POCKET NOTEBOOK

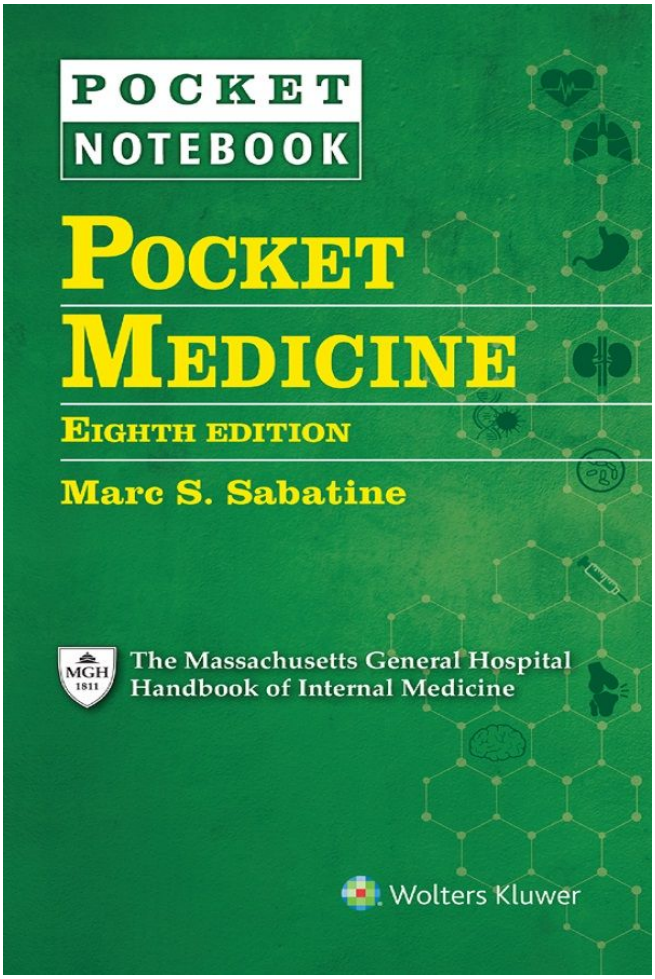
POCKET MEDICINE

EIGHTH EDITION

Marc S. Sabatine

The Massachusetts General Hospital Handbook of Internal Medicine

Wolters Kluwer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MGH
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Handbook of Internal Medicine
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Pocket MEDICINE

Eighth Edition

Edited by
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A Massachusetts General Hospital Handbook

Wolters Kluwer
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Joe Cho
Development Editor: Thomas Celona
Editorial Coordinator: Christopher Rodgers
Production Manager: Sadie Buckallew
Manufacturing Coordinator: Beth Welsh
Marketing Manager: Kirsten Watrud
Creative Director: Stephen Druding
Prepress Vendor: S4Carlisle Publishing Services

Eighth Edition

9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data

ISBN-13: 978-1-975182-99-1
ISBN-10: 1-975182-99-5

Library of Congress Control Number: 2022908538

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FOREWORD

To the 1st Edition

It is with the greatest enthusiasm that I introduce *Pocket Medicine.* In an era of information glut, it will logically be asked, "Why another manual for medical house officers?" Yet, despite enormous information readily available in any number of textbooks, or at the push of a key on a computer, it is often that the harried house officer is less helped by the description of differential diagnosis and therapies than one would wish.

Pocket Medicine is the joint venture between house staff and faculty expert in a number of medical specialties. This collaboration is designed to provide a rapid but thoughtful initial approach to medical problems seen by house officers with great frequency. Questions that frequently come from faculty to the house staff on rounds, many hours after the initial interaction between patient and doctor, have been anticipated, and important pathways for arriving at diagnoses and initiating therapies are presented. This approach will facilitate the evidence-based medicine discussion that will follow the workup of the patient. This well-conceived handbook should enhance the ability of every medical house officer to properly evaluate a patient in a timely fashion and to be stimulated to think of the evidence supporting the diagnosis and the likely outcome of therapeutic intervention. *Pocket Medicine* will prove to be a worthy addition to medical education and to the care of our patients.

DENNIS A. AUSIELLO, MD
Physician-in-Chief, Massachusetts General Hospital
Jackson Professor of Clinical Medicine, Harvard Medical School

PREFACE

To my parents, Matthew and Lee Sabatine; to their namesake grandchildren, Matteo and Natalie; and to my wife, Jennifer

Written by residents, fellows, and attendings, the mandate for *Pocket Medicine* was to provide, in as concise a manner as possible, the key information a clinician needs for the initial approach to and management of the most common inpatient medical problems.

The tremendous response to the previous editions suggests we were able to help fill an important need for clinicians. With this eighth edition come several major improvements. We have updated every topic thoroughly. In particular, we have included data on the newest pharmacotherapies for heart failure and the latest treatment algorithms for valvular heart disease. We have added a section for pharmacomechanical therapy for VTE and updated the treatment for pulmonary hypertension. We now include a section on other solid tumors including gastric & esophageal cancer, ovarian cancer, and melanoma, and we expanded the sections on immunotherapy and cellular therapy. Naturally we now have a section on COVID-19 and have also added a section on sexually transmitted infections. We continue to expand the discussion of SGLT2i and GLP1-RA for diabetes. As always, we have incorporated key references to the most recent high-tier reviews and important studies published right up to the time *Pocket Medicine* went to press. We welcome any suggestions for further improvement.

Of course, medicine is far too vast a field to ever summarize in a textbook of any size. Long monographs have been devoted to many of the topics discussed herein. *Pocket Medicine* is meant only as a starting point to guide one during the initial phases of diagnosis and management until one has time to consult more definitive resources. Although the recommendations herein are as evidence-based as

possible, medicine is both a science and an art. As always, sound clinical judgment must be applied to every scenario.

I am grateful for the support of the house officers, fellows, and attendings at the Massachusetts General Hospital. It is a privilege to work with such a knowledgeable, dedicated, and compassionate group of physicians. I always look back on my time there as chief resident as one of my best experiences. I am grateful to several outstanding clinical mentors, including Hasan Bazari, Larry Friedman, Nesli Basgoz, Eric Isselbacher, Mike Fifer, and Roman DeSanctis, as well as the late Charlie McCabe, Mort Swartz, and Peter Yurchak.

This edition would not have been possible without the help of Kate Brennan, my academic coordinator. She shepherded every aspect of the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be. This edition also naturally builds on the work of the many contributors to prior editions of *Pocket Medicine*, whom we thank for creating such an impressive foundation.

Lastly, special thanks to my parents for their perpetual encouragement and love and, of course, to my wife, Jennifer Tseng, who, despite being a surgeon, is my closest advisor, my best friend, and the love of my life.

I hope that you find *Pocket Medicine* useful throughout the arduous but incredibly rewarding journey of practicing medicine.

