prevention of Peptic Ulcers and Oesophagitis in Patients Taking Low-dose Aspirin (FAMOUS): A Phase III, Randomised, Double-blind, Placebo-controlled Trial **Purpose:** Evaluate the efficacy of famotidine in the prevention of peptic ulcers and erosive esophagitis, in patients receiving low-dose aspirin. **Methods:** Patients without erosions or ulcers on upper endoscopy, currently on low-dose aspirin, were randomized to famotidine 20 mg BID or placebo. The primary endpoint was development of new stomach ulcers. **Results:** At 12 wk, gastric ulcers occurred in 3.4% of famotidine patients and 15% of placebo-matched patients (OR 0.20; 95% CI 0.09 to 0.47; P=0.0002). Duodenal ulcers developed in 0.5% of famotidine patients and 8.5% of placebo patients (OR 0.05; 95% CI 0.01 to 0.40; P=0.0045). **Conclusions:** Famotidine is effective in the prevention of gastric and duodenal ulcers, and erosive esophagitis in patients taking low-dose aspirin.
INFLAMMATORY BOWEL DISEASE		
SONIC	NEJM 2010;362:1383-95	**Title:** Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease **Purpose:** Compare the efficacy and safety of infliximab and azathioprine therapy alone or in combination, in patients with CD. **Methods:** CD patients who had not undergone previous biologic or immunosuppressive therapy were randomized to infliximab 5 mg/kg IV infusion or 2.5 mg oral azathioprine, or combination therapy of both drugs. **Results:** Among patients receiving combination therapy, 56.8% were in steroid-free remission, compared with 44.4% of patients receiving infliximab monotherapy, and 30% receiving azathioprine monotherapy (P<0.001 for comparison with combination; P=0.06 for comparison with infliximab). **Conclusions:** Patients' CD treated with infliximab monotherapy or infliximab-azathioprine combination had better corticosteroid-free remission than azathioprine monotherapy recipients.
A Comparison of Methotrexate with Placebo for the Maintenance of Remission in Crohn's Disease	NEJM 2000;342:1627-32	**Title:** A Comparison of Methotrexate with Placebo for the Maintenance of Remission in Crohn's Disease **Purpose:** Evaluate the role of methotrexate in maintaining remission of CD. **Methods:** Patients with chronically active CD who entered remission were randomized to methotrexate 15 mg IM or placebo for 15 wk. The primary endpoint was rates of remission at wk 40. **Results:** At the follow-up period of 40 wk, 65% of methotrexate patients were in remission compared to 39% of patients in the placebo group (risk reduction 26.1%; 95% CI 4% to 47.8%; P=0.04). None of the methotrexate patients reported serious adverse events. **Conclusions:** Patients with CD in remission saw increased remission rates and fewer relapse treatments at 40 wk.
Adalimumab Induction Therapy for Crohn's Disease Previously Treated with Infliximab	Ann Intern Med 2007;146:829-38	**Title:** Adalimumab Induction Therapy for Crohn's Disease Previously Treated with Infliximab **Purpose:** Determine the efficacy of adalimumab in symptomatic CD patients despite infliximab treatment. **Methods:** 325 adults with moderate-severe active CD were randomized to induction doses of adalimumab 160 mg and 80 mg at 0 and 2 wk respectively, or time-matched placebo. The primary endpoint was induction of remission at 4 wk. **Results:** Remission was achieved at 4 wk in 21% of adalimumab patients compared with 7% of placebo patients (95% CI 6.7% to 21.6%). **Conclusions:** Adalimumab induces remission more frequently than placebo in adult patients with symptomatic CD despite infliximab therapy.
UNIFI	NEJM 2019;381:1201-14	**Title:** Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis **Purpose:** Determine the effectiveness of ustekinumab as induction and maintenance therapy in patients with UC. **Methods:** 961 patients with moderate-severe UC were randomized to IV induction ustekinumab (130 mg), or placebo. The primary endpoint was clinical remission determined by the Mayo scale. **Results:** The primary endpoint occurred in 15.6% of patients in the intervention group compared with 5.3% of placebo patients (P<0.001). The incidence of serious adverse events was similar between groups. **Conclusions:** Ustekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe UC.
VARSITY	NEJM 2019;381:1215-26	**Title:** Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis **Purpose:** Compare efficacy of vedolizumab versus adalimumab in patients with moderate-severe UC. **Methods:** Adults with moderate-severe active UC were randomized to IV infusions of vedolizumab 300 mg or subcutaneous adalimumab 40 mg (total weekly dose 160 mg). The primary outcome was clinical remission at wk 52 as determined by the Mayo scale. **Results:** At wk 52, clinical remission was observed in 31.3% of vedolizumab patients compared to 22.5% of adalimumab patients (95% CI 2.5 to 15.0; P=0.006). Steroid-free remission occurred in 12.6% of vedolizumab patients and 21.8% of adalimumab patients (95% CI 18.9 to 0.4). **Conclusions:** In patients with moderate-to-severe UC, vedolizumab was superior to adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.

Trial Name	Reference	Clinical Trial Details
LIVER DISEASE		
MELD Score as A Predictor Of Death in Chronic Liver Disease	Gastroenterology 2003;124:91-96	**Title:** MELD Score as A Predictor Of Death in Chronic Liver Disease **Purpose:** Assess the capability for the MELD score to correctly rank potential liver transplant recipients. **Methods:** The MELD score was prospectively applied to estimate 3-mo mortality in 3437 adult liver transplant candidates with chronic liver disease. **Results:** Waiting list mortality increased directly in proportion to the MELD score. Using 3-mo mortality as the endpoint, the ROC curve for MELD was 0.83 compared to 0.76 for the Child-Turcotte-Pugh score. **Conclusions:** MELD score can be applied for allocation of donor livers as it accurately predicts 3-mo mortality in patients with chronic liver failure.
PROVE 3	NEJM 2010;362:1292-1303	**Title:** Telaprevir for Previously Treated Chronic HCV Infection **Purpose:** Study the efficacy of telaprevir in patients without a sustained virologic response to peginterferon therapy. **Methods:** Patients with HCV genotype 1 without sustained virologic response to peginterferon therapy were randomized to one of four telaprevir and peginterferon treatment groups. The primary endpoint was sustained virologic response 24 wk after the last dose. **Results:** The rates of sustained virologic response in the three telaprevir groups were significantly higher than the control group rates (14%, P<0.001, P<0.001, P=0.02). Discontinuation of the drugs due to adverse events was more frequent in the telaprevir groups than in the control group (15% vs. 4%). **Conclusions:** In HCV-infected patients in whom initial peginterferon therapy failed, retreatment with telaprevir in combination with peginterferon and ribavirin was more effective than the latter two alone.
SPRINT-2	NEJM 2011;364:1195-1206	**Title:** Boceprevir for Untreated Chronic HCV Genotype 1 Infection **Purpose:** Evaluate virologic response with additional boceprevir treatment in patients with HCV genotype 1 infection. **Methods:** Previously untreated adults with HCV genotype 1 infection were randomized to placebo plus peginterferon-ribavirin or boceprevir plus peginterferon-ribavirin. The primary endpoint was sustained virologic response. **Results:** A virologic response was achieved in 40% of group 1, 67% in group 2 and 68% in group 3. **Conclusions:** The addition of boceprevir to standard therapy of peginterferon-ribavirin, compared with standard therapy alone, increased rates of sustained virologic response in chronically HCV infected adults.
Rifaximin Treatment in Hepatic Encephalopathy	NEJM 2010;362:1071-81	**Title:** Rifaximin Treatment in Hepatic Encephalopathy **Purpose:** Evaluate the efficacy of rifaximin in the prevention of hepatic encephalopathy secondary to cirrhosis. **Methods:** 299 patients in remission from recurrent hepatic encephalopathy were randomized to rifaximin 550 mg BID or placebo for 6 mo. The primary endpoint was time for the first breakthrough episode. **Results:** Rifaximin reduced the risk of a hepatic encephalopathy episode (hazard ratio 0.42; 95% CI 0.28 to 0.64; P<0.001). A breakthrough episode occurred in 22.1% of rifaximin-treated patients compared to 45.9% of placebo patients (hazard ratio 0.5; 95% CI 0.29 to 0.87; P=0.01). The incidence of adverse events was similar between groups. **Conclusions:** The antibiotic rifaximin was successful in maintaining remission from hepatic encephalopathy and reducing hospitalizations.
Prednisolone or Pentoxifylline For Alcoholic Hepatitis	NEJM 2015;372:1619-28	**Title:** Prednisolone or Pentoxifylline For Alcoholic Hepatitis **Purpose:** To elucidate the benefits of pentoxifylline and prednisolone for the treatments of severe alcoholic hepatitis. **Methods:** Patients with severe alcoholic hepatitis were randomized to one of four groups: double-matched placebo, prednisolone plus matched placebo, pentoxifylline plus matched placebo, or prednisolone plus pentoxifylline. The primary endpoint was mortality at 28 d. **Results:** Mortality at 28 d was 17% in the first group, 14% in the second group, 19% in the third group, and 13% in the fourth group. At 90 d and 1 yr, there were no significant differences between groups. **Conclusions:** For alcoholic hepatitis, prednisolone improved survival at a level below statistical significance. Pentoxifylline did not improve survival.

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GS General and Thoracic Surgery

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Acronyms

5-FU	5-fluorouracil
AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ABI	ankle brachial index
ALND	axillary lymph node dissection
APR	abdominoperineal resection
ARDS	acute respiratory distress syndrome
ATN	acute tubular necrosis
AXR	abdominal x-ray
BRBPR	bright red blood per rectum
BCS	breast conserving surgery
CBD	common bile duct
CEA	carcinoembryonic antigen
CF	cystic fibrosis
CHD	common hepatic duct
CRC	colorectal cancer
CVA	costovertebral angle
CVP	central venous pressure
DCIS	ductal carcinoma in situ
DHEAS	dehydroepiandrosterone sulfate
DIC	disseminated intravascular coagulation
DPL	diagnostic peritoneal lavage
DRE	digital rectal exam
EBL	estimated blood loss
ERCP	endoscopic retrograde cholangiopancreatography
EUA	examination under anesthesia
EUS	endoscopic ultrasound
FAP	familial adenomatous polyposis
FAST	focused abdominal sonography for trauma
FNA	fine needle aspiration
FNH	focal nodular hyperplasia
FOBT	fecal occult blood test
GERD	gastroesophageal reflux disease
GIST	gastrointestinal stromal tumour
GU	genitourinary
HCC	hepatocellular carcinoma
HDGC	hereditary diffuse gastric carcinoma
HIDA	hepatobiliary imino-diacetic acid
HNPCC	hereditary nonpolyposis colorectal cancer
I&D	incision and drainage
IBD	inflammatory bowel disease
IPAH	idiopathic pulmonary arterial hypertension
IPF	idiopathic pulmonary fibrosis
IUGR	intrauterine growth restriction
IVC	inferior vena cava
IVIG	intravenous immune globulin
LAR	low anterior resection
LBO	large bowel obstruction
LCIS	lobular carcinoma in situ
LES	lower esophageal sphincter
LGIB	lower gastrointestinal bleed
LLQ	left lower quadrant
LMWH	low molecular weight heparin
LUQ	left upper quadrant
LVRS	lung volume reduction surgery
MALT	mucosa-associated lymphoid tissue
MBP	mechanical bowel preparation
MEN	multiple endocrine neoplasia
MIBG	metaiodobenzylguanidine
MIS	minimally invasive surgery
MRCP	magnetic resonance cholangiopancreatography
MSAFP	maternal serum α-fetoprotein
NET	neuroendocrine tumour
NS	normal saline
OCP	oral contraceptive pill
OGD	oesophagogastroduodenoscopy
PMN	polymorphonuclear neutrophils
POD	postoperative day
PPI	proton pump inhibitor
PTC	percutaneous transhepatic cholangiography
PTT	partial thromboplastin time
PUD	peptic ulcer disease
RAI	radioactive iodine
RL	Ringer's lactate
RLQ	right lower quadrant
RUQ	right upper quadrant
SBO	small bowel obstruction
SBFT	small bowel follow-through
SCC	squamous cell carcinoma
SIADH	syndrome of inappropriate anti-diuretic hormone
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SNLB	sentinel lymph node biopsy
TED	thromboembolic deterrent
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
UC	ulcerative colitis
UGI	upper gastrointestinal series
UGIB	upper gastrointestinal bleed
URTI	upper respiratory tract infection
VATS	video-assisted thoracoscopic surgery
VIP	vasoactive intestinal peptide
VTE	venous thromboembolism

Basic Anatomy Review

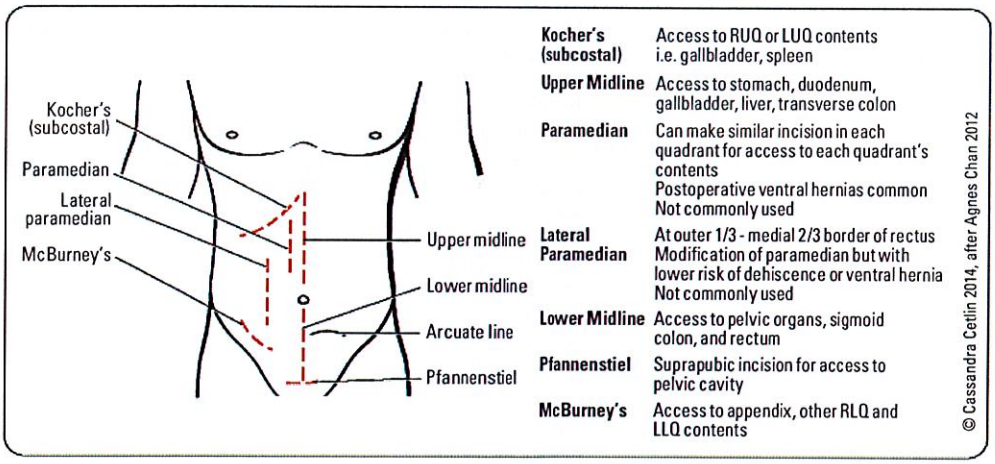


Figure 1. Abdominal incisions

Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)