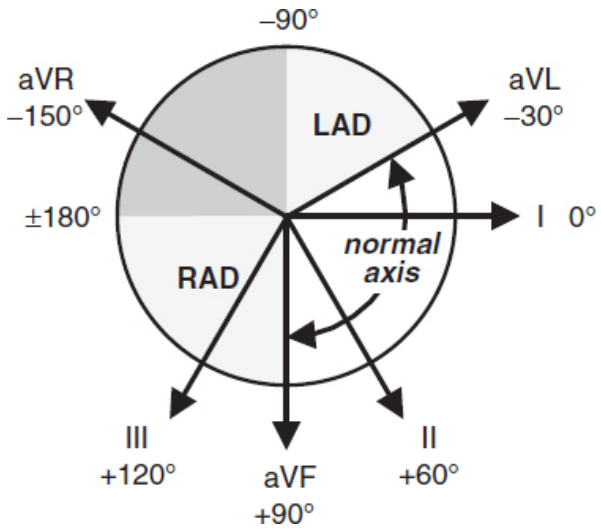
MARC S. SABATINE, MD, MPH

ELECTROCARDIOGRAPHY

Approach (a systematic approach is vital)

- **Rate** (? tachy or brady), **rhythm** (? P waves, regularity, P & QRS relationship)
- **Intervals** (PR, QRS, QT), **axis** (? LAD or RAD), **chamber abnl** (? LAA, RAA, LVH, RVH)
- **QRST changes** (? Q waves, poor R-wave progression V_1–V_6, ST ↑/↓ or T-wave Δs)

Figure 1-1 QRS axis



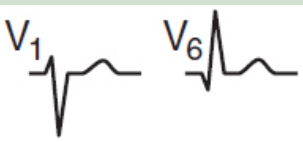
Left axis deviation (LAD)

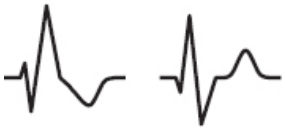
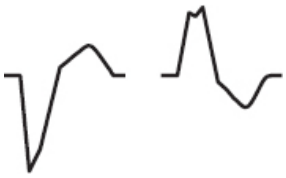
- **Definition:** axis beyond –30° (S >R in lead II)
- **Etiologies:** LVH, LBBB, inferior MI, WPW
- **Left anterior fascicular block (LAFB):** LAD (–45 to –90°) *and* qR in aVL *and* QRS <120 msec *and* no other cause of LAD (eg, IMI)

Right axis deviation (RAD)

- **Definition:** axis beyond +90° (S >R in lead I)
- **Etiologies:** RVH, PE, COPD (usually not >+110°), septal defects, lateral MI, WPW
- **Left posterior fascicular block (LPFB):** RAD (90–180°) *and* rS in I & aVL *and* qR in III & aVF *and* QRS <120 msec *and* no other cause of RAD

Bundle Branch Blocks (*Circ* 2009;119:e235)

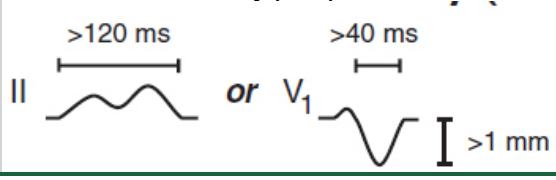
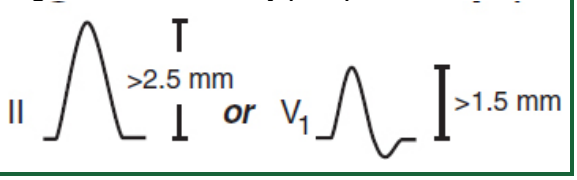
Normal		Initial depol. left to right across septum (r in V_1 & q in V_6; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB).

Bundle Branch Blocks (*Circ* 2009;119:e235)		
RBBB		1. QRS ≥120 msec (110–119 msec = IVCD or "incomplete") 2. rSR′ in R precordial leads (V_1, V_2) 3. Wide S wave in I and V_6 4. ± ST↓ or TWI in R precordial leads
LBBB		1. QRS ≥120 msec (110–119 msec = IVCD or "incomplete") 2. Broad, slurred, monophasic R in I, aVL, V_5–V_6 (± RS in V_5–V_6 if cardiomegaly) 3. Absence of Q in I, V_5, and V_6 (may have narrow q in aVL) 4. Displacement of ST & Tw opposite major QRS deflection 5. ± PRWP, LAD, Qw's in inferior leads

Bifascicular block: RBBB + LAFB/LPFB. "Trifascicular block": bifascicular block + 1° AVB.

Prolonged QT interval (*NEJM* 2008;358:169; www.torsades.org)

- Measure QT using threshold method (start of QRS to end of Tw at isoelectric line) or tangent (QRS to where tangent of Tw downslope intersects baseline) when long tail. Use longest QT (often V_2 or V_3) and omit U wave (*Circ* 2018;138:2345).
- QT varies w/ HR → corrected w/ Bazett formula: $QTc = QT/\sqrt{RR}$ (RR in sec), overcorrects at high HR, undercorrects at low HR (nl QTc <450 msec ♂, <460 msec ♀)
- Fridericia's formula preferred at very high or low HR: $QTc = QT/\sqrt[3]{RR}$
- QT prolongation a/w ↑ risk TdP (espec >500 msec); establish baseline QT and monitor if using QT prolonging meds, no estab guidelines for stopping Rx if QT prolongs
- Etiologies:
  - **Antiarrhythmics:** class Ia (procainamide, disopyramide), class III (amio, sotalol, dofet)
  - **Psych drugs:** antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? SSRI, TCA
  - **Antimicrobials:** macrolides, quinolones, azoles, pentamidine, atazanavir
  - **Other:** antiemetics (droperidol, 5-HT_3 antagonists), alfuzosin, methadone, ranolazine
  - **Electrolyte disturbances:** hypoCa (nb, hyperCa a/w ↓ QT), ± hypoK, ? hypoMg
  - **Autonomic dysfxn:** ICH (deep TWI), Takotsubo, stroke, CEA, neck dissection
  - **Congenital** (long QT syndrome): K, Na, & Ca channelopathies (*Circ* 2013;127:126)
  - **Misc:** CAD, CMP, bradycardia, high-grade AVB, hypothyroidism, hypothermia, BBB

Bundle Branch Blocks (*Circ* 2009;119:e235)		
ECG P-wave criteria	**Left Atrial Abnormality (LAA)**	**Right Atrial Abnormality (RAA)**
		

Left ventricular hypertrophy (LVH) (*Circ* 2009;119:e251)

- Etiologies: HTN, AS/AI, HCM, coarctation of aorta
- Criteria (all w/ Se <50%, Sp >85%; accuracy affected by age, sex, race, BMI)
  - **Sokolow-Lyon:** S in V_1 + R in V_5 or V_6 ≥35 mm or R in aVL ≥11 mm (↓ Se w/ ↑ BMI)

Cornell: R in aVL + S in V_3 >28 mm in men or >20 mm in women

Romhilt-Estes point-score system (4 points = probable; 5 points = diagnostic): ↑ volt: limb lead R or S ≥20 mm *or* S in V_1 or V_2 ≥30 mm *or* R in V_5 or V_6 ≥30 mm (3 pts)

ST displacement opposite to QRS deflection: w/o dig (3 pts); w/ dig (1 pt)

LAA (3 pts); LAD (2 pts); QRS duration ≥90 msec (1 pt)

Intrinsicoid deflection (QRS onset to peak of R) in V_5 or V_6 ≥50 msec (1 pt)

If LAFB present: S in III + max (R+S) in any lead ≥30 mm in men or ≥28 mm in women

Right ventricular hypertrophy (RVH) (*Circ* 2009;119:e251; *JACC* 2014;63:672)

- Etiologies: cor pulmonale, congenital (tetralogy of Fallot, TGA, PS, ASD, VSD), MS, TR
- Criteria [all insensitive, but specific (except in COPD); all w/ poor PPV in general population]

  R >S in V_1, R in V_1 ≥6 mm, S in V_5 ≥10 mm, S in V_6 ≥3 mm, R in aVR ≥4 mm

  RAD ≥110° (LVH + RAD *or* prominent S in V_5 or V_6 → consider *biventricular* hypertrophy)

Ddx of dominant R wave in V_1 or V_2

- Ventricular abnl: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCM; Duchenne's
- Posterior MI: anterior R wave = posterior Q wave; often with IMI
- Abnormal depolarization: RBBB (QRS >120 msec, rSR′); WPW (↓ PR, δ wave, ↑ QRS)
- Other: dextroversion; counterclockwise rotation; lead misplacement; nl variant

Poor R wave progression (PRWP) (*Am Heart J* 2004;148:80)

- Definition: loss of anterior forces w/o frank Q waves (V_1–V_3); R wave in V_3 ≤3 mm
- Etiologies: old anteroseptal MI (w/ R wave V_3 ≤1.5 mm, ± persistent ST ↑ or TWI V_2 & V_3)

  LVH (delayed RWP w/ ↑ left precordial voltage); RVH; COPD (may also have RAA, RAD, limb lead QRS amplitude ≤5 mm, $S_I S_{II} S_{III}$ w/ R/S ratio <1 in those leads)

  LBBB; WPW; clockwise rotation of the heart; lead misplacement; CMP; PTX

Pathologic Q waves

- Definition: ≥30 msec (≥20 msec V_2–V_3) or >25% height of R wave in that QRS complex
- Small (septal) q waves in I, aVL, V_5 & V_6 are nl, as can be isolated Qw in III, aVR, V_1
- "Pseudoinfarct" pattern may be seen in LBBB, infiltrative dis., HCM, COPD, PTX, WPW

ST elevation (STE) (*NEJM* 2003;349:2128; *Circ* 2009;119:e241 & e262)

- **Acute MI:** upward convexity STE (ie, a "frown") ± TWI (or prior MI w/ persistent STE)
- **Coronary spasm:** Prinzmetal's angina; transient STE in a coronary distribution
- **Pericarditis:** diffuse, upward concavity STE (ie, a "smile"); a/w PR ↓; Tw usually upright
- **HCM, Takotsubo CMP, ventricular aneurysm,** cardiac contusion

- **Pulmonary embolism:** occ. STE V_1–V_3; classically a/w TWI V_1–V_4, RAD, RBBB, $S_1Q_3T_3$
- **Repolarization abnormalities:**
  - LBBB (↑ QRS duration, STE discordant from QRS complex; see "ACS" for dx MI in LBBB)
  - LVH (↑ QRS amplitude); Brugada syndrome (rSR′, downsloping STE V_1–V_2); pacing
  - Hyperkalemia (↑ QRS duration, tall Ts, no P's); epsilon waves (late afterdepol.) in ARVC
- **aVR:** STE >1 mm a/w ↑ mortality in STEMI; STE aVR > V_1 a/w left main disease
- **Early repolarization:** most often seen in V_2–V_5 in young adults (*Circ* 2016;133:1520)
  - 1–4 mm elev of notch peak or start of slurred downstroke of R wave (ie, J point); ± up concavity of ST & large Tw (∴ ratio of STE/T wave <25%; may disappear w/ exercise)
  - ? early repol in inf leads may be a/w ↑ risk of VF (*NEJM* 2009;361:2529; *Circ* 2011;124:2208)
- **Post-ROSC:** transient STE can be seen w/in 1st ~8 mins; not indicative of ACS

ST depression (STD)
- **Myocardial ischemia** (± Tw abnl)
- **Acute true posterior MI:** posterior STE appearing as anterior STD (± ↑ R wave) in V_1–V_3 ✓ posterior ECG leads; manage as a STEMI with rapid reperfusion (see "ACS")
- Digitalis effect: downsloping ST ± Tw abnl; does *not* correlate w/ dig levels
- Hypokalemia (± U wave)
- Repolarization abnl a/w LBBB or LVH (usually in leads V_5, V_6, I, aVL, called "LV strain")

T wave inversion (TWI; generally ≥1 mm; deep if ≥5 mm) (*Circ* 2009;119:e241)
- Ischemia or infarct; *Wellens' sign* (deep, symm precordial TWI) → critical prox LAD lesion
- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec if TWI V_1–V_4)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"); BBB; nl variant if QRS predom. ⊖
- Posttachycardia or postpacing ("memory" T waves)
- Electrolyte, digoxin, PaO_2, $PaCO_2$, pH/core temp Δ's, intracranial bleed ("cerebral Tw")

Low voltage
- QRS amplitude (R + S) <5 mm in all limb leads & <10 mm in all precordial leads
- Etiol: COPD, pericardial/pleural effusion, myxedema, ↑ BMI, infiltrative CMP, diffuse CAD

Electrolyte abnormalities
- ↑ **K:** tented Tw, ↓ QT, ↑ PR, AVB, wide QRS, STE; ↓ **K:** flattened Tw, U waves, ↑ QT
- ↑ **Ca:** ↓ QT, flattened Tw & Pw, J point elevation; ↓ **Ca:** ↑ QT; Tw Δs

ECG in young athletes (*JACC* 2017;69:805)
- Normal patterns may include LVH, RVH, early repolarization

- Evaluate if: arrhythmia, HR <30, ↑ QT, ε/δ waves, LBBB, Brugada pattern, QRS >140 ms, PR >400 ms, Mobitz II, 3˚ AVB, ST depression, TWI