1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   - Camper's fascia (fatty) → Dartos muscle/fascia
   - Scarpa's fascia (membranous) → Colles' superficial perineal fascia
3. muscle (see *Figure 2 and Figure 3, GS3*)
   - external oblique → inguinal ligament → external spermatic fascia
   - internal oblique → cremasteric muscle/fascia
   - transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

Midline Abdominal Wall Layers (superficial to deep)

1. skin
2. superficial fascia
3. rectus abdominis muscle: in rectus sheath, divided by linea alba (see *Figure 3, GS3*)
   - above arcuate line (midway between symphysis pubis and umbilicus)
     - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
     - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   - below arcuate line
     - aponeuroses of external oblique, internal oblique, and transversus abdominis all pass in front of rectus abdominis

4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle (superficial to posterior rectus sheath above arcuate line)
5. transversalis fascia
6. peritoneum

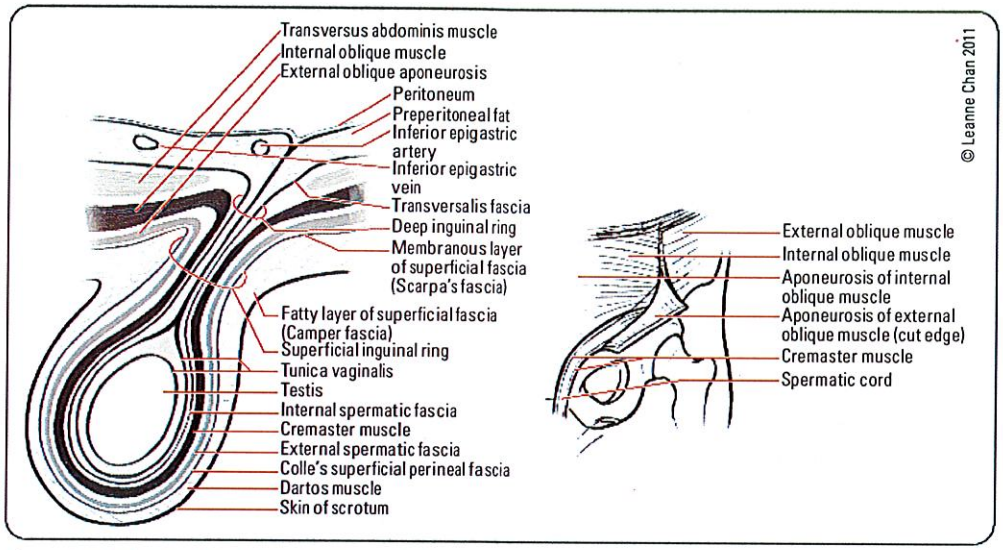


Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord

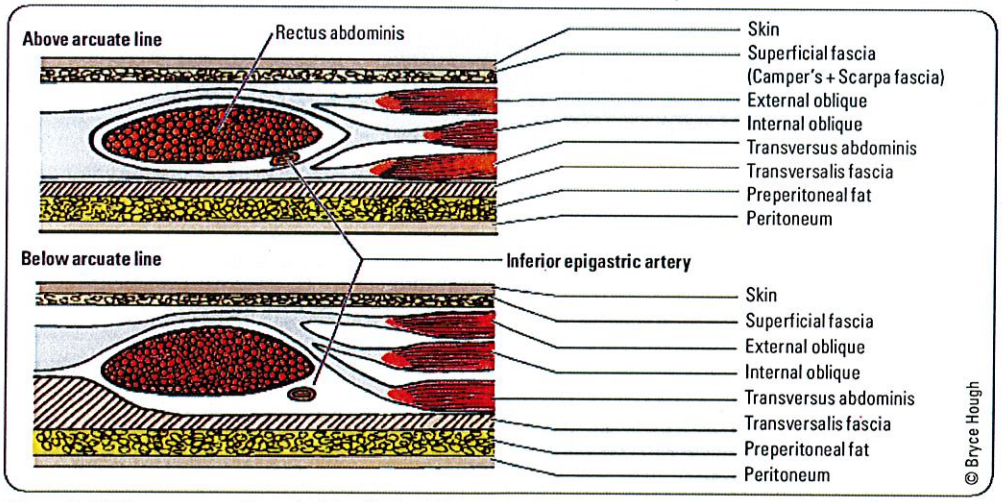


Figure 3. Midline cross-section of abdominal wall

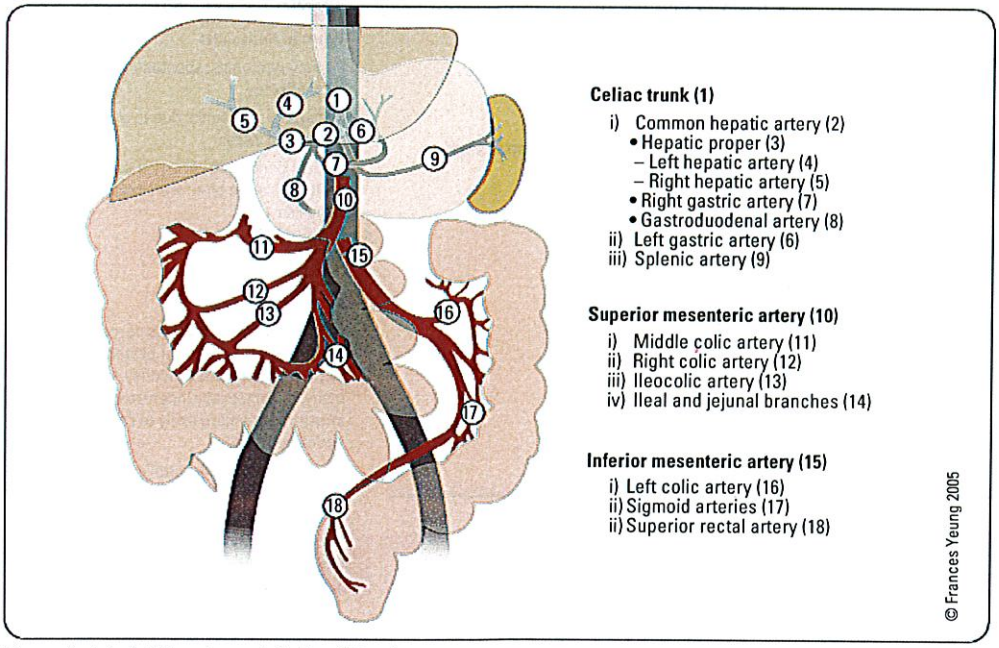
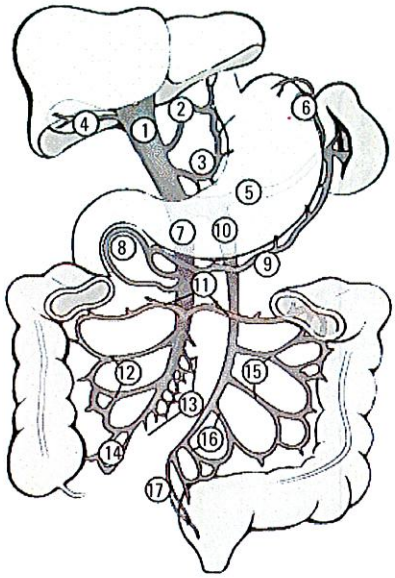


Figure 4. Arterial blood supply to the GI tract

Organ	Arterial Blood Supply
Liver	Left and right hepatic (branches of hepatic proper)
Spleen	Splenic
Gallbladder	Cystic (branch of right hepatic)
Stomach	Lesser curvature: right and left gastric Greater curvature: right (branch of gastroduodenal) and left (branch of splenic) gastroepiploic Fundus: short gastrics (branches of splenic)
Duodenum	Gastroduodenal Pancreaticoduodenals (superior branch of gastroduodenal, inferior branch of superior mesenteric)
Pancreas	Pancreatic branches of splenic Pancreaticoduodenals
Small intestine	Superior mesenteric branches: jejunal, ileal, ileocolic
Large intestine	Superior mesenteric branches: right colic, middle colic Inferior mesenteric branches: left colic, sigmoid, superior rectal

Venous Flow



Portal vein (1)

Superior mesenteric vein (7)

i) Ileal and jejunal veins (13)
ii) Ileocolic vein (14)
iii) Right colic vein (12)
iv) Middle colic vein (11)
v) Pancreaticoduodenal vein (8)
vi) Right gastroepiploic vein (9)

Splenic vein (5)

i) Inferior mesenteric vein (10) (superior rectal vein until crossing common iliac vessels)
- Left colic veins (15)
- Sigmoid veins (16)
- Superior rectal veins (17)

ii) Pancreatic veins
iii) Left gastroepiploic vein
iv) Short gastric veins (6)

Left gastric (coronary) vein (2)

Right gastric vein (3)

Cystic vein (4)

Paraumbilical vein – (within round ligament, not shown)

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Figure 5. Venous drainage of the GI tract

Differential Diagnoses of Common Presentations

Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention, including:
  - peritonitis
  - bowel obstruction

Table 1. Differential Diagnosis of Acute Abdominal Pain

Right Upper Quadrant (RUQ)	Right Lower Quadrant (RLQ)
Hepatobiliary	**Gastrointestinal**
Biliary colic	Appendicitis*
Cholecystitis*	Crohn's disease
Cholangitis	Tuberculosis of the ileocecal junction
CBD obstruction (e.g. stone, tumour)	Cecal tumour
Hepatitis (includes perihepatitis/Fitz-Hugh-Curtis syndrome)	Intussusception
Gastrointestinal	Mesenteric lymphadenitis (Yersinia)
Pancreatitis	Cecal diverticulitis
Presentation of gastric, duodenal, or pancreatic pathology	Cecal volvulus*
Hepatic flexure pathology (e.g. CRC, subcostal incisional hernia)	Hernia: femoral, inguinal obstruction, Amyand's (and resulting cecal distention)
Genitourinary	**Gynecological**
Nephrolithiasis*	See 'suprapubic'
Pyelonephritis	**Genitourinary**
Renal: mass, ischemia, trauma	See 'suprapubic'
Cardiopulmonary	**Extraperitoneal**
Right lower lobe pneumonia	Abdominal wall hematoma/abscess
Effusion/empyema	Psoas abscess
CHF (causing hepatic congestion and right pleural effusion)	
MI	
Pericarditis	
Pleuritis	
Miscellaneous	
Herpes zoster	
Trauma	
Costochondritis (Infectious*)	

*indicated need for urgent surgical evaluation

In All Patients Presenting with an Acute Abdomen, Order the Following:

Key Tests for Specific Diagnosis
- ALP, ALT, AST, bilirubin
- Lipase/ amylase
- Urinalysis
- β-hCG (in women of childbearing age)
- Troponins
- Lactate

Key Tests for OR Preparation
- CBC, electrolytes, creatinine, glucose
- INR/PTT
- CXR (if history of cardiac or pulmonary disease)
- ECG if clinically indicated by history or if >69 yr and no risk factors

Note: Choosing Wisely does not recommend routine preoperative blood work for ambulatory/elective surgery

Types of Peritonitis

Primary peritonitis: spontaneous without clear etiology

Secondary peritonitis: due to a perforated viscus

Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

Localization of Pain

Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation; kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

Parietal peritoneum: supplied by somatic sensory nerves of body wall. Pain is sharp and well-localized

Visceral peritoneum: supplied by autonomic sensory fibres. Pain is colicky and poorly localized

Table 1. Differential Diagnosis of Acute Abdominal Pain

Left Upper Quadrant (LUQ)	Left Lower Quadrant (LLQ)
Pancreatic Pancreatitis (acute vs. chronic) Pancreatic pseudocyst Pancreatic tumours* **Gastrointestinal** Gastritis PUD Splenic flexure pathology (e.g. CRC, ischemia) **Splenic** Splenic infarct/abscess* Splenomegaly Splenic rupture* Splenic artery aneurysm **Cardiopulmonary (see RUQ and Epigastric)** **Genitourinary (see RUQ)**	**Gastrointestinal** Diverticulitis* Diverticulosis Colon/sigmoid/rectal cancer Fecal impaction Proctitis (e.g. UC, infectious; i.e. gonococcus or *Chlamydia*) Sigmoid volvulus* Hernia (incarcerated/strangulated*) **Gynecological** See 'suprapubic' **Genitourinary** See 'suprapubic' **Extraperitoneal** Abdominal wall hematoma/abscess* Psoas abscess See Gynecology, Urology, Respirology, and Cardiology and Cardiac Surgery for further details regarding respective etiologies of acute abdominal pain

EPIGASTRIC	SUPRAPUBIC	DIFFUSE
Cardiac Aortic dissection/ruptured AAA* MI Pericarditis Gastrointestinal Gastritis GERD/esophagitis PUD Pancreatitis Mallory-Weiss tear	**Gastrointestinal (see RLQ/LLQ)** Acute appendicitis* IBD **Gynecological** Ectopic pregnancy* Pelvic inflammatory disease Endometriosis Threatened/incomplete abortion* Hydrosalpinx/salpingitis Ovarian torsion* Hemorrhagic fibroid Tubo-ovarian abscess Gynecological tumours **Genitourinary** Cystitis (infectious, hemorrhagic) Hydroureter/urinary colic Epididymitis Testicular torsion* Acute urinary retention **Extraperitoneal** Rectus sheath hematoma	**Gastrointestinal** Peritonitis* Early appendicitis, perforated appendicitis* Mesenteric ischemia* Gastroenteritis/colitis Constipation Bowel obstruction* Pancreatitis IBD Irritable bowel syndrome Ogilvie's syndrome **Cardiovascular/Hematological** Aortic dissection* Ruptured AAA* Sickle cell crisis **Genitourinary/Gynecological** Perforated ectopic pregnancy* Pelvic inflammatory disease Acute urinary retention **Endocrinological** Carcinoid syndrome* Diabetic ketoacidosis Addisonian crisis Hypercalcemia **Other** Lead poisoning Tertiary syphilis