CHEST PAIN

Disorder	Typical Characteristics & Diagnostic Studies
	Cardiovascular Causes
Angina/ACS (<10% of chest pain in ED)	Substernal "pressure" (⊕ LR 1.3) → neck, jaw, arm (⊕ LR 1.3–1.5) Sharp, pleuritic, positional, or reprod. w/ palp all w/ ⊕ LR ≤0.35 Diaphoresis (⊕ LR 1.4), dyspnea (⊕ LR 1.2), a/w exertion (⊕ LR 1.5–1.8) ≈ prior MI (⊕ LR 2.2); ↓ w/ NTG/rest (but not reliable; *Annals EM* 2005;45:581) ± ECG Δs: STE, STD, TWI, hyperacute Tw, Qw. ± ↑ Troponin.
Pericarditis & myo-pericarditis	Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG Δs (diffuse STE & PR ↓, opposite in aVR) ± pericardial effusion. If myocarditis, same as above + ↑ Tn and ± s/s HF and ↓ EF.
Aortic dissection	Sudden severe tearing pain (absence ⊖ LR 0.3). ± Asymm (>20 mmHg) BP or pulse (⊕ LR 5.7), focal neuro deficit (⊕ LR >6), AI, widened mediast. on CXR (absence ⊖ LR 0.3); false lumen on imaging.
PE	Sudden onset pleuritic pain. ↑ RR & HR, ↓ S_aO_2, ECG Δs (sinus tach, RAD, RBBB, $S_IQ_{III}T_{III}$, TWI V_1–V_4, occ STE V_1–V_3), + CTA or V/Q, ± ↑ Tn.
Pulm HTN	Exertional pressure, DOE. ↓ S_aO_2, loud P_2, RV heave, right S_3 and/or S_4.
	Pulmonary Causes
Pneumonia	Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.
Pleuritis	Sharp, pleuritic pain. ± Pleuritic friction rub.
PTX	Sudden onset, sharp pleuritic pain. Hyperresonance, ↓ BS. PTX on CXR.
	GI Causes
Esoph reflux	Substernal burning, acid taste in mouth, ↑ by meals. See "GERD."
Esoph spasm	Intense substernal pain. ↑ by swallowing, ↓ by NTG/CCB. Manometry.
Mallory-Weiss	Esoph tear precipitated by vomiting. ± Hematemesis. Dx w/ EGD.
Boerhaave	Esoph rupture. Severe pain, ↑ w/ swallow. Mediastinal air palpable & on CT.
PUD	Epigastric pain, relieved by antacids. ± GIB. EGD, ± *H. pylori* test.
Biliary dis.	RUQ pain, N/V. ↑ by fatty foods. RUQ U/S, CT, MRCP; ↑ LFTs.
Pancreatitis	Epigastric/back discomfort. ↑ amylase & lipase; abdominal CT.
	Musculoskeletal and Miscellaneous Causes
Costochond	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
Zoster	Intense unilateral pain. Pain may precede dermatomal rash.
Anxiety	"Tightness," dyspnea, palpitations, other somatic symptoms

(*Braunwald's Heart Disease*, 12th ed, 2022; *JAMA* 2015;314:1955)

Initial diagnostic studies

- **Focused history:** quality, severity, location, radiation; provoking/palliating factors; intensity at onset; duration, freq, & pattern; setting; assoc sx; cardiac hx & risk factors
- **Targeted exam:** VS (incl. BP in both arms); gallops, murmurs, rubs; signs of vascular dis. (carotid/femoral bruits, ↓ pulses) or CHF; lung & abd. exam; chest wall for reproducibility

- • **12-lead ECG:** obtain w/in 10 min; comp to priors & obtain serial ECGs; consider *posterior leads* (V_7–V_9) if hx c/w ACS but stnd ECG unrevealing or ST ↓ V_1–V_3 & pain refractory
- **Troponin:** *>99th %ile w/ rise and/or fall in approp. setting is dx of AMI* (*Circ* 2018;138:e618)
  - High-sens Tn (hsTn) detectable 1 h after injury, peaks ~24 h, can be elevated for >1 wk
  - ✓ at presentation & 1–3 h later; repeat if clinical or ECG Δs; assess absolute level & Δ
  - Ddx: *MI* (type 1 [plaque rupture] or 2 [supply-demand mismatch not due to Δ in CAD), *non-ischemic cardiac* (eg, myocarditis, ADHF, Takotsubo, defibrillation, contusion), *systemic illness* (eg, PE, PHT, stroke, SAH, critical illness)
- **CXR;** other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing

Initial approach (*Circ* 2021;144:e368)

- • R/o life-threatening causes (ACS, PE, AoD, myopericarditis, etc.)
- If possible ACS, risk stratify w/ clinician decision pathway (clinical factors + ECG + Tn)
- **Low prob ACS** (eg, H&P unconcerning, ⊖ ECG & Tn): d/c to home; risk factor mgmt
- **Intermed prob ACS** (neither low nor high clinical risk, ± borderline Tn): ✓ TTE and
  - If no known CAD → CCTA or stress (former ↓ LOS c/w fxnal testing; *NEJM* 2012;366:1393)
  - If recent mildly ⊕ stress or known non-obstructive CAD → CCTA
  - If obstructive but not high-risk CAD → stress test
  - If recent mod-severely ⊕ stress or high-risk CAD (LM, prox LAD, MVD) → invasive angio
- **High prob ACS** (eg, ECG Δs, ⊕ Tn, new ↓ LVEF): invasive coronary angiography
- Pts w/ acute CP: CCTA vs. stress testing → ↓ time to dx & LOS (less so in era of hsTn), but ↑ probability of cath/PCI (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880)

NONINVASIVE EVALUATION OF CAD

Stress testing (*J Nucl Cardiol* 2016;23:606; *EHJ* 2020;41:407)

- **Indications:** evaluate possible CAD sx or Δ in clinical status in Pt w/ known CAD, risk stratify after chest pain, evaluate exercise tolerance, localize ischemia (imaging required)
- **Contraindications** (*Circ* 2002;106:1883; & 2012;126:2465)
  - **Absolute:** AMI w/in 48 h, high-risk UA, acute PE, severe sx AS, uncontrolled HF, uncontrolled arrhythmias, severe HTN (SBP >200), myopericarditis, acute AoD
  - **Relative** (discuss with stress lab): left main CAD, mod symptomatic valvular stenosis, HCM w/ LVOT obstruction, high-degree AVB, severe electrolyte abnl

Exercise tolerance test (w/ ECG alone)

- Generally preferred if Pt can meaningfully exercise; ECG Δs w/ Se ~65%, Sp ~80%
- Typically via treadmill w/ Bruce protocol (modified Bruce or submax if decond. or recent MI)
- Hold anti-isch. meds (eg, nitrates, βB) if dx'ing CAD but give to assess adequacy of meds

Pharmacologic stress test (nb, requires imaging because ECG not interpretable)

- Use if unable to exercise, low exercise tolerance, or recent MI. Se & Sp ≈ exercise.
- Preferred if LBBB, WPW or V-paced, because higher prob of false ⊕ imaging with exercise
- *Coronary vasodilator:* diffuse vasodilation → relative perfusion defect in vessels w/ fixed epicardial disease. Reveals CAD, but *not* if Pt *ischemic w/ exercise.* Regadenoson (↓ side effects), dipyridamole, adenosine. Side effects: flushing, ↓ HR, AVB, SOB, bronchospasm.
- *Chronotropes/inotropes* (dobuta): more physiologic, but longer test; may precip arrhythmia

Imaging for stress test

- Use if uninterpretable ECG (V-paced, LBBB, resting ST ↓ >1 mm, digoxin, LVH, WPW), after indeterminate ECG test, or if pharmacologic test
- Use when need to localize ischemia (often used if prior coronary revasc)
- Radionuclide myocardial perfusion imaging w/ images obtained at rest & w/ stress
  SPECT (eg, ^{99m}Tc-sestamibi): Se ~85%, Sp ~80%
  PET (rubidium-82): Se ~90%, Sp ~85%; requires pharmacologic stress, not exercise
  ECG-gated imaging allows assessment of regional LV fxn (sign of ischemia/infarction)
- **Echo** (exercise or dobuta): Se ~80%, Sp ~85%; no radiation; operator dependent

Test results

- **HR** (must achieve ≥85% of max pred HR [220-age] for *exer.* test to be dx), **BP** response, peak **double product** (HR × BP; nl >20k), HR recovery ($HR_{peak} - HR_{1\ min}$

$_{later}$; nl >12)
- **Max exercise capacity** achieved (METS or min); **occurrence of symptoms**
- **ECG Δs:** *downsloping* or *horizontal* ST ↓ (≥1 mm) 60–80 ms after QRS predictive of CAD (but does *not* localize ischemic territory); however, STE highly predictive & localizes
- Duke treadmill score = exercise min – (5 × max ST dev) – (4 × angina index) [0 none, 1 nonlimiting, 2 limiting]; score ≥5 → <1% 1-y mort; –10 to + 4 → 2–3%; ≤–11 → ≥5%
- **Imaging:** radionuclide defects or echocardiographic regional wall motion abnormalities
  reversible defect = ischemia; fixed defect = infarct; transient isch dilation → ? severe 3VD
  false ⊕: breast → ant defect; diaphragm → inf defect. False ⊖: balanced (3VD) ischemia.

High-risk test results (PPV ~50% for LM or 3VD, ∴ consider coronary angio)
- ECG: ST ↓ ≥2 mm *or* ≥1 mm in stage 1 *or* in ≥5 leads *or* ≥5 min in recovery; ST ↑; VT
- Physiologic: ↓ or fail to ↑ BP, <4 METS, angina during exercise, Duke score ≤–11; ↓ EF
- Radionuclide: ≥1 lg or ≥2 mod. reversible defects, transient LV cavity dilation, ↑ lung uptake

Myocardial viability (*Circ CV Imaging* 2020;13:e53)
- Goal: identify hibernating myocardium that could regain fxn after revascularization
- Options: **MRI** (Se ~95%, Sp ~50%), **PET** (Se ~90%, Sp ~65%), **dobutamine stress echo** (Se ~80%, Sp ~80%); **SPECT/rest-redistribution** (Se ~85%, Sp ~65%)
- Pts w/ ischemic CMP (EF <35%), viability predicts ↑ EF w/ CABG but not survival or benefit of CABG vs. medical Rx (*NEJM* 2011;364:1617 & 2019;381:739)

Coronary CT angiography (*JCCT* 2021;15:192)
- *Gated* CT of heart timed during peak contrast enhancement in coronary arteries
- NTG given to dilate coronary arteries. β-blockers commonly used to lower HR.
- CT-FFR: uses computational fluid dynamics to estimate fxnal significance of focal lesions
- CAD-RADS score in stable CP improves risk stratif. of CV events (*JACC Img* 2020;13:1534)
- In stable outPt w/ CP: CCTA added to stnd of care → ↑ early but not overall angiography/revasc; ↑ use of preventive med Rx, and ↓ coronary death/MI by 5 y (*NEJM* 2018;379:924)

Coronary artery calcium (CAC) score
- Quantifies extent of calcium; thus, *estimates* plaque burden (but *not* % coronary stenosis)
- CAC sensitive (91%) but not specific (49%) for presence of CAD; high NPV to r/o CAD
- In intermediate-risk or selected borderline-risk adults (ie, 10-year ASCVD risk of 5–20%), if decision about statin remains uncertain, reasonable to use CAC score to help guide

CORONARY ANGIOGRAPHY & PCI

Precath checklist

- Peripheral arterial exam (radial, femoral, DP, PT pulses; bruits); palmar arch eval (eg, w/ pulse oximetry & plethysmography) not routinely done. ✓ can lie flat × hrs, NPO >6 h.
- ✓ CBC, PT-INR (ideally ≤2), Cr; hold ACEI/ARB if renal dysfxn. Blood bank sample.
- ↓ risk of contrast-induced kidney injury: hold ACEI/ARB/ARNI, NSAIDs, diuretics. PreRx w/ isotonic IVF: data mixed, but may be helpful if high risk (*Lancet* 2017;389:1312).
- If iodinated contrast allergy, preRx w/ steroids & antihistamines

Vascular access

- Radial access preferred for coronary angiography: ↓ major bleeding & vascular complications, and possibly mortality benefit (*Circ CI* 2018;11:e000035)
- Femoral artery commonly used; high puncture ↑ risk of retroperitoneal bleed; low puncture ↑ risk of arterial complic. (eg, AV fistula, superficial femoral artery cannulation)

Periprocedural pharmacotherapy for PCI

- **ASA** 325 mg × 1. **$P2Y_{12}$ inhibitor**: ticagrelor or prasugrel preferred over clopidogrel in ACS. Outside of STEMI, preRx load not recommended when anatomy unknown. Cangrelor (IV $P2Y_{12}$ inhib) ↓ peri-PCI events vs. clopi w/o PreRx (*NEJM* 2013;368:1303).
- GP IIb/IIIa inhibitor: sometimes added if periprocedural thrombotic complication
- **Anticoagulant:** UFH or bivalirudin (if HIT) typically given during case and stopped at end

PCI and peri-PCI interventions

- *Physiology:* fractional flow reserve (FFR): ratio of max flow (induced by adenosine) distal vs. prox to stenosis to ID hemodyn. signif. lesions (≤0.80). Instantaneous wave-free ratio (iFR) similar, doesn't require vasodilator; iFR threshold ≤0.89 (*NEJM* 2017;376:1813 & 1824).
- *Advanced imaging:* intravascular U/S (IVUS) or optical coherence tomography (OCT)
- Drug-eluting stents (DES): ↓ cardiac death, MI, repeat revasc, & stent thrombosis vs. BMS (*Lancet* 2019;393:2503). Balloon angioplasty alone reserved for lesions too narrow to stent.

Peri-PCI complications

- No or slow reflow: Rx with local delivery of vasodilators
- Coronary artery dissection: treat with stent
- Coronary perforation: immediate balloon tamponade, ✓ for effusion, seal w/ covered stent

Vascular access post-PCI complications

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr

- **Bleeding**: reverse/stop anticoag (d/w interventionalist); IV fluids/PRBC/plts as required
  hematoma/overt bleeding: **manual compression**
  retroperitoneal bleed: may p/w ↓ Hct ± flank or back pain. CT abd/pelvis (I^-) or angio if unstable. If does not auto-tamponade, intravascular balloon and/or covered stent.
- **Vascular damage** (~1% of dx angio, ~5% of PCI; *Circ* 2007;115:2666)
  pseudoaneurysm: triad of pain, expansile mass, systolic bruit; diagnose w/ U/S; Rx (if pain or >2 cm): U/S-directed thrombin injection, surgical repair if former fails
  AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair if large or sx
  limb ischemia (emboli, dissection, clot): cool, mottled extremity, ↓ distal pulses; Dx: loss of pulses, ↓ pulse volume recording, angio; Rx: percutaneous or surgical repair
  radial artery occlusion: if sx, consider 4 weeks LMWH