*indicated need for urgent surgical evaluation

Referred Pain

Biliary colic: to right shoulder or scapula

Renal colic: to groin

Appendicitis: periumbilical to RLQ

Pancreatitis: to back

Ruptured AAA: to back or flank

Perforated ulcer: to RLQ (right paracolic gutter)

Hip pain: to groin

Ovarian torsion: to flank or groin

Most Common Presentations of Surgical Pain

Sudden onset with rigid abdomen = perforated viscus

Pain out of proportion to physical findings = ischemic bowel

Vague pain that subsequently localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum

Waves of colicky pain = bowel obstruction

Acute Abdominal Pain Mnemonic

ABDOMINAL
Appendicitis
Biliary tract disease
Diverticulitis
Ovarian disease
Malignancy
Intestinal obstruction
Nephritic disorders
Acute pancreatitis
Liquor/ethanol

Abdominal Mass

Table 2. Differential Diagnosis of Abdominal Mass

RUQ	Upper Midline	LUQ
Gallbladder: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis **Biliary tract:** Klatskin tumour Liver: hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)	**Pancreas:** pancreatic adenocarcinoma, other pancreatic neoplasms, pseudocyst **Abdominal aorta:** AAA (pulsatile) **GI:** gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma	**Spleen:** splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly **Stomach:** tumour
RLQ	**Lower Midline**	**LLQ**
Intestine: stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhlitis, intussusception, Crohn's inflammation **Ovary:** ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg) **Fallopian tube:** ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour	**Uterus:** pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra **GU:** bladder distention, tumour	**Intestine:** stool, tumour, abscess (see RLQ) **Ovary:** see RLQ **Fallopian tube:** see RLQ

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate surgical intervention

Gastrointestinal Bleeding

- see Gastroenterology, G28 and G30

Indications for Surgery

- failure of medical management (after at least 2 endoscopic attempts at management)
- exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage with up to two attempts of endoscopic hemostasis
- prolonged bleeding with transfusion requirement >3 units
- bleeding at rate >1 unit/8h



Indications for Urgent Operation

IHOP
Ischemia
Hemorrhage
Obstruction
Perforation

Surgical Management of GI Bleeding

- UGIB
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia), may present with anemia, hypovolemic shock
  - initial management with PPIs and endoscopy; if fails, then consider surgical management appropriate to etiology
  - PUD accounts for approximately 55% of severe UGIB
- LGIB
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon, rarely melena (right-sided colonic bleeding)
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues, barium enema should NOT be performed
  - angiography or RBC scan to determine source as indicated
  - surgery indicated if bleeding is persistent - aimed at resection of area containing source of bleeding
  - for obscure bleed conduct wireless capsule endoscopy, may require blind total colectomy if the source is not found
  - diverticular bleeding is the most common cause of LGIB (accounting for 40% of cases)



Overt Bleeding: obvious hematemesis, hematochezia or melena per rectum (i.e. visible to naked eye)
Occult Bleeding: bleeding per rectum is not obvious to naked eye (e.g. positive guaiac FOBT)
Obscure Bleeding: bleeding with no identifiable source after colonoscopy and endoscopy (source usually in small bowel). Can be either overt or occult

Table 3. Differential Diagnosis of GI Bleeding

Anatomical Source	Etiology	
Hematological	Excess anticoagulation (warfarin, heparin, etc.) Excess antiplatelet (clopidogrel, ASA)	DIC Congenital bleeding disorders
Nose	Epistaxis	
Esophagus	Esophageal varices Mallory-Weiss tear Esophagitis	Aorto-esophageal fistula (generally post endovascular aortic repair)* Esophageal cancer
Stomach	Gastritis Gastric varices Dieulafoy's lesion	Gastric ulcer Gastric cancer*
Duodenum	Duodenal ulcer Perforated duodenal ulcer*	Duodenal cancer*
Jejunum	Tumours* Polyps Ulcers	
Ileum and Ileocecal Junction	Meckel's diverticulum Small bowel obstruction	Crohn's disease* Tuberculosis of ileocecal junction
Large Intestine	Colorectal cancer* Mesenteric thrombosis/ischemic bowel* UC* (subtotal colectomy if failure of medical management) Angiodysplasia Diverticulosis (*if bleeding is persistent)	Crohn's disease (less frequently presents with bleeding)* Pancolitis (infectious, chemotherapy, or radiation induced) Bleeding post-gastrointestinal anastomosis
Sigmoid	Diverticulosis (*if bleeding is persistent) Sigmoid cancer* Bleeding post-polypectomy	Polyps (*if not amenable to colonoscopic polypectomy) IBD
Rectum and Anus	Hemorrhoids Fissures Rectal cancer* Anal varices	Polyps (*if not amenable to colonoscopic polypectomy) Crohn's or UC* Solitary rectal ulcer syndrome

*Managed surgically in most cases



Bloodwork for GI Bleeds
CBC (including platelet count), serum chemistries (electrolytes, BUN, LFTs, etc.), coagulation studies (INR, PT, PTT), blood type and crossmatch if anticipate transfusion

Jaundice

- see Gastroenterology, G45



Biochemical Signs for Differentiating Jaundice
Hepatocellular: Elevated bilirubin + elevated ALT/AST
Cholestatic: Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary U/S
Hemolysis: ↓ haptoglobin ↑ LDH



Note: cholestatic jaundice is often surgical

Preoperative Preparations

Considerations

- informed consent (see Ethical, Legal, and Organizational Medicine, ELOM12)
- screening questionnaire to determine risk factors e.g. age, exercise capacity, medication use, allergies, exposure to people with infection (i.e. COVID-19)
- consider preoperative anesthesia, medicine consult as indicated to optimize patient status
- NPO according to fasting guidelines (see Anesthesia, A5)
- IV-balanced crystalloid at maintenance rate (4:2:1 rule for paediatrics, roughly 100-125 cc/h for adults): NS or RL (RL most common); bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patients can take their regular medications except for hypoglycemic agents, diuretics, and ACEis
- patients with primary adrenal insufficiency (e.g. Addison's disease) or secondary adrenal insufficiency (e.g. glucocorticoid use) may require additional glucocorticoid stress dose coverage
- anticoagulation/antiplatelet medication must be managed to decrease surgical bleeding but not put patient at risk for increased thrombotic events (e.g. Bridging: switching from warfarin to LMWH, easier to start/stop as needed)
- prophylactic antibiotics depending on wound class (immediately/within 1 h prior to incision): cefazolin (skin flora coverage) ± metronidazole (GI flora coverage) for contaminated cases
- role of MBP: Current evidence suggests that use of MBP preoperatively has no impact on postoperative complications, and therefore, routine use of MBP for non-LAR elective colorectal surgery is not recommended
  - MBP is indicated in open or laparoscopic anterior resection i.e. rectal resection where anastomosis is at or below sacral promontory; given with antibiotics
- assess risk for postoperative VTE prior to surgery based on procedure- and patient-related factors; tools such as Caprini Score can be used
  - only hold VTE prophylaxis if epidural is expected
- smoking cessation and weight loss preoperatively can significantly decrease postoperative complications
- infection: delay elective surgery until infection managed, including respiratory infection (particularly in asthma patients)
- when scheduling elective surgeries following a COVID-19 diagnosis, consider the severity of COVID-19 illness, the risks of complications, and risks of delaying surgery

Table 4. Recommendations for Timing of Surgery following Recovery from COVID-19 with Consideration of Individual Risk/Benefits

Priority of Surgical Procedure	Clinical Severity of COVID-19 Infection			
	Mild	Moderate	Severe	Critically ill
	Mild (suspected or confirmed) COVID-19 and/or asymptomatic and/or upper respiratory tract infection	Moderate symptomatic COVID-19 not requiring hospitalization and/or persistent symptoms	Lung involvement requiring hospitalization and/or significant comorbidities and/or immunocompromised	Severe COVID-19 with ICU admission and/or meet criteria for severe disease and/or severely immunocompromised
Urgent or Emergent <2 wk ACATS and PCATS Urgent within 3, 7 or 14 d	Do case urgently/ emergently	Do case urgently/ emergently	<7 wk post-infection consider non-operative options if safe and available	<7 wk post-infection consider non-operative options if safe and available
Urgent (28 or 42 d) 2-6 wk ACATS/PCATS	4-7 wk post infection	7 wk post infection	7 wk post infection	12 wk post infection
Elective (>43 d) >6 wk ACATS/PCATS				

Investigations

- see Anesthesia, A4
- routine preoperative laboratory investigations for elective procedures should be selective
  - only ASA class and surgical risk have been found to independently predict postoperative adverse effects
- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, creatinine
- INR/PT, PTT
- CXR (PA and lateral) for patients with history of cardiac or pulmonary disease
- ECG as indicated by history or age>69 and no risk factors
- β-hCG testing in all women of reproductive age
- for patients undergoing low-risk surgery without systemic disease (ASA I or II), routine preoperative chest x-rays, CBC, INR, and PTT should be avoided

Bilirubin Levels

	Pre-hepatic	Intra-hepatic	Post-hepatic
Serum Bilirubin			
Indirect	↑	↑	N
Direct	N	↑	↑
Urine			
Urobilinogen	↑	↑	–
Bilirubin	–	+	+
Fecal			
Urobilinogen	↑	↑	–

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out

Surgical Emergencies: Take an AMPLE History

Allergies
Medications
Past medical/surgical history (including anesthesia and bleeding disorders)
Last meal
Events – HPI

Best Practice in General Surgery (BPIGS)
http://www.bpigs.ca/
Best Practice in Surgery is a resource from the quality improvement program at the University of Toronto Department of Surgery. Since its inception, it has expanded beyond general surgery best practices and provides EBM guidelines for a variety of fields and procedures

Mechanical Bowel Preparation Strategies: A Clinical Practice Guideline developed by the University of Toronto's Best Practice in Surgery
Informed by: Can J Surg 2010;53:385-395
14 RCTs (5071 participants), 8 meta-analyses

1. All open/laparoscopic colorectal procedures (excluding LARs ± diverting stoma)
   - No MBP
   - No dietary restrictions before NPO
   - Fleet enema for left colon anastomoses with transrectal stapling
2. Open/laparoscopic LAR ± diverting stoma
   - MBP
   - No dietary restrictions before MBP; clear fluids after MBP complete

Drains

- NG tube
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding, and/or administration of medications, if necessary
  - 2 types: NG tube (for drainage or feeding) and Dobhoff (for feeding only)
  - insertion should be done in stages with x-ray protocol to avoid injury
  - contraindications: suspected basal skull fracture, obstruction of nasal passages, esophageal stricture, esophageal varices
- Foley catheter with urometer
  - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury and difficult insertion of catheter



Drain Size
Measured by the unit French:
French = diameter (mm) x 3

Surgical Complications

- general principles in preventing complications during the postoperative period include:
  - frequent examination of the patient (daily or more) and their wound
  - removal of surgical tubes as soon as possible (e.g. Foley catheters and surgical drains)
  - early mobilization
  - monitor fluid balance and electrolytes
  - analgesia - enough to adequately address pain (minimize opioids through routine use of anti-inflammatories and acetaminophen)

Postoperative Fever

- postoperative fever is considered a temperature higher than 38°C on two consecutive postoperative days or higher than 39°C on any postoperative day
- fever does not necessarily imply infection, particularly in the first 24-48 h postoperatively
- fever may not be present or may be blunted if patient is receiving chemotherapy, glucocorticoids, or other immunosuppressive agents
- timing of fever may help identify cause
- hours after surgery - POD #1
    - inflammatory reaction in response to physiological stress from surgery; most common cause of fever on POD #1-3 and unlikely to be infectious (unless necrotizing fasciitis or another severe infection)
    - reaction to blood products received during surgery
    - malignant hyperthermia
  - POD #1-2 (acute)
    - atelectasis
    - early necrotizing fasciitis wound infection (especially *Clostridium perfringens*, β-hemolytic Group A *Streptococcus*); feel for crepitus and look for "dishwater" drainage
    - aspiration pneumonitis
    - other: acute adrenal insufficiency, thyroid storm, and transfusion reaction
  - POD #3-7: likely infectious
    - UTI, surgical site infection, IV site/line infection (commonly with *Staphylococcus*), septic thrombophlebitis, and leakage at bowel anastomosis (tachycardia, hypotension, oliguria, and abdominal pain)
  - POD #8+
    - intra-abdominal abscess, DVT/PE (can be anytime postoperative, most commonly POD #8-10, may occur earlier but recognition is often delayed), and drug fever
    - other: URTI, infected seroma/biloma/hematoma, *C. difficile* colitis, and endocarditis

Treatment

- resuscitation then treat primary cause

Wound/Incisional Complications

WOUND CARE (see Plastic Surgery, PL8)

- can shower POD #2-3 after epithelialization of wound (or earlier depending on dressing)
- most dressings can be removed POD #2 and left uncovered if dry
- Steri strips or dermabond glue should be left on for up to 2 wk
- examine wound for wet dressing, signs of infection (fever, tachycardia, and pain)
- skin sutures and staples can be removed POD #7-10
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, or immunosuppressed) removed POD #14 or earlier if there are signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin or ulcer)

DRAINS

- drains may be placed selectively at the time of surgery to prevent fluid accumulation (blood, pus, serum, bile, and urine)
  - can be used to assess quantity of third space fluid accumulation postoperatively
- potential route of infection; to decrease risk of wound infection bring out through separate incision (vs. operative wound) and remove as soon as possible
- types of drains
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) gravity drainage (e.g. Foley catheter); 2) underwater-seal drainage system (e.g. chest tube); 3) suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NG tube)
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually <30-50 cc/24 h)
- drains do not guarantee that the patient will not form a collection of fluid
- ridged drains can erode through internal structures, and excessive suction can cause necrosis
- evidence does not support routine postoperative drainage of abdominal cavity