Other complications (*NEJM* 2017;377:1513)

- **Contrast-induced AKI:** w/in 48 h, peak 3–5 d; pre-hydration reasonable (see "CIAKI")
- **Stroke**: ~0.1–0.4% of cases. Usually ischemic from atheroembolic event during cath. Rx depends on sx/location/timing but includes thrombectomy, tPA, DAPT if ischemic.
- **Cholesterol emboli syndrome**: typically in Pts w/ large burden Ao atheroma; mesenteric ischemia (abd pain, LGIB, pancreatitis); intact distal pulses but livedo and toe necrosis

Stent post-PCI complications

- **Stent thrombosis:** acute clot formation in stent usually in 1st mo but can occur anytime. Typically p/w AMI. Often due to premature d/c antiplt Rx or mech prob. (stent underexpansion or unrecognized dissection, typically presents early).
- **In-stent restenosis:** develops in previously stented segment mos after PCI. Typically p/w gradual ↑ angina. Due to elastic recoil and neointimal hyperplasia; ↓ w/ DES.

Duration of dual antiplatelet therapy (*JACC* 2016;68:1082 & *EHJ* 2018;39:213)

- DAPT duration determined by patient presentation (ACS vs. SIHD), long-term ischemic risk (patient and procedural risk factors), and bleeding risk
- Antiplt Rx: DAPT (ASA 81 + $P2Y_{12}$ inhib) in SIHD for 4 wk (BMS) or ≥6 mo (DES); in *ACS* (qv) for 12 mo and possibly beyond (*JAMA Cards* 2016;1:627). Data emerging for DAPT 1–3 mo, followed by $P2Y_{12}$ inhib monotherapy (*Circ* 2020;142:538).
- If need long-term oral anticoag, consider clopi+DOAC and consider stopping ASA (? after ~1 wk) as ↓ bleed, but trend small ↑ ischemic risk (*JAMA* Cardiol. 2020;5:582)

STABLE ISCHEMIC HEART DISEASE

Definition

- SIHD refers to asx and stably sx Pts as well as low-risk new-onset chest pain felt to be due to IHD, and excludes Pts w/ rapidly progressive sx or rest sx (ie, ACS)

Noninvasive testing (*Circ* 2012;126:e354 & 2021;144;e368)

- Noninvasive dx testing most valuable when pretest probability is *intermediate* (variably defined as anywhere from 30–70% to 10–90%)
- Several pretest probability scores that take into account age, sex, nature of sx, risk factors
- Exercise ECG testing or CAC reasonable in some low-risk Pts
- In intermediate/high-risk Pts, stress test w/ imaging or CCTA (see "Noninv Eval of CAD")
- If known nonobstructive CAD & stable chest pain: stress testing or CCTA ± FFR
- If obstructive CAD & stable chest pain: stress testing or invasive angio if high-risk CAD

Coronary angiography for SIHD (*Circ* 2014;130:1749)

- High-risk noninvasive testing results suggestive of left main or multivessel CAD
- Angina that is refractory to optimal medical therapy
- Uncertain dx after noninvasive testing, occupational need (eg, pilot)
- Unexplained heart failure or ↓ EF

Major risk factor modification (*Circ* 2012;126:e354)

- Lipids: **statin** (typically high-intensity) ± ezetimibe & PCSK9i (see "Dyslipidemia")
- **BP <$_1$30/80** (see "Hypertension"); in SIHD may opt for ACEI and βB (if angina)
- **Diabetes** management (qv): Hb_{A1c} ≤7% and consider GLP1RA or SGLT2i
- **Smoking cessation**; influenza vaccine
- Diet (↑ vegetables, fruits, whole grains; ↓ saturated fat, *trans* fatty acids, sweets, red meat, Na); target BMI 18.5–24.9 kg/m^2; 30–60 min mod-to-vigorous physical activity ≥5×/wk

Optimal medical therapy (OMT) (*Circ* 2012;126:e354)

- **ASA** 75–162 mg/d; can substitute clopi if ASA-intolerant. ~12 mos after PCI, clopi monoRx ↓ risk of ischemic and bleeding events by ~30% c/w ASA monoRx (*Lancet* 2021;397:2487).
- **βB** for 3 years post-MI or if ↓ EF; can consider in all Pts w/ SIHD
- **ACEI** (or ARB if intolerant of ACEI) if HTN, DM, CKD, or ↓ EF (*Lancet* 2006;368:581)
- Dual antiplatelet therapy (ASA + $P2Y_{12}$ inhibitor): ↓ CV events by ~10% in Pts with known IHD w/o MI but w/ DM, but ↑ bleeding (THEMIS, *NEJM* 2019; 381:1309)
- Rivaroxaban 2.5 mg bid + ASA 100 mg/d: 24% ↓ CV events and 18% ↓ death vs. ASA alone, but ↑ major bleeding in stable ASCVD (COMPASS, *NEJM* 2017;377:1319)
- Colchicine (0.5 mg/d): ↓ CV events by 31%, but ? ↑ non-CV death (*NEJM* 2020;383:1838)

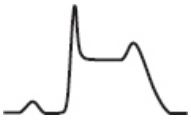
Medical therapies for symptomatic relief (*Circ* 2014;130:1749)

- **Beta-blockers** *1st-line therapy*; CCB (except short-acting dihydropyridines)
- **Long-acting nitrates**
- Ranolazine (↓ late inward Na+ current to ↓ myocardial demand): 2nd-line anti-anginal

Revascularization (*JAMA* 2021;325:1765; *Circ* 2022;145:e18)

- OMT should be initial focus if stable & w/o evidence of critical anatomy & w/ normal EF
- Goal of revasc should be to ↓ risk of CV morbidity & mortality or to relieve refractory sx
- *Older studies:* survival benefit w/ revascularization (CABG) vs. medical Rx (pre-statin era) if: left main disease (≥50% stenosis); 3VD (≥70% stenoses) especially if ↓ EF, 2VD w/ critical proximal LAD, DM, ? 1–2 VD w/ large area of viable, ischemic myocardium
- *More recent studies:* revascularization (largely if not exclusively PCI) vs. OMT did not Δ risk of death, ↑ peri-PCI MI, and ± ↓ spontaneous MI (*NEJM* 2007;356:1503 & 2020;382:1395)
- In the most recent trial (ISCHEMIA, *NEJM* 2020;382:1395), which enrolled Pts w/ moderate-severe ischemia by noninvasive testing w/o LM disease and w/ preserved LVEF, revasc (~¾ PCI, ~¼ CABG) ↑ 5-yr rate of peri-procedural MI by ~2% and ↓ 5-yr rate of spontaneous MI by 3%. Nonsignificant ~1% lower rate of CV death by 5 yrs that appeared to start to emerge after 2 yrs. Magnitude of benefit tended to be greater in those with multivessel disease, proximal LAD disease, or diabetes.
- In Pts w/ CAD, HF, & LVEF <35%, CABG compared w/ medical Rx ↓ mortality by 16% and ↓ CV mortality by 21% after a median of 10 yrs (STICHES, *NEJM* 2016;374:1511)
- Thus, recommendations (*Circ* 2012;126:e354 & *EHJ* 2019;40:87) for revascularization include:
  - *Indicated in:* ≥50% left main stenosis, 3VD (≥70% stenoses), 2VD w/ proximal LAD, unacceptable angina despite OMT
  - *Reasonable if:* 2VD + extensive myocardial ischemia, MVD or proximal LAD disease + ↓ EF, proximal LAD disease + extensive ischemia, MVD + diabetes (if can get CABG)
- Trials of PCI vs. CABG in Pts w/ MVD or LM disease have shown CABG ↓ risk of spontaneous MI, repeat revascularization, ± death. These benefits appear greater in those with more complex coronary anatomy or with diabetes (*Lancet* 2018;391:939 & 2021;398:2247).