SURGICAL SITE INFECTION

Etiology

- most surgical wounds are contaminated by bacteria often consisting of normal endogenous flora from skin, respiratory, GU, or GI tracts (depending on surgery)
  - e.g. skin flora (Gram positive cocci: *S. aureus, Streptococcus* spp.) and GI flora (Gram-positive microbes: *Enterococcus* spp., Clostridium spp.; Gram-negative rods: *E. coli*; anaerobic species)

Risk Factors

Table 5. Classification of Surgical Wound Contamination

Classification	Clean	Clean-Contaminated	Contaminated	Dirty/Infected
Definition	Incision under sterile conditions; nontraumatic; no entrance of hollow organ	Incision under sterile conditions; ENTRANCE of hollow viscus with no spillage; no evidence of active infection; minimal contamination with no spillage	Incision under sterile conditions; MAJOR contamination of wound during procedure (i.e. gross spillage of stool, infection in biliary, respiratory, or GU systems)	Established infection present before wound is made in skin; traumatic wound with delayed treatment Traumatic wound with delayed treatment
Example	Hernia repair	Routine cholecystectomy; colon resection	Bowel obstruction with enterotomy and spillage of contents; necrotic bowel resection; fresh traumatic wounds	Appendiceal abscess; traumatic wound with contaminated devitalized tissue; perforated viscus
Infection Rate	<2%	3-4%	7-10%	30-40%
Wound Closure	Primary closure	Primary closure	Often secondary closure	Secondary closure

- patient characteristics
  - age, DM, steroids, immunosuppression, smoking, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, and chemotherapy
- other factors
  - prolonged preoperative hospitalization, skin preparation, multiple antibiotics, reduced blood flow, break in sterile technique, foreign bodies (drains, sutures, grafts), excessive tension, hematoma, seroma, hypoxemia, and hypothermia

Prophylaxis

- preoperative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamicin or vancomycin)
  - within 1 h pre-incision; can re-dose at 1-2 half-lives (~q4-8 h) in the OR
  - not required for low-risk or clean surgery, e.g. elective thyroidectomy, cholecystectomy, hemorrhoidectomy, fistulotomy, and sphincterotomy for fissure
  - important to review patient factors and clinical context; immunosuppression (transplant, Cushing's, malignancy, etc.) would likely warrant preoperative antibiotics
  - some evidence suggests role in breast surgery
  - important that redosing antibiotics is performed if surgery is longer than the half-life of antibiotics
- reserve postoperative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C in the OR)
- hyperoxygenation (consider FiO_2 of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving done at the time of surgery
- consider delayed primary closure of incision for contaminated wounds
- use sterile closing tray for laparotomy

Clinical Features

- typically fever POD #5-8 (*Streptococcus* and *Clostridium* can present in 24 h)
- localized pain, blanchable erythema, induration, purulent discharge, and warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, and hernia

Complication	Laboratory/Imaging Tests
Wound Complication	Wound culture, CBC, CT scan
Fever	CBC, electrolytes, glucose, creatinine, BUN, U/A, CXR, urine/blood/sputum and wound culture if applicable
Respiratory Distress	EKG, echo, CXR, ABG, CT-angiography of the chest
AKI/Oliguria	Electrolytes, glucose, creatinine, BUN, U/A with microscopy, urine electrolytes, EKG, renal U/S
Hypotension	CBC, electrolytes, glucose, creatinine, BUN, lactate, ABG, ACTH stimulation testing, cortisol level, and coagulation studies
Ileus	Electrolytes, glucose, creatinine, BUN, AXR
Stress Ulcer	CBC, upper endoscopy

Preoperative Skin Antiseptics for Preventing Surgical Wound Infections after Clean Surgery
Cochrane DB Syst Rev 2015;4:CD003949
Purpose: To determine whether preoperative skin antisepsis prior to clean surgery prevents surgical-site infection (SSI) and to compare the effectiveness of other antiseptics.
Methods: Systematic review of RCTs part of the Cochrane Wounds Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL). Main outcome was SSI. Secondary outcomes included quality of life, mortality, and resource use.
Results: 13 RCTs (n=2623 patients) were included that made 11 total comparisons between skin antiseptics. A single study found that 0.5% chlorhexidine solution in methylated spirits was significantly superior in preventing SSIs after clean surgery compared to alcohol-based povidone iodine solution. No other statistically significant differences were found.
Conclusions: Further research is warranted to determine the effectiveness of one antiseptic over the others at preventing SSI post clean surgery.

Primary vs. Delayed Primary Incision Closure in Contaminated Abdominal Surgery: A Meta-Analysis
J Surg Res 2019;239:22-30
Purpose: To determine if delayed primary incision closure (DPC) has lower rates of surgical site infections (SSI) and length of stay (LOS) compared to primary incision closure (PC) in contaminated abdominal surgery.
Methods: Systematic review and meta-analysis of RCTs in Medline, Embase, and Cochrane database between 1980-2017.
Results: 12 RCTs were included and analyzed. Using a fixed-effect model, DPC showed significantly reduced SSI with risk ratio of 0.64 (95% CI 0.51-0.79; P<0.0001) and reduced LOS with a mean difference of less than one day compared with PC. However, using a random-effect model, there was no significant difference in SSI or LOS.
Conclusions: DPC may be the preferential option in contaminated abdominal incisions, however higher quality research is required to provide a more comprehensive evidence base.

Treatment
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- reopen affected part of incision, drain, pack, heal by secondary intention in most cases
- for deeper or necrotizing infections, debride necrotic and non-viable tissue
- antibiotics and demarcation of erythema only if cellulitis or immunodeficiency

WOUND HEMORRHAGE/HEMATOMA

Risk Factors
- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, and severe cough
- more common with transverse incisions through muscle due to vascularity of muscle
- more clinically relevant in small working spaces such as breast or thyroid surgery (airway edema/compression)

Clinical Features
- pain, swelling, discolouration of wound edges, and leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency: consider having a suture kit at bedside in all neck surgery in the event of having to open the wound emergently (most important treatment in this case is to protect the airway with intubation)

Treatment
- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete source)

SEROMA
- fluid collection related to serous lymph drainage
- secondary to transection of lymph vessels
- increased infection risk if drained

Treatment
- observation
- consider pressure dressing ± needle drainage (this may increase infection risk)

WOUND DEHISCENCE
- disruption of a wound that was primarily closed, causing loss of barrier of skin or fascia

Risk Factors
- local: technical failure of closure, excessive tension on the wound, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, and transverse incision
- systemic: male, smoking, malnutrition (hypoalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, others (e.g. age, sepsis, and uremia)
- DM alone is not a risk factor
- when removing staples, those at high risk should have alternate staples removed first in a small area to ensure the fascia is intact before removing more (PRO TIP)



Small Bites vs. Large Bites for Closure of Abdominal Midline Incisions (Stitch): A Double-Blind, Multicentre, Randomised Controlled Trial
Lancet 2015;386:1254-1260
Purpose: To compare the large bites suture technique with the small bites technique for fascial closure of midline laparotomy incisions.
Methods: RCT conducted at 10 hospitals in the Netherlands. Patients undergoing elective abdominal surgery randomized (1:1) to small or large bite technique. Primary outcome was incisional hernia occurrence.
Results: At one year follow-up, the large bites group had a greater incidence of incisional hernia occurrence than the small bites group (21% vs. 13%, respectively). Rates of adverse events did not differ between the groups.
Conclusion: Small bites suture technique is superior to the large bites technique for prevention of incisional hernia in midline incisions and is not associated with a higher rate of adverse events.

Clinical Features
- typically POD #1-3 or #7-10; most common presentation sign is serosanguinous (salmon-coloured) drainage from wound; erythema or leakage of enteric material
- ± evisceration
- palpation of wound edge: should normally feel a "healing ridge" from abdominal wall closure (raised area of tissue under incision)

Treatment
- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins
- evisceration (i.e. 'burst abdomen') is a surgical emergency: take patient for operative re-closure

INCISIONAL HERNIA
- a late complication of fascial dehiscence and failure of fascial closure; GI contents are still contained within sack of peritoneum
  - hernia can develop 6-8 wk postoperatively due to poor wound healing and/or increased stress on abdominal wall
- symptoms aggravated by coughing or straining
- smaller fascial defects such as laparoscopic port sites have a higher risk of incarceration
- definitive treatment: surgical repair
  - large hernias that pose little risk of incarceration do not need to be repaired as minimal chance of bowel obstruction

Urinary and Renal Complications

URINARY RETENTION

- may occur after any operation with general anesthesia or more commonly with spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia and patients on anticholinergics but can also happen in young, healthy patients

Clinical Features

- abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

Treatment

- in-and-out catheter to rest bladder, then trial of voiding
- often accompanied by an α-blocker such as tamsulosin (does not start working for 48 h)
- if postoperative retention: patients may need to be sent home with foley catheter and leg-bag (urometer) to follow-up within the week for trial-of-void

OLIGURIA/ANURIA

Etiology

- prerenal (e.g. hypovolemia due to transient renal hypoperfusion) vs. renal (e.g. ATN, acute interstitial nephritis (AIN), acute glomerulonephritis) vs. postrenal (e.g. urinary tract obstruction)
- most common postoperative cause is prerenal ± ischemic ATN
  - external fluid loss: hemorrhage, dehydration, and diarrhea
  - internal fluid loss: third-spacing due to bowel obstruction and pancreatitis

Clinical Features

- urine output <0.5 cc/kg/h (e.g. <450 cc in 75 kg patient in 12 h), increasing Cr and BUN

Treatment

- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

Postoperative Dyspnea

- see *Respiratory Complications* and *Cardiac Complications, GS12*

Etiology

- respiratory: atelectasis, pneumonia/pneumonitis, pulmonary embolism (PE), ARDS, asthma, and pleural effusion
- cardiac: MI, arrhythmia, and CHF
- inadequate pain control

Respiratory Complications

ATELECTASIS

- comprises 90% of postoperative pulmonary complications

Risk Factors

- COPD, smoking, obesity, and elderly persons
- upper abdominal/thoracic surgery, oversedation, significant postoperative pain, and poor inspiratory effort

Clinical Features

- postoperative atelectasis may be asymptomatic or present as low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, and tachypnea

Treatment

- preoperative prophylaxis
  - smoking cessation (best if >8 wk preoperative)
- postoperative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, and intermittent positive-pressure breathing
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressive drugs, and ensure adequate pain control, and early ambulation

PNEUMONIA/PNEUMONITIS

- may be secondary to aspiration of gastric contents during anesthetic induction or extubation causing a chemical pneumonitis

Risk Factors

- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NG tube, pregnancy, and seizure disorder
- non-aspiration: atelectasis, immobility, and pre-existing respiratory disease

Clinical Features
- productive cough and fever
- tachycardia, cyanosis, respiratory failure, and decreased LOC
- CXR: pulmonary infiltrate

Treatment
- prophylaxis: see atelectasis prophylaxis, preoperative NPO/NG tube, and rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- empiric IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. piperacillin-tazobactam, cefepime + metronidazole)

PULMONARY EMBOLUS

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset dyspnea, pleuritic chest pain, tachycardia, and fever
- most commonly POD #8-10, but can occur anytime postoperatively, even after discharge
- diagnosis made by chest CT scan usually

Treatment
- initial treatment: IV heparin or subcutaneous LMWH, bridging to therapeutic anticoagulation is required for a minimum of 3 mo (usually 6 mo); for patients with cancer, or other risk factors for hypercoagulability, the duration of anticoagulation may be longer; severe cases may require endovascular thrombectomy and thrombolysis
- Greenfield (IVC) filter if contraindications to anticoagulation helps prevent worsening of PE
- prophylaxis: subcutaneous heparin (5000 units BID/TID; less preferred) or LMWH, compression stockings (TED™ Hose), and sequential compression devices

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess fluid overload, left ventricular (LV) failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, and alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia



New onset "asthma" and wheezing in the elderly is cardiogenic until proven otherwise

Clinical Features
- shortness of breath, crackles at lung bases, and CXR abnormal

Treatment (LMNOP)
- Lasix® (furosemide)
- Morphine (decreases symptoms of dyspnea, venodilator, and afterload reduction)
- Nitrates (venodilator)
- Oxygen + non-invasive ventilation
- Position (sit patient up)

RESPIRATORY FAILURE

Clinical Features
- dyspnea, cyanosis, and evidence of obstructive lung disease
- earliest manifestations - tachypnea and hypoxemia (RR >25, PO_2 <60)
- pulmonary edema and unexplained decrease in SaO_2

Treatment
- ABCs, O_2, ± positive pressure ventilation, and intubation
- bronchodilators and diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO_2 >60, consider ARDS (see Respirology, R24)

Cardiac Complications

- abnormal ECGs common in postoperative period (compare to preoperative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, and MI)

MYOCARDIAL INFARCTION
- see Cardiology and Cardiac Surgery, C9
- surgery increases risk of MI
- incidence
  - 0.5% in previously asymptomatic men ages >50
  - 40-fold increase in men ages >50 with previous MI

Risk Factors
- preoperative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intraoperative hypotension
- operations >3 h
- angina

Clinical Features
- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, and hypotension

Intra-Abdominal Abscess

Definition
- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology
- usually polymicrobial: Gram-negative bacteria, and anaerobes
  - consider Gram-positives if coexisting cellulitis

Risk Factors
- emergency surgery and contaminated OR
- GI surgery with anastomotic leak
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid redistribution occurs

Clinical Features
- manifests at least 5-7 d after surgery. Cannot manifest earlier as it takes time to form collection
- persistent spiking fever, dull pain, and weight loss
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised and elderly)
- coexisting effusion (pleural effusion with subphrenic abscess)
- mass is often difficult to palpate
- common sites if disseminated peritonitis: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac or local peritonitis: peri-appendiceal, post-surgical anastomosis, diverticular, and psoas

Investigations
- CBC, blood cultures x2
- CT ± IV and water-soluble contrast
- C&S from drain

Treatment
- drain placement by interventional radiology (preferred), laparoscopy, and open drainage
- subsequent antibiotic coverage; ceftriaxone + metronidazole or piperacillin-tazobactam (Pip-Tazo)