ACUTE CORONARY SYNDROMES

Spectrum of Acute Coronary Syndromes			
Dx	**UA**	**NSTEMI**	**STEMI**
Coronary thrombosis	Subtotal occlusion		Total occlusion
History	Angina that is new-onset, crescendo or at rest; usually <30 min		Angina at rest
ECG	± ST depression and/or TWI 		ST elevations 
Troponin/CK-MB	⊖	⊕	⊕ ⊕

Ddx (causes of myocardial ischemia/infarction other than atherosclerotic plaque rupture)

- **Ischemia w/o plaque rupture** ("type 2" MI): ↑ demand (eg, ↑ HR), ↓ supply (eg, HoTN). More likely in older, ♀, non-CAD comorbidities (CKD, etc.) (*JACC* 2021;77:848). Distinguishing from ACS is clinical dx; angiography is gold standard.
- **Nonatherosclerotic coronary artery disease** (*JACC* 2018;72:2231)
  - Spasm: Prinzmetal's variant, cocaine-induced (6% of chest pain + cocaine use r/i for MI)
  - Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI) or mechanical (PCI, surgery, trauma)
  - Embolism (*Circ* 2015;132:241): AF, thrombus/myxoma, endocard., prosth valve thrombosis
  - Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, Churg-Strauss, SLE, RA
  - Congenital: anomalous origin from aorta or PA, myocardial bridge (intramural segment)
- **Direct myocardial injury:** myocarditis; Takotsubo/stress CMP; toxic CMP; cardiac contusion

Clinical manifestations (*JAMA* 2015;314:1955)

- **Cardiac chest pain ("angina"):** retrosternal pressure/pain/tightness ± radiation to neck, jaw, arms. Precipitated by exertion (physical or emotional), ↓ w/ rest or NTG. In ACS: new-onset, crescendo or at rest.
- **Associated symptoms:** dyspnea, diaphoresis, N/V, palpitations or light-headedness
- Nonclassic sx (incl N/V & epig pain) ? more common in ♀, elderly, diabetes, inf. ischemia

Physical exam (may be seen, but often are not)

- Signs of ischemia: S_4, new MR murmur 2° pap. muscle dysfxn, paradoxical S_2, diaphoresis
- Signs of HF (eg, if large MI or ischemic MR): ↑ JVP, crackles, ⊕ S_3, HoTN, cool extremities
- Signs of other vascular disease: asymmetric BP, carotid or femoral bruits, ↓ distal pulses

Diagnostic studies (*NEJM* 2017;376:2053)

- **ECG:** ST ↓/↑, TWI, new LBBB, hyperacute Tw; Qw/PRWP may suggest prior MI & ∴ CAD
  - ✓ ECG w/in 10 min of presentation, with any Δ in sx & at 6–12 h; compare w/ baseline
- STEMI dx challenging w/ old LBBB or ventricular pacing:
  - Sgarbossa: ≥1 mm STE *concordant* w/ QRS (Se 73%, Sp 92%), STD ≥1 mm V_1–V_3 (Se 25%, Sp 96%), STE ≥5 mm *discordant* w/ QRS (Se 31%, Sp 92%)
  - Barcelona: ST deviation ≥1 mm *concordant* w/ QRS in any lead, or ST deviation ≥1 mm *discordant* w/ QRS in leads with max voltage (largest R or S) ≤6 mm (Se 93%, Sp 94%)

Localization of MI

Anatomic Area	ECG Leads w/ STE	Coronary Artery
Septal	V_1–V_2 ± aVR	Proximal LAD
Anterior	V_3–V_4	LAD
Apical	V_5–V_6	Distal LAD, LCx, or RCA
Lateral	I, aVL	LCx
Inferior	II, III, aVF ± aVR	RCA (~85%), LCx (~15%)
RV	V_1–V_2 & V_4R (most Se)	Proximal RCA
Posterior	ST *depression* V_1–V_3 (= STE V_7–V_9 posterior leads, ✓ if clinical suspicion)	RCA or LCx

If ECG non-dx & suspicion high, ✓ leads V_7–V_9 (⊕ if ≥0.5 mm STE) to assess distal LCx/RCA territory. ✓ R-sided precordial leads in IMI to detect RV involvement (STE in V_4R most Se). STE in III >STE in II and lack of STE in I or aVL suggest RCA rather than LCx culprit in IMI. STE in aVR suggests LM, prox LAD, or diffuse ischemia.

- **Cardiac biomarkers:** ✓ Tn (pref. over CK-MB) at presentation & 3–6 h if stnd assay or 1 h later if high-sens assay; repeat if clinical or ECG Δs. **Universal definition of MI:** >99th %ile w/ rise and/or fall in appropriate clinical setting (eg, sx, ECG Δs, WMA on TTE, thrombus on coronary angiography).
- If low prob, **stress test** or **CT angio** to r/o CAD; new wall motion abnl on TTE suggests ACS
- **Coronary angio** gold standard for epicardial CAD

Prinzmetal's (variant) angina

- Coronary spasm → transient STE usually w/o MI (*but* MI, AVB, VT can occur)
- Pts usually young, smokers, ± other vasospastic disorders (eg, migraines, Raynaud's)
- Angiography: nonobstructive CAD (spasm can be provoked during cath but rarely done)

- Treatment: high-dose CCB & standing nitrates (+SL prn), ? α-blockers/statins; d/c smoking; avoid high-dose ASA (can inhibit prostacyclin and worsen spasm), nonselect βB, triptans
- Cocaine-induced vasospasm: CCB, nitrates, ASA; ? avoid βB, but labetalol appears safe

MI in absence of obstructive CAD (MINOCA)

- Definition: MI but w/o coronary stenosis ≥50% in any major epicardial vessel
- More common in younger Pts, women, Black/Pacific race or Hispanic
- Advanced coronary imaging (eg, OCT) & cardiac MRI to exclude missed coronary obstruction, other causes of myocyte injury (eg, myocarditis), other causes of ↑ Tn (eg, PE)
- ~75% ischemic (ie, plaque disruption identified) and 25% alternative dx (eg, myocarditis)