Paralytic Ileus

- see *Paralytic Ileus, GS31*

Delirium

- see Psychiatry, PS23 and Neurology, N21

Thoracic and Foregut Surgery

Approach to the Solitary Pulmonary Nodule

- see Medical Imaging, MI8

Definition
- lesion up to 3 cm, which may or may not be calcified and is surrounded by normal lung
- can be benign or malignant



Differential Diagnosis of Upper GI Symptoms

GI Causes	Non-GI Causes
Cholelithiasis	MI
Diverticulitis	Angina
Peptic ulcer	Pericarditis
Achalasia	
Pancreatitis	
GERD	
Gastritis	
Hiatus hernia	



Horner has a MAP of the Coast
A Pancoast tumour compresses the cervical sympathetic plexus causing Horner's syndrome:
Miosis
Anhydrosis
Ptosis



Differential of an Anterior Compartment Mass

4 Ts
Thymoma
Thyroid enlargement (goitre)
Teratoma
Tumours (lymphoma, parathyroid, angiomatous)

Table 6. Differential Diagnosis for Benign vs. Malignant Solitary Nodule

Benign (70%)	Malignant (30%)	
Infectious granuloma (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria) - most common	**Bronchogenic carcinoma**	**Metastatic lesions**
Other infections (bacterial abscess, PCP, aspergilloma)	Adenocarcinoma	Breast
Benign neoplasms (hamartoma, lipoma, fibroma)	SCC	Head and neck
Vascular (AV malformation, pulmonary varix)	Large cell carcinoma	Melanoma
Developmental (bronchogenic cyst)	Small cell carcinoma	Colon
Inflammatory (granulomatosis with polyangiitis, rheumatoid nodule, sarcoidosis, amyloidosis)	Small cell lung cancer	Kidney
Other (infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma)		Sarcoma
		Germ cell tumours

Investigations

- CXR: always compare with previous CXR
- CT and contrast-enhanced CT of thorax
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  - if a biopsy is non-diagnostic, whether to observe, re-biopsy, or resect will depend on the level of suspicion
- watchful waiting: repeat CT scan at 3, 6, 12 mo depending on nodule characteristics and patient risk
- PET scan can narrow the differential diagnosis

Table 7. CT Characteristics of Benign vs. Malignant Solitary Nodule

Parameters	Benign	Malignant
Size	Nodule (<3 cm)	Mass (>3 cm)
Borders	Smooth or lobulated	Irregular or spiculated
Features	Calcified pattern: diffuse, central, laminated, "popcorn" pattern if hamartoma, usually no cavitation; if cavitating, wall is smooth and thin, no other lung pathology	Usually not calcified; if calcified, pattern is eccentric, stippled, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy
Doubling Time	Doubles in <20 or >400 d	Doubles between 20 and 400 d

Table 8. Evaluation of a Solitary Pulmonary Nodule

	SOLID NODULES		
Nodule Type	**Size <6 mm (<100 mm^2)**	**Size 6-8 mm (100-250 mm^2)**	**Size >8 mm (>250 mm^2)**
Single			
Low-Risk	No routine follow-up	CT at 6-12 mo, then consider CT at 18-24 mo	Consider CT a 3 mo, PET/CT or tissue sampling
High-Risk	Optional CT at 12 mo	CT at 6-12 mo, then at 18-24 mo	Consider CT a 3 mo, PET/CT or tissue sampling
Multiple			
Low-Risk	No routine follow-up	CT at 3-6 mo, then consider CT at 18-24 mo	CT at 3-6 mo, then consider CT at 18-24 mo
High-Risk	Optional CT at 12 mo	CT at 3-6 mo, then at 18-24 mo	CT at 3-6 mo then at 18-24 mo
	SUBSOLID NODULES		
Nodule Type	**Size <6 mm (<100 mm^2)**	**Size ≥6 mm (>100 mm^2)**	
Single			
Ground Glass	No routine follow-up	CT at 6-12 mo to confirm persistence then CT every 2 yr until 5 yr	
Part Solid	No routine follow-up	CT at 3-6 mo to confirm persistence If unchanged and solid component remains <6 mm, annual CT should be performed for 5 yr	
Multiple	CT at 3-6 mo. If stable consider CT at 2 and 4 yr	CT at 3-6 mo Subsequent management based on the most suspicious nodule(s)	

Adapted from: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images. The Fleischner Society 2017. Radiology Journal. doi:10.1148/radiol.2017161659. Feb 23 2017.

Lung Cancer

Classification

- lung tumours can be classified as:
  - primary or secondary
  - benign or malignant
  - endobronchial or parenchymal
- bronchogenic carcinoma (epithelial lung tumours) are the most common type of primary lung tumour (other types make up less than 1%)
  - small cell lung cancer (SCLC): 10-15%

- non-small-cell lung cancer (NSCLC): 85-90%
  - SCC: arise from the proximal respiratory epithelium
  - adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
    - mucinous adenocarcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
  - large cell carcinoma
- benign epithelial lung tumours can be classified as papillomas or adenomas

Table 9. Characteristics of Lung Cancer

Cell Type	Percentage of Lung Cancer	Correlation with Smoking	Location	Histology	Metastasis	5 Yr Survival Rates
SCLC	10-15%	Strong	Central	Oat cell, neuroendocrine	Disseminated at presentation Origin in endobronchial cells	10-13% limited stage, 1-2% extensive stage
Adenocarcinoma	M: 35% F: 40%	Moderate	Peripheral	Papillary, lepidic, acinar, mucinous, solid	Early, distant	70% early stage, 7% advanced stage
SCC	30%	Strong	Central	Keratin, intercellular bridges	Local invasion and distant spread, may cavitate	47% early stage, 6% advanced stage
Large Cell Carcinoma	10-15%	Strong	Peripheral	Anaplastic, undifferentiated	Early, distant	53% early stage, 5% advanced stage

US Mortality Files, National Center for Health Statistics, CDC



Canadian Task Force on Preventive Health (2016)

Screening with low-dose CT recommended for high-risk patients only:

55-74 yr

≥30 pack-yr smoking Hx

Current smoker or quit within last 15 yr

Annual screening low-dose CT up to 3 yr

Risk Factors

- cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers
- risk of lung cancer increases with number of cigarettes smoked per day (linear) and duration of smoking (exponential)
- other risk factors: cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 5), asbestos with smoking (relative risk is 92), metals (e.g. chromium, arsenic, nickel), radon gas, ionizing radiation, and genetics

Clinical Features

- may be due to primary lesion, metastasis, or paraneoplastic syndrome
- primary lesion
  - cough (75%): beware of chronic cough that changes in character
  - dyspnea (60%)
  - chest pain (45%)
  - hemoptysis (35%)
  - other pain (25%)
  - clubbing (21%)
  - constitutional symptoms: anorexia, weight loss, fever, and fatigue
- metastasis
  - lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing, post-obstructive pneumonia
  - pericardium: pericardial effusion, pericardial tamponade
  - esophageal compression: dysphagia
  - phrenic nerve: paralyzed diaphragm, dyspnea
  - recurrent laryngeal nerve: hoarseness
  - superior vena cava syndrome
    - obstruction of SVC causing neck and facial swelling
    - other symptoms: dyspnea, cough, hoarseness, tongue swelling, epistaxis, and hemoptysis
    - physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton's sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
    - milder symptoms if obstruction is above the azygos vein
  - lung apex (Pancoast tumour): Horner's syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
  - rib and vertebrae: erosion, pain
  - distant metastasis to brain, bone, liver, and adrenals
- paraneoplastic syndromes
  - most often associated with SCLC



Malignant lung tumours are the most common cause of cancer mortality in both men and women worldwide



Endobronchial Ultrasound (EBUS)

Allows visualization of peri-bronchial structures and lung lesions

Allows for guided biopsies of lymph nodes and tumours

Used for diagnosis and staging

Table 10. Paraneoplastic Syndromes

System	Clinical Features	Associated Malignancy
Skeletal	Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)	Non-small cell lung cancer (NSCLC)
Dermatologic	Acanthosis nigricans	Lung cancer
	Dermatomyositis	
Endocrine	Hypercalcemia (osteolysis or PTHrP)	SCC
	Hypophosphatemia	SCC
	Hypoglycemia	Sarcoma
	Cushing's syndrome (ACTH)	Small cell lung cancer (SCLC)
	Carcinoid syndrome	Bronchial carcinoid
	SIADH	SCLC
Neuromyopathic	Lambert-Eaton syndrome	SCLC
	Polymyositis	
	Subacute cerebellar degeneration	
	Spinocerebellar degeneration	
	Peripheral neuropathy	
Vascular/Hematologic	Nonbacterial endocarditis	Lung cancer
	Trousseau's syndrome (migratory thrombophlebitis)	NSCLC
	DIC	
Renal	Nephrotic syndrome	Lung carcinoma

2/3 of primary lung cancer is found in the upper lung; 2/3 of metastases occur in the lower lung (hematogenous spread secondary to increased blood flow to the base of the lung)

Investigations

- initial diagnosis
  - imaging: CXR, CT chest + abdomen, PET scan
  - biopsy: bronchoscopy, EBUS, CT-guided percutaneous needle biopsy
- staging workup
  - TNM staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  - blood work: electrolytes, LFTs, calcium, ALP
  - imaging: CXR, CT thorax and abdomen, PET scan, bone scan (-in confirmed stage 4 cancer), neuroimaging (MRI Brain)
  - invasive: bronchoscopy (EBUS), mediastinoscopy, VATS

Table 11. SCLC vs. NSCLC

	Stage	Definition	Treatment	Median Survival
SCLC	Limited stage	Confined to single radiation port (one hemithorax and regional lymph nodes)	Radiation ± chemotherapy ± prophylactic to brain	1-2 yr (12 wk without treatment)
	Extensive stage	Extension beyond a single radiation port	Chemotherapy	6 mo (5 wk without treatment)

	Stage	TNM	Treatment	5 Yr Survival (%)*
NSCLC	0	TisN0M0	1st line is complete surgical resection (VATS or open thoracotomy) with possible postoperative adjuvant chemotherapy with stage IB and stage II; radiotherapy for non-surgical candidates	
	IA1	T1aN0M0		90-92
	IA2	T1bN0M0		83-85
	IA3	T1cN0M0		77-80
	IB	T2aN0M0		68-73
	IIA	T2bN0M0		60-65
	IIB	T3N0M0 or T1N1M0 or T2N1M0		53-56
	IIIA	T4N0M0 or T4N1M0 or T3M1N0 or T1N2M0 or T2N2M0	Combined modality approach (chemo ± radiation, and sometimes surgical resection)	36-41
	IIIB	T3N2M0 or T4M2N0 or T1N3M0 or T2N3M0		24-26
	IIC	T3N3M0 or T4N3M0		12-13
	IVA	T1-4N0-3M1a-1b	Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation); isolated metastasis may be resected	10
	IVB	T1-4N0-3M1c		0

* Depends on clinical vs. pathologic stage Refer to AJCC Cancer Staging Manual, 8th ed. 2017 for complete TNM classification

Treatment

- options include surgery, radiotherapy, ablation, chemotherapy, and palliative care for end-stage disease
- surgery not usually performed for SCLC since it is generally non-curable
- contraindications for surgery
  - spread to contralateral mediastinal lymph nodes or distant sites
    - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)
    - postoperative estimated FEV ^{1}and DLCO must be at least 40% of predicted to tolerate surgery
- chemotherapy (used in combination with other treatments)
  - common agents: cisplatin-vinorelbine (standard of care), etoposide, ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  - pembrolizumab, a PD-1 monoclonal antibody is used in those with tumour PD-L1 levels >50%; for those with PD-L1 levels <50%, combination of doublet chemotherapy and pembrolizumab is initiated

Prevention
Smoking cessation
Avoidance of exposures
Early detection

Terminology
- "Nodule" <3 cm
- "Mass" >3 cm

Mutations in endothelial growth factor receptor are more common in non-smoking patients with adenocarcinoma

Corona Radiata Sign on Chest CT

Fine striations that extend linearly from a nodule in a spiculated fashion

Highly associated with malignancy

Carcinoids

Early onset (40-60 yr)

Most are central and can produce symptoms and signs of bronchial obstruction

Hemoptysis is present in ~50% of cases

Assuming adequate pulmonary function, surgical resection (i.e. segmentectomy, wedge resections, and lobectomy) is the preferred treatment approach

- targeted therapies such as EGFR tyrosine kinase inhibitors and ALK tyrosine kinase inhibitors are used if tumour tests positive for these mutations
- complications
  - acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
  - chronic: neurologic damage, leukemia, additional primary neoplasms

Pleura, Lung, and Mediastinum

- see Respirology, R23

Complicated Parapneumonic Effusion

Definition
- persistent bacteria in the pleural space but fluid is non-purulent
- neutrophils, pleural fluid acidosis (pH<7.20), low glucose (<40 mg/dL)
- often no bacteria grown since rapidly cleared from pleural space

Clinical Features
- fever, pleuritic chest pain, dyspnea, and sputum production

Treatment
- antibiotics depending on Gram stain and culture
- chest tube drainage

Empyema

Definition
- bacteria in pleural space or an effusion with organisms seen on a Gram stain or culture (e.g. pleural fluid is grossly purulent in advanced stage empyema)
- positive culture is not required for diagnosis

Etiology
- contiguous spread from lung infection (most commonly anaerobes) or infection through chest wall (e.g. trauma, surgery)

Clinical Features
- fever, pleuritic chest pain, dyspnea, and sputum production

Investigations
- CT chest
- thoracentesis
  - PMNs (lymphocytes in TB) ± visible organisms on Gram stain

Treatment
- antibiotic therapy for at least 4-6 wk (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage with VATS, or fibrinolysis (surgical or tPA/DNAse) to allow lung re-expansion (decortication)

Pneumothorax

Definition
- presence of air in the pleural space
- can be classified as:
  - primary or secondary
  - open or closed
  - simple or tension or occult (only visible on CT scan)

Pathophysiology
- entry of air into pleural space raises intrapleural pressure causing partial or complete lung deflation

Etiology
- traumatic: penetrating or non-penetrating chest injuries
- iatrogenic: central venous catheter, thoracentesis, mechanical ventilation with barotrauma, surgery



Hamartomas

10% of benign lung lesions

Composed of tissues normally present in lung (fat, epithelium, fibrous tissue, and cartilage), but they exhibit disorganized growth

Peak incidence is age 60, more common in men

Usually peripheral and clinically silent

CXR shows clustered "popcorn" pattern of calcification (pathognomonic for hamartoma)

Peripheral small hamartomas can generally be observed with occasional follow-up to monitor growth; symptomatic endobronchial hamartomas are removed via rigid transbronchial resection

- spontaneous: no history of trauma or other underlying cause
  - primary (no underlying lung disease)
    - spontaneous rupture of apical subpleural bleb (pockets of air) of lung into pleural space
    - smoker, male, family history, Marfan's syndrome
  - secondary (underlying lung disease)
    - rupture of subpleural bleb in the pleural space which can migrate along bronchioalveolar bronchoalveolar sheath to the mediastinum then to the intrapleural space
    - necrosis of lung tissue adjacent to pleural surface
    - pneumonia, abscess, PCP, lung cancer, COPD, CF, TB, lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), lung metastasis (e.g. sarcoma)

Clinical Features
- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
- tachypnea, tachycardia
- tracheal deviation (contralateral deviation in tension pneumothorax)
- shock (in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonance
- ipsilateral diminished breath sounds

Investigations
- CXR
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: decreased density and decreased volume of lung on side of pneumothorax
  - see Medical Imaging, MI4 and MI9



Tube thoracostomy can be completed under U/S guidance

Treatment
- primary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + O_2
  - symptomatic or large (>3 cm): aspiration or chest tube
  - unstable/tension pneumothorax: needle decompression then chest tube, VATS bullectomy, and pleurodesis if unsuccessful (25-50%)
- secondary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + O_2
  - symptomatic, large, or unstable: chest tube and VATS pleurodesis with or without bullectomy if unsuccessful

Tube Thoracostomy

Indications
- to drain abnormal air or fluid collections in the pleural space
  - hemothorax, pleural effusion, chylothorax, and empyema
  - pneumothorax, if:
    - large or progressive
    - patient is on mechanical ventilation
    - bronchopleural fistula
    - tension pneumothorax
- to treat symptomatic and/or recurrent pleural effusion
  - see Respirology, R24
  - for long-term drainage of malignant effusions use: 1. Tunneled pleural catheter; 2. Pleural drainage and Talc pleurodesis
  - via facilitation of pleurodesis - obliteration of the pleural space by instilling talc to cause fusion of parietal and visceral pleura

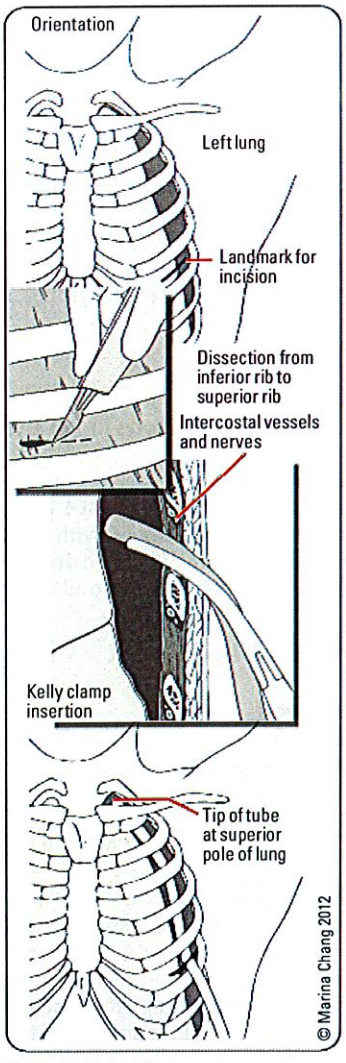


Figure 6. Tube thoracostomy

Complications
- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators
  - tubes may be placed outside the pleural cavity in the chest wall, or below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma, liver, spleen or vasculature
- risk of re-expansion pulmonary edema when large volumes of fluid are drawn off quickly (>1.0-1.5 L)

Lung Transplantation

Conditions Leading to Transplantation
- obstructive: chronic acquired lung disease (e.g. COPD), CF, and emphysema due to α-1 antitrypsin deficiency
- restrictive interstitial lung disease: IPF, hypersensitivity pneumonitis
- vascular: idiopathic pulmonary arterial HTN (IPAH), secondary pulmonary HTN, and Eisenmenger's syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis

Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and have risk of death >50% over the next 2 yr

Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

Absolute Contraindications
- uncontrolled or untreatable pulmonary or extrapulmonary infection
- active TB infection
- malignancy in the last 2 yr
- dysfunction of vital organs including glomerular filtration rate of <40 mL/min/1.73 m^3, stroke within 30 d, acute liver failure or cirrhosis, acute coronary syndrome within 30 d or heart disease not amenable to revascularization, and untreatable hematologic disorders
- active cigarette smoking
- BMI ≥35 kg/m^2
- unresolved psychosocial problems or non-adherence to medical therapy
- smoking
- absence of social support system

Relative Contraindications
- ages >70 yr and low physiologic reserve
- BMI 30-34.9 kg/m^2
- limited functional status including severe malnutrition or osteoporosis
- HIV infection, HBV infection
- alcohol (required to stay within healthy drinking guidelines)

Postoperative Complications
- primary graft dysfunction
- airway anastomotic complications (bronchial necrosis and dehiscence, tracheobronchomalacia, stenosis)
- chronic lung allograft dysfunction (bronchiolitis obliterans syndrome and restrictive allograft syndrome)
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, and mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disorders, colon, breast, Kaposi's sarcoma, and bladder)

Prognosis
- median survival for all adult recipients: 6.5 yr; bilateral transplant survival higher than single (7.6 vs. 4.7 yr, respectively)
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

Chronic Obstructive Pulmonary Disease

- see Respirology, R9

Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation

- contraindications
  - ages >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality (e.g. severe CAD or HF)
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - severe cachexia or obesity, chest wall deformity, or pulmonary HTN (PA systolic pressure >45 mmHg)
  - diffusing capacity of lung for carbon monoxide <20% of predicted, $PaCO_2$ >60 mmHg, PaO_2 <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS (preferred)

Complications of Treatment
- arrhythmias, pneumonia (may require reintubation and mechanical ventilation), prolonged air leak from chest tube

Prognosis
- worse early mortality but better exercise capacity and quality of life with LVRS

Mediastinal Masses

Definition
- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies, and the pleura
- can be broken down into 3 compartments: anterior, middle, and posterior

Etiology and Pathophysiology
- diagnosis is aided by location and patient's age
- anterior compartment: more likely to be malignant
  - "Four Ts" (see sidebar), lymphadenopathy, lipoma, pericardial cyst, goitre, and ascending aortic aneurysm thymic tumours/cysts
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphadenopathy, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphadenopathy, diaphragmatic hernias, esophageal tumours, aortic aneurysm

Clinical Features
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner's syndrome (see sidebar), facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis (thymomas))

Investigations
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- echocardiogram: best for assessment of structures in close proximity to the heart and pericardium
- radionuclide scanning: ^{131}I (for thyroid), gallium (for lymphoma), PET/CT
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, β-hCG, LDH
- biopsy (mediastinoscopy, bronchoscopy, and EBUS, percutaneous needle aspiration)

Management
- excision – symptomatic benign mass that is enlarging or a mass with concerns for malignancy
- resect bronchogenic cysts and localized neurogenic tumours via VATS or open surgery
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- no biopsy if AFP, β-hCG, LDH elevated – pathognomonic for germ cell tumour



Differential of an Anterior Compartment Mass

4 Ts
Thymoma
Thyroid enlargement (goitre)
Teratoma
Tumours (lymphoma, parathyroid, esophageal, angiomatous)



Mediastinal Components
Anterior: sternum to pericardium and great vessels. Includes: thymus, extra-pericardial aorta and branches, great veins, lymphatic tissues
Middle: pericardium (anteriorly), posterior pericardial reflection, diaphragm, thoracic inlet. Includes: heart, intrapericardial great vessels, trachea
Posterior: posterior pericardial reflection, posterior border of vertebral bodies, first rib to the diaphragm. Includes: esophagus, vagus nerve, thoracic duct, sympathetic chain, azygous venous system



Masaoka Staging System
Stage I: completely encapsulated
Stage II: invasion beyond capsule
Stage III: into another organ
Stage IVa: pleural/pericardial mets
Stage IVb: hematogenous/lymphatic mets

Thymoma

Definition
- rare neoplasms in thymus, located in anterior mediastinum

Epidemiology
- patients between 40 and 60 yr
- M=F
- no known risk factors, strong association with myasthenia gravis and other paraneoplastic syndromes

Clinical Features
- frequently asymptomatic: incidental finding on imaging
- symptoms related to tumour size and location (chest pain, SOB, cough, and phrenic nerve palsy)
- DDx includes intrathoracic goitre, lymphoma, and other anterior mediastinal tumours (see *Mediastinal Masses, GS20*)

Investigations
- CT chest (and/or MRI): assess resectability
- germ cell tumour markers (β-hCG, AFP, LDH), thyroid function, acetylcholinesterase antibodies (to rule out myasthenia gravis), and PFTs
- Masaoka staging system widely used

Treatment
- for patients with resectable disease
  - surgical resection of the thymoma and the thymus via median sternotomy or VATS depending on the size
  - ± postoperative radiation based on Masaoka staging
    - radiation considered for stage II/III disease
- for potentially unresectable disease (i.e. invasion into heart and great vessels) or non-surgical patients
  - definitive or palliative chemo and radiation therapy
- re-evaluation if debulking procedure feasible in situations where preoperative chemo- and radiation therapy is offered
- common chemotherapy regimens include: 1) cyclophosphamide, doxorubicin, and cisplatin, or 2) cisplatin and etoposide

Prognosis
- depends upon stage of disease and resectability
- generally slow-growing tumours and have good prognosis

Esophageal Carcinoma

Epidemiology
- M:F=3:1
- onset 50-60 yr
- upper (20-33%), middle (33%), and lower (33-50%)
- main types
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in lower 1/3 of esophagus

Risk Factors
- SCC
  - underlying esophageal disease such as strictures, diverticula, and achalasia
  - smoking, alcohol, and hot liquids
  - more common in Black and Asian populations
- adenocarcinoma
  - Barrett's esophagus (most important), smoking, obesity (increased reflux), and GERD
  - more common in White populations

Clinical Features
- progressive dysphagia (mechanical): first solids then liquids, then saliva
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis and anemia
- direct, hematogenous, or lymphatic spread
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac, and mediastinal nodes

Investigations and Staging
- barium swallow: shows narrowing – suggestive but not diagnostic
- endoscopic biopsy to assess location, resectability, and confirm diagnosis
- both SCC and adenocarcinoma use TNM staging system but have separate stage groupings according to histology
- endoscopic U/S (EUS)
  - visualize local disease
  - regional nodal involvement (number of nodes may be more important than location)
- bronchoscopy and laryngoscopy
  - rule out airway invasion in tumours of the upper and middle esophagus
- full metastatic workup (CXR, bone scan, CT head, CT chest/abdomen/pelvis, and LFTs, etc.)
- PET scan more sensitive than CT in detecting metastatic disease

Treatment
- if early stage (non-transmural and without evidence of nodal disease)
  - endoscopic mucosal resection can be considered for early mucosal cancer or high-grade dysplasia
  - esophagectomy (transthoracic or trans-hiatal approach) and lymphadenectomy
    - anastomosis in chest or neck
    - stomach is used for reconstruction; colon is rarely used
- if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and fluorouracil)
    - possibility of curative esophagectomy after chemoradiation if unable to tolerate multimodal therapy or if highly advanced disease, consider radiotherapy, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if present with distant metastatic disease, treat with systemic therapy and treat symptoms (esophageal stent or radiation)

Prognosis
- TNM status - usually poor because presentation is usually at advanced stage

OTHER DISORDERS
- esophageal motor disorders (see Gastroenterology, G8)
- esophageal varices (see Gastroenterology, G9)
- Mallory-Weiss tear (see Gastroenterology, G30)

Esophageal Perforation

Etiology
- iatrogenic (most common)
  - endoscopic, dilatation, biopsy, intubation, operative, and NG tube placement (rare)
- barogenic
  - trauma
  - repeated, forceful vomiting (Boerhaave's syndrome)
  - other: convulsions, defecation, or labour (rare)
- ingestion injury
  - foreign body or corrosive substance
- carcinoma
- penetrating trauma

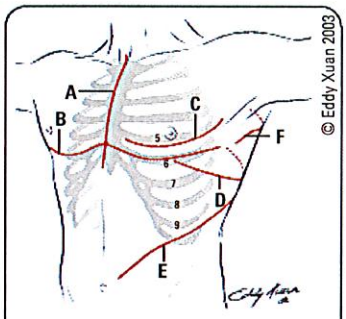
Clinical Features
- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, and respiratory compromise
- subcutaneous emphysema, pneumothorax, pleural effusion, voice changes, and hematemesis

Investigations
- CXR: subcutaneous emphysema, pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air, and widened mediastinum
- CT chest with oral and IV contrast: pneumomediastinum, pleural effusion, pneumothorax, contrast in the chest, and subcutaneous emphysema
- contrast esophagram
  - Gastrografin® (water-soluble contrast) upper GI study is the first choice
  - if negative, followed by dilute barium upper GI study: contrast extravasation

Treatment
- supportive if rupture is contained (see sidebar Cameron's Criteria)
- NPO, antibiotics, IV fluids, percutaneous drainage of mediastinal collections/abscess if needed, enteral/parenteral feed, and repeat imaging
- surgical (preferred treatment in progressively deteriorating or toxic patient)
  - <24 h from perforation
    - primary closure of a healthy esophagus with buttressed intercostal muscle flap or resection of diseased esophagus
  - >24 h from perforation, non-viable esophagus, or morbidly toxic patient
    - diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, and gastrostomy/jejunostomy for decompression/feeding)

Complications
- sepsis, abscess, fistula, empyema, mediastinitis, and death
- postoperative esophageal leak
- mortality 10-50% depending on timing of diagnosis, or etiology of the perforation, and underlying health and age of the patient

Cameron's Criteria for Conservative Management of Esophageal Perforation
- Perforation contained in mediastinum
- Contrast drains back into esophagus
- No signs of sepsis
- Minimal symptoms



A. Median sternotomy
B. Transverse thoracotomy (clam shell)
C. Anterolateral thoracotomy
D. Lateral thoracotomy
E. Thoracoabdominal thoracotomy
F. Posterolateral thoracotomy

Figure 7. Typical thoracic surgery incisions

Boerhaave's syndrome: transmural esophageal perforation
Mallory-Weiss tear: non-transmural esophageal tear (partial thickness tear)
Both are associated with forceful emesis

Standard of Care in 2019
1. Pre and postoperative FLOT chemotherapy for gastric and GE junction adenocarcinoma (docetaxel, oxaliplatin, and fluorouracil/leucovorin)
2. Neoadjuvant CROSS chemoradiotherapy for esophageal cancer with squamous histology or mid-body adenocarcinoma (carboplatin and paclitaxel plus radiotherapy)

6Ss of SCC
Smoking
Spirits (alcohol)
Seeds (betel nut)
Scalding (hot liquid)
Strictures
Sack (diverticula)

Hiatus Hernia

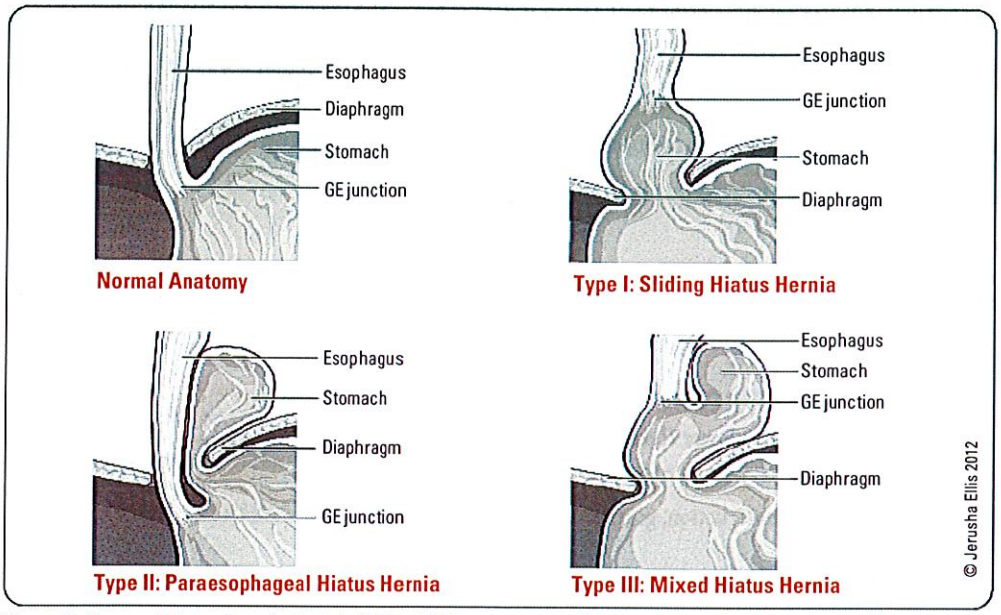


Figure 8. Types of hiatus hernia: Type I: Sliding (GE junction above the level of the diaphragm) Type II: Paraesophageal (GE junction below the diaphragm, fundus rolls past it) Type III: Mixed and Type IV: Massive (not shown) (containing another intra-abdominal organ: bowel/spleen/etc.)

SLIDING HIATUS HERNIA (TYPE I)

- reducible and/or limited herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

Risk Factors

- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, and heavy lifting)
- smoking

Clinical Features

- majority are asymptomatic
- symptoms in decreasing frequency are heartburn, regurgitation, eructation, sour taste, and cough

Complications

- complications are due to acid reflux when clinically significant and include these three categories:
  - esophagitis (dysphagia and heartburn)
  - consequences of esophagitis (peptic stricture, Barrett's esophagus, and esophageal carcinoma)
  - extra-esophageal complications (aspiration pneumonitis/pneumonia, bronchospasm, cough, and laryngitis)

Investigations

- barium study
- CXR or CT scan
- 24 h esophageal pH monitoring to quantify reflux and esophageal manometry (technique for measuring LES pressure)
- endoscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's esophagus, and cancer

Treatment

- lifestyle modification
  - smoking cessation, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, chocolate, and fatty foods
- medical
  - PPI, antacid, H2-antagonist, prokinetic agent
- surgical (<15% of cases)
  - consider if: volume regurgitation, patient unwilling or unable to stay on PPI indefinitely, suboptimal medical therapy, complications of GERD such as pharyngitis, esophageal stricture, recurrent nocturnal aspiration, Barrett's esophagus, patient preference
  - laparoscopic hiatus hernia repair and fundoplication
    - fundus of stomach is wrapped around the gastroesophageal junction and sutured in place

- operative principles are reduction of hernia, removal of hernia sac, fundoplication, and partial closure of hiatus
- 360 degree wrap: Nissen Fundoplication (most commonly performed). Dor, and Toupet are partial fundoplications
- expect transient postoperative clinical changes: dysphagia, bloating, excessive gas
- long-term complications may include post-prandial diarrhea and hernia recurrence in minority of patients
- dysphagia and gas bloat may be less with partial fundoplications (Toupet/Dor), however accompanied with higher risk of mild reflux symptoms
- 90% success rate for alleviating GERD



WebSurg
https://websurg.com/en/
WebSurg is an excellent resource which allows trainees to learn many different surgical techniques via videos and lectures. This resource primarily focuses on laparoscopic surgeries

PARAESOPHAGEAL HIATUS HERNIA (TYPE II)

- least common esophageal hernia (<10%)
- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction

Clinical Features

- usually asymptomatic due to normal GE junction
- dysphagia (most common), chest pain, and pressure sensation in lower chest

Complications

- hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron's lesion – causes Fe-deficiency anemia)



Elective laparoscopic procedures for paraesophageal hiatal hernia repair are associated with relatively low mortality. However, this value increases greatly with emergency repairs (7.5% vs. 0.5%)

MIXED HIATUS HERNIA (TYPE III)

- most common indication for surgical repair
- second most common type of hernia – combination of types I and II
- includes giant hernias or intrathoracic stomach
- rare incidence of gastric volvulus (Borschadt's Triad: chest pain, retching, inability to pass NG tube)
- may present with long-standing Fe-deficiency anemia of unknown etiology

Clinical Features

- symptoms may include reflux or heartburn
- most common symptoms: abnormal postprandial fullness after normal-sized meal, chest pain or retrosternal discomfort (gastric angina), and bloating
- can present with gastric outlet obstruction or gastric necrosis secondary to strangulation in the setting of gastric volvulus

Treatment

- surgery to address symptoms or treat/prevent complications
- reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
- may consider suturing stomach to anterior abdominal wall (gastropexy) to reduce the risk of gastric reherniation
- in very elderly patients at high surgical risk consider reduction of hernia and PEG (percutaneous endoscopic gastrostomy) insertion to anchor the stomach in the abdomen

TYPE IV HERNIA

- herniation of stomach and other abdominal organs into thorax: colon, spleen, pancreas, and small bowel
- similar presentation as type III hernia and may include intermittent large bowel symptoms (pain, hematochezia, constipation, etc.) if it is herniated

Achalasia

- esophageal smooth muscle motility disorder which occurs because the lower esophageal sphincter fails to relax
- esophagus does not have peristalsis
- in 50% of patients, the lower esophageal tone is hypertensive resulting in obstruction at the GE junction

Risk Factors

- spinal cord injury

Clinical Features

- dysphagia, initially solid than to liquids though a majority of patients will initially present with dysphagia to both solids and liquids
- regurgitation
- late symptoms include chest pain, nocturnal cough, and weight loss from difficulty eating

Investigations
- barium esophagram with a classic finding of smooth tapering of the lower esophagus to a "bird's beak" appearance
- upper endoscopy
- esophageal manometry will show incomplete lower esophageal sphincter relaxation in response to swallowing and sometimes a lack of peristalsis in the lower esophagus

Treatment
- non-surgical treatment:
  - pharmacologic: nitrates, calcium channel blockers, and phosphodiesterase-5 inhibitors to reduce LES pressure
  - endoscopic botulinum toxin injection
  - pneumatic dilation
- surgical treatment options:
  - laparoscopic Heller myotomy
  - peroral endoscopic myotomy

Complications
- esophageal perforation
- GERD
- bloating

Stomach and Duodenum

Peptic Ulcer Disease

GASTRIC ULCERS
- see Gastroenterology, G11

Indications for Surgery
- treat complications: bleeding (common indication for emergency management), perforation and obstruction (3x greater risk compared to duodenal ulcers)
- refractory to medical management–time period is unclear but generally after 8-12 wk of medical therapy
- suspicion of malignancy (even if biopsy is benign), especially if ulcer fails to heal after 12 wk of medical therapy
- surgery is becoming increasingly rare due to H. pylori eradication, medical treatment, endoscopic treatments (injection therapy with adrenaline, polidocanol, or fibrin glue) and coagulation therapy (heater probe or argon plasma)

Procedures
- ligation of bleeding vessels
- distal gastrectomy with ulcer excision: Billroth II, Roux-en-Y gastrojejunostomy, or Billroth I (rarely) reconstruction
- vagotomy and pyloroplasty only if acid hypersecretion (very rare)
- wedge resection if possible
- biopsy for suspicion of malignancy, followed by gastroscopy to minimize further bleeding and aid with healing

DUODENAL ULCERS
- see Gastroenterology, *Peptic Ulcer Disease*, G11
- most within 2 cm of pylorus (duodenal bulb)

Indications for Surgery
- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
- refractory to medical and endoscopic management

Procedures
- omental (Graham) patch: plication of perforated ulcer supported by overlying omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- treat with *H. pylori* eradication protocol postoperatively

Complications of Gastric Surgery
- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome

Table 12. Complications of Duodenal Ulceration

Complication	Clinical Features	Management
Perforated Ulcer (typically on anterior surface)	Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter) Acute abdomen: rigid, diffuse guarding Ileus Initial chemical peritonitis followed by bacterial peritonitis	Investigation CXR free air under diaphragm (70% of patients) Treatment Oversew ulcer (plication) and omental (Graham) patch most common treatment
Penetration to Nearby Organs	Elevated amylase/lipase if penetration into pancreas Elevated hepatic transaminases if penetration into liver (rare, but serious) Constant mid-epigastric pain burrowing into back, unrelated to meals	Management should follow the intensive measures for refractory ulcers
Hemorrhage (typically on posterior surface)	Gastroduodenal artery involvement	Resuscitation initially with crystalloids; blood transfusion if necessary Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope Consider interventional radiology: angiography with embolization/coiling Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty
Gastric Outlet Obstruction	Ulcer can lead to edema, fibrosis of pyloric channel, and neoplasm N/V (undigested food, non-bilious), dilated stomach, and crampy abdominal pain Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken) Auscultate gas and fluid movement in obstructed organ	NG tube decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high-dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty, or gastrojejunostomy

Gastric Carcinoma

Epidemiology

- 5th most common cancer in the world
- M:F=3:2
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr
- incidence highest in Asian, Latin American, and Caribbean countries

Risk Factors

- compensatory epithelial cell proliferation via gastric atrophy from:
  - *H. pylori*, causing chronic atrophic gastritis
  - pernicious anemia associated with achlorhydria and chronic atrophic gastritis
  - previous partial gastrectomy (>10 yr post-gastrectomy)
- lifestyle and environmental factors:
  - salt and salt-preserved food (e.g. salted fish, cured meat, and salted vegetables)
  - obesity
  - cigarette smoking
  - EBV infection
  - abdominal radiation therapy
- host-related factors
  - blood type A – also associated with pernicious anemia
  - hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
  - gastric adenomatous polyps
  - hypertrophic gastropathy
  - genetic syndromes: hereditary diffuse gastric cancer (e.g. E-cadherin (CDH1)) gene

Clinical Features

- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, pseudoachalasia (in older patients), vague epigastric pain
  - anorexia or weight loss
  - eructation, N/V, dyspepsia, and dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, and iron-deficiency anemia
- metastasis
  - peritoneum, ovarian, liver, lung, and brain

Investigations

- OGD and biopsy; consider EUS to assess preoperative T-stage and N-stage
- CT chest/abdomen/pelvis (with gastric protocol)

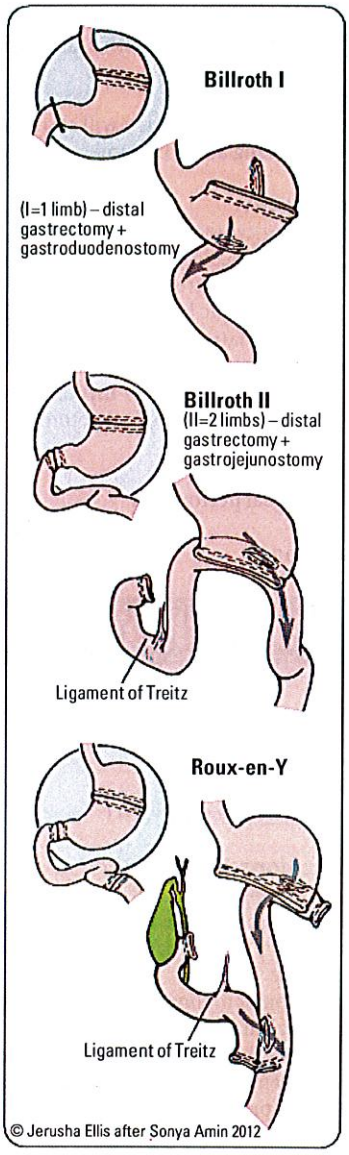


Figure 9. Billroth I and Billroth II with Roux-en-Y reconstruction (gastrojejunostomy)

Kissing Ulcer: combination of perforation and bleeding

Signs of Metastatic Gastric Carcinoma
Virchow's Node: left supraclavicular node
Blumer's Shelf: mass in pouch of Douglas
Krukenberg Tumour: metastases to ovary
Sister Mary Joseph Node: umbilical metastases
Irish's Node: left axillary nodes

Table 13. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2017, 8th edition)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional node metastasis	M1	Distant metastasis
Tis	Carcinoma *in situ*	N1	Metastasis in 1-2 regional nodes		
T1a	Invasion into lamina propria or muscularis mucosae	N2	Metastasis in 3-6 regional nodes		
T1b	Invasion into submucosa	N3a	Metastasis in 7-15 regional nodes		
T2	Invasion into muscularis propria	N3b	Metastasis in ≥16 regional nodes		
T3	Penetration of subserosal connective tissue without tissue invasion of visceral peritoneum or adjacent structures				
T4a	Invasion into serosa				
T4b	Invasion into adjacent structures				

Staging and 5 Yr Survival Rates for Gastric Cancer

Stage	TNM	5 Yr Survival
IA	T1N0M0	71%
IB	T2N0M0	57%
	T1N1M0	
IIA	T3N0M0	45%
	T2N1M0	
	T1T2M0	
IIB	T4aN0M0	33%
	T3N1M0	
	T2N2M0	
	T1N3M0	
IIIA	T4aN1M0	20%
	T3T2M0	
	T2N3M0	
IIIB	T4bN0M0	14%
	T4bN1M0	
	T4aN2M0	
	T3N3M0	
IIIC	T4bN2M0	9%
	T4bN3M0	
	T4aN3M0	
IV	TxNxM1	4%

Treatment

- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - subtotal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes (D2 lymphadenectomy) with Roux-en-Y or Billroth II reconstruction
  - adjuvant therapies
    - perioperative chemotherapy or postoperative chemoradiotherapy in addition to surgery is standard of care in a curative intent strategy
  - palliation
    - limited gastric resection or endoscopic stenting to decrease bleeding and relieve obstruction, enables the patient to eat
    - radiation therapy
    - studies are showing larger role for palliative chemotherapy
- lymphoma
  - *H. pylori* eradication, chemotherapy ± radiation, and surgery in limited cases (perforation, bleeding, and obstruction)

Gastrointestinal Stromal Tumour

Epidemiology

- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- often discovered incidentally on CT, laparotomy, or endoscopy

Neoadjuvant Chemotherapy in Advanced Gastric and Esophago-Gastric Cancer. Meta-Analysis of Randomized Trials
Int J Surg 2018;51:120-127
Study: Meta-analysis evaluating the effects of neoadjuvant chemotherapy on advanced gastric cancer.
Results/Conclusions: Neoadjuvant chemotherapy and resection reduces overall mortality at 3 and 5 yr in advanced gastric cancer (RR=0.74; 0.82 respectively). Morbidity and perioperative mortality rate are not influenced by NACT. Recurrence rate is reduced by NACT + surgery in EGC (RR=0.80).

Risk Factors

- Carney triad: gastric GISTs, extra-adrenal paraganglioma, and pulmonary chondroma
- type I neurofibromatosis
- Carney-Stratakis syndrome

Clinical Features

- most commonly in stomach (40-60%) and jejunum (25-30%)
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- sometimes asymptomatic (13-18%)
- nonspecific symptoms (8-17%): bloating, early satiety, abdominal pain/discomfort
- overt or occult GI bleeding (50% of gastric GISTs)

Investigations

- contrast-enhanced CT is preferred imaging for screening and staging; MRI if IV contrast not feasible
- preoperative biopsy (EUS): useful for indeterminate lesions (not recommended if high index of suspicion for GIST)
- given that lesions are submucosal, mucosal biopsies are sometimes non-diagnostil

Treatment
- surgical resection if >2 cm; follow with serial endoscopy if <2 cm (gastric GIST) and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT required as GISTs rarely metastasize to lymph nodes
  - consider adjuvant treatment with imatinib (Gleevec®) if high-risk of relapse (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - palliative intent chemotherapy with imatinib
  - metastasectomy may be considered for liver limited disease

Prognosis
- risk of metastatic potential depends on
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures/50 HPF)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- frequently metastasize to the liver and omentum; nodal and lung metastases rare



Extent of Lymph Node Dissection for Adenocarcinoma of the Stomach
Cochrane DB Syst Rev 2015;12:CD001964
Study: Systematic review and meta-analysis on the evidence that existed regarding the impact of the three main types of progressively more extended lymph node dissection (that is, D1, D2 and D3 lymphadenectomy) on the clinical outcome of patients with primary resectable carcinoma of the stomach.
Results/Conclusions: Data suggested no significant difference in overall survival between D2 and D3 type dissection. There was no significant difference in overall survival between D1 and D2 type node dissection. In contrast, D2 lymphadenectomy was associated with a significantly better disease specific survival compared to D1 lymphadenectomy but was also associated with a higher postoperative mortality rate.

Bariatric Surgery

- weight reduction surgery for morbid obesity
- indications: BMI ≥35 without illness or BMI ≥30 with 1+ serious comorbidity (e.g. DM, CAD, sleep apnea, GERD, or severe joint disease)
  - Asian patients: growing evidence to lower BMI criteria by 2.5 (i.e. BMI ≥37.5 or BMI ≥35.5) due to higher prevalence of truncal obesity
- consult with a multidisciplinary bariatric team: nutrition, psychological deterrents, life modifications, lifelong surveillance, reliable bariatric program (details realistic outcomes) to optimize success post-operation



Surgery for Weight Loss in Adults
Cochrane DB Syst Rev 2014;8:CD003641
Study: Update of a 2003 Cochrane review assessing the effects of bariatric surgery and control of comorbidities.
Conclusions: Surgery resulted in decreased BMI one to two years postoperative. 3 RCTs found that laparoscopic Roux-en-Y gastric bypass achieved significantly greater weight loss and BMI reduction up to 5 yr after surgery compared with laparoscopic adjustable gastric banding (mean difference -5.2 kg/m^2; 95% CI -6.4 to -4.0). More patients experienced remission of diabetes with lap R-en-Y, however, different definitions were used. Risks of surgery include leaks, hernias, infection, pulmonary embolism, cholecystitis, and postoperative mortality.

Surgical Options
- combination malabsorptive and restrictive
  - laparoscopic Roux-en-Y gastric bypass (most common, most effective; higher complication rates)
    - small gastric pouch (restrictive), from distal stomach, anastomosed with Roux limb of small bowel (malabsorptive); connect to biliopancreatic limb to maintain digestive enzymes and bile
    - complications: gastric remnant distention, stomal stenosis, marginal ulcers, cholelithiasis, ventral incisional hernia, short bowel syndrome, dumping syndrome, metabolic perturbations, gastrogastric fistula
  - restrictive laparoscopic sleeve gastrectomy
    - creation of tubular stomach via removal of majority of greater curvature
    - complications: bleeding from gastric or short gastric vessels from dissection of greater curve, stenosis at the gastroesophageal junction, gastric leaks
- malabsorptive
  - biliopancreatic diversion with duodenal switch (performed as a rescue operation after traditional Roux-en-y)
    - anastomosis of stomach to distal ileum, anastomosis of biliopancreatic limb to terminal Ileum
    - complications: protein calorie malnutrition, anemia, metabolic bone disease, fat-soluble vitamin deficiency

Complications of Gastric Surgery
- most resolve within 1 yr
- important to note that morbidly obese patients usually do not present with the symptoms and signs shown below; often times, the only presenting sign is tachycardia

Alkaline Reflux Gastritis
- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment
  - medical: H2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome
- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Landmark Medical Genetics Trials

Trial Name	Reference	Clinical Trial Details
PHENYLKETONURIA		
Glycomacropeptide for Nutritional Management of Phenylketonuria: A Randomized, Controlled, Crossover Trial	Am J Clin Nutr 2016; 104(2):334-345	**Title:** Glycomacropeptide for Nutritional Management of Phenylketonuria: A Randomized, Controlled, Crossover Trial **Purpose:** To evaluate the efficacy and safety of a low-phenylalanine (Phe) diet in combination with either glycomacropeptide medical foods (GMP-MFs) or traditional amino acid medical foods (AA-MFs) in individuals with phenylketonuria (PKU). **Methods:** Thirty early-treated individuals aged 15-49 yr with PKU participated in a 2-stage, randomized crossover trial involving consumption of a low-Phe diet with AA-MFs or GMP-MFs for periods of 3 wk each. **Results:** Dietary management of PKU with GMP-MFs compared to AA-MFs resulted in higher intake among participants. GMP-MFs were rated as more acceptable in terms of taste and had less side effects. **Conclusions:** GMP-MFs are safe for dietary management of PKU. GMP-MFs may improve dietary adherence for patients with PKU.
PRISM	Mol Genet Metab 2018; 124(1):27-38	**Title:** Pegvaliase for the Treatment of Phenylketonuria: Results of a Long-Term Phase 3 Clinical Trial Program (PRISM) **Purpose:** Evaluate the efficacy and safety of pegvaliase treatment in adults with phenylketonuria (PKU). **Methods:** Pegvaliase-naive participants with blood Phe >600 µmol/L were randomized to receive 20 mg/d or 40 mg/d of pegvaliase. **Results:** Pegvaliase treatment was given to 261 participants. Within 24 mo, 68.4% of participants achieved blood Phe ≤600 µmol/L. Reductions in blood Phe were associated with neuropsychiatric outcomes, which were maintained with long-term treatment. The vast majority of adverse events (99%) were mild or moderate in severity. **Conclusions:** Results from this trial suggest pegvaliase is safe and efficacious in treating adults with PKU.
CYSTIC FIBROSIS		
Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele	Am J Respir Crit Care Med 2021;203(12):1522	**Title:** Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele **Purpose:** Elexacaftor/tezacaftor/ivacaftor as a combination therapy was effective in treating patients aged greater than 12 years with CF and an accompanying F508del. This 24-week study served to evaluate the efficacy of treatment in patients less than <12 yr. **Methods:** RCT consisting of 66 children aged between 6 and 11 with CF who were assessed for the primary outcome of interest being safety and tolerability of the proposed treatment of oral Elexacaftor 100 mg once daily, Tezacaftor 50 mg once daily, and Ivacaftor 75 mg q12 h for children weighing ≤30 kg and oral Elexacaftor 200 mg once daily, Tezacaftor 100 mg once daily, and Ivacaftor 150 mg q 12 h for children weighing ≤30 kg. Additionally, efficacy of the treatment was also assessed (FEV_1, and Cystic Fibrosis Questionnaire–Revised respiratory domain score). **Results:** Commonly reported side effects included cough, headache, and fever. Treatment also resulted in improvements in predicted FEV_1 (10% improvement), and Cystic Fibrosis Questionnaire-Revised respiratory domain score (7.0 points improvement). **Conclusion:** Results show that treatment of CF with accompanying F508del using Elexacaftor/Tezacaftor/Ivacaftor resulted in significant improvements in patients aged under 12.
NON-SMALL CELL LUNG CANCER		
FLAURA	N Engl J Med 2018; 378(2):113-125	**Title:** Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer (NSCLC) **Purpose:** To compare Osimertinib (a third-generation EGFR inhibitor) against existing standard EGFR inhibitors in patients with previously untreated EGFR mutation-positive NSCLC **Methods:** Double-blind, RCT consisting of 556 previously untreated EGFR mutation positive NSCLC patients. Patients were randomized to receive osimertinib or a standard EGFR-TKI. Outcome of interest included clinician-assessed progression-free survival. **Results:** Median progression-free survival was greater in osimertinib when compared to standard EGFR-TKIs in EGFR mutation positive NSCLC patients (18.9 mo vs. 10.2 mo). **Conclusion:** Results of this study show that osimertinib had superior efficacy when compared to standard EGFR-TKIs.
ALKAPTONURIA		
SONIA-2	Lancet Diabetes Endocrinol. 2020 Sep;8(9):762-772	**Title:** Using Once-Daily Nitisinone for Treatment of Alkaptonuria **Purpose:** No homogentisic acid (HGA) lowering medications have been for treatment of Alkaptonuria. **Methods:** RCT consisting of 138 patients aged 25 or older with confirmed alkaptonuria were randomized to receive either oral nitisinone 10 mg daily or no treatment. The outcome of interest was daily urinary HGA excretion (u-HGA24) after 12 mo. **Results:** 55 patients in the nitisinone group and 53 in the control group completed the study. u-HGA24 at 12 mo was significantly decreased by 99·7% in the nitisinone group compared with the control group. Conclusion: Nitisinone was well tolerated within the treatment group and shows evidence of being an effective treatment for alkaptonuria.
ACHONDROPLASIA		
C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia	N Engl J Med 2019; 378(1):25-35	**Title:** C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia **Purpose:** To assess the efficacy and safety of vosoritide at treating achondroplasia in children **Methods:** RCT consisting of 35 children aged 5 to 14 with achondroplasia. Dosages were stratified based on weight; dose of 2.5 µg per kilogram of body weight (8 patients in cohort 1), 7.5 µg per kilogram (8 patients in cohort 2), 15.0 µg per kilogram (10 patients in cohort 3), or 30.0 µg per kilogram (9 patients in cohort 4). Patients were observed for 24 mo. The outcomes of interest were prevalence of adverse events and growth velocity. **Results:** Each patient experienced minor adverse effects such as pyrexia, hypothermia, erythema, cough, swelling and headaches. 4/35 patients experienced severe adverse effects including grade 3 obstructive sleep apnea, grade 1 tonsillar hypertrophy, grade 3 thyroglossal cyst, and grade 3 syrinx. At 6 mo, there were increases in annualized growth velocity in all cohorts except for that which received 2.5 µg. **Conclusion:** Although associated with mild side effects, with larger scale trials, vosoritide may be used as a treatment for achondroplasia in children.

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