Likelihood of ACS *(Circ 2007;116:e148; Circ 1994;90[1]:613-22)*			
Feature	**High** (any of below)	**Intermediate** (no high features, any of below)	**Low** (no high/inter. features, may have below)
History	Chest or L arm pain like prior angina, h/o CAD (incl MI)	Chest or arm pain, age >70 y, male, diabetes	Atypical sx (eg, pleuritic, sharp or positional pain)
Exam	HoTN, diaphoresis, HF, transient MR	PAD or cerebrovascular disease	Pain reproduced on palp.
ECG	New STD (≥1 mm) TWI in mult leads	Old Qw, STD (0.5-0.9 mm), TWI (>1 mm)	TWF/TWI (<1 mm) in leads w/ dominant R wave
Biomarkers	⊕ Tn or CK-MB	Normal	Normal

Acute Anti-Ischemic and Analgesic Treatment	
Nitrates (SL or IV) 0.3–0.4 mg SL q5min × 3, then consider IV if still sx	Use for relief of sx, Rx for HTN or HF. No clear ↓ in mortality. *Caution* if preload-sensitive (eg, HoTN, AS, sx RV infarct); contraindicated if recent PDE5 inhibitor use.
β-blockers eg, metop 25–50 mg PO q6h titrate slowly to HR 50–60 IV only if HTN and no HF	↓ ischemia & progression of UA to MI (*JAMA* 1988;260:2259) STEMI: ↓ arrhythmic death & reMI, but high doses can ↑ cardiogenic shock early (espec if signs of HF) (*Lancet* 2005;366:1622) *Contraindic.* PR >0.24 sec, HR <60, 2°/3° AVB, severe bronchospasm, s/s HF or low output, risk factors for shock (eg, >70 y, HR >110, SBP <120, late presentation STEMI)
CCB (nondihydropyridines)	If cannot tolerate βB b/c bronchospasm
Morphine	Relieves pain/anxiety; venodilation ↓ preload. Do not mask refractory sx. May delay antiplt effects of $P2Y_{12}$ inhib.
Oxygen	Use prn to keep S_aO_2 >90% (*NEJM* 2017;377:1240)

Other early adjunctive therapy

- **High-intensity statin therapy** (eg, atorva 80 mg qd; PROVE-IT TIMI 22, *NEJM* 2004;350:1495); ↓ ischemic events w/ benefit emerging w/in wks (*JAMA* 2001;285:1711 & *JACC* 2005;46:1405); ↓ peri-PCI MI (*JACC* 2010;56:1099); ? ↓ contrast-induced nephropathy (*NEJM* 2019;380:2156)
- **Ezetimibe:** ↓ CV events when added to statin (IMPROVE-IT, *NEJM* 2015;372:2387)
- **ACEI/ARB:** start once hemodynamics and renal function stable (hold if anticipate CABG)

Strong indication for ACEI/ARB if heart failure, EF <40%, HTN, DM, CKD; ~10% ↓ mortality, greatest benefit in ant. STEMI or prior MI (*Lancet* 1994;343:1115 & 1995;345:669)

• IABP: can be used for refractory angina when PCI not available

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NSTE-ACS (*Circ* 2014;130:e344; *EHJ* 2021;42:1289)

Key issues are antithrombotic regimen and decision regarding angiography

Antiplatelet Therapy	
Aspirin 162–325 mg × 1, then 81 mg qd (non–enteric-coated, chewable)	50–70% ↓ D/MI (*NEJM* 1988;319:1105) Low dose (~81 mg) pref long term (*NEJM* 2010;363:930) If allergy, use clopi and/or desensitize to ASA
P2Y$_{12}$ (ADP receptor) inhibitor (choose one of the following in addition to ASA). Timing (on presentation or at angiography) remains controversial.	
• **Ticagrelor** (preferred over clopi) 180 mg × 1 → 90 mg bid Reversible, but wait 3–5 d prior to surg. Antidote being developed (*NEJM* 2019;380:1825).	More rapid and potent plt inhib c/w clopi 16% ↓ CVD/MI/stroke & 21% ↓ CV death c/w clopi; ↑ non-CABG bleeding (*NEJM* 2009;361;1045) Given upstream or at time of PCI Dyspnea (but S_aO_2 & PFTs nl) & ventricular pauses
• **Prasugrel** (preferred over clopi) 60 mg × 1 at PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery Contraindicated if h/o TIA/CVA; caution if >75 y	More rapid and potent plt inhib c/w clopi 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs. clopi, but ↑ bleeding (*NEJM* 2007;359:2001), incl fatal bleeds In NSTE-ACS, should be given at time of PCI and not upstream due to ↑ bleeding (*NEJM* 2013;369:999) ? ↓ MACE vs ticagrelor (*NEJM* 2019;381:1524)
• **Clopidogrel** 300–600 mg × 1 → 75 mg qd ~6 h to steady state Wait 5 d prior to surgery	ASA+clopi → 20% ↓ CVD/MI/stroke vs. ASA alone. ~30% pop has ↓ fxn CYP2C19 → ↑ CV events if PCI on clopi (*NEJM* 2009;360:354).
• **Cangrelor**[*] Only IV P2Y$_{12}$ inhibitor Rapid onset/offset; t½ 3–5 min	22% ↓ CV events (mostly peri-PCI MI and stent thrombosis) vs. clopi 300 mg at time of PCI; no significant ↑ bleeding (*NEJM* 2013;368:1303) Consider for rapidly reversible P2Y$_{12}$ inhib peri-PCI or as bridge to surgery in high-risk Pts who need to stop P2Y$_{12}$
GP IIb/IIIa inhibitors (GPI) abciximab; eptifibatide; tirofiban Infusions given ≤24 h peri & post PCI; shorter (~2 h) as effective w/ ↓ bleeding (*JACC* 2009;53:837)	No clear benefit for routinely starting prior to PCI and ↑ bleeding (*NEJM* 2009;360:2176) Consider if refractory ischemia despite optimal Rx while awaiting angio or in high-risk Pts (eg, large clot burden) at time of PCI, espec if using clopi and no preRx.

[*]Transition from cangrelor to oral P2Y$_{12}$ inhib.: ticagrelor loading dose during infusion or immediately after d/c of infusion; prasugrel or clopidogrel loading dose only immediately *after* d/c of infusion.

Anticoagulant Therapy (choose one)	
UFH: 60 U/kg IVB (max 4000 U) then 12 U/kg/h (max 1000 U/h initially) × 48 h or until end of PCI	24% ↓ D/MI (*JAMA* 1996;276:811) Titrate to aPTT 1.5–2× control (~50–70 sec) Hold until INR <2 if already on warfarin
Enoxaparin (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IVB) (qd if CrCl <30) × 2–8 d or until PCI	~10% ↓ D/MI vs. UFH (*JAMA* 2004;292:45,89). Can perform PCI on enox (*Circ* 2001;103:658), but ↑ -bleeding if switch b/w enox and UFH.
Bivalirudin (direct thrombin inhibitor) 0.75 mg/kg IVB at PCI → 1.75 mg/kg/h	No diff in bleeding, MI, or death c/w UFH (*NEJM* 2017;377:1132). Use instead of UFH if HIT.

Anticoagulant Therapy (choose one)	
Fondaparinux (Xa inh) 2.5 mg SC qd	Rarely used; must supplement w/ UFH if PCI.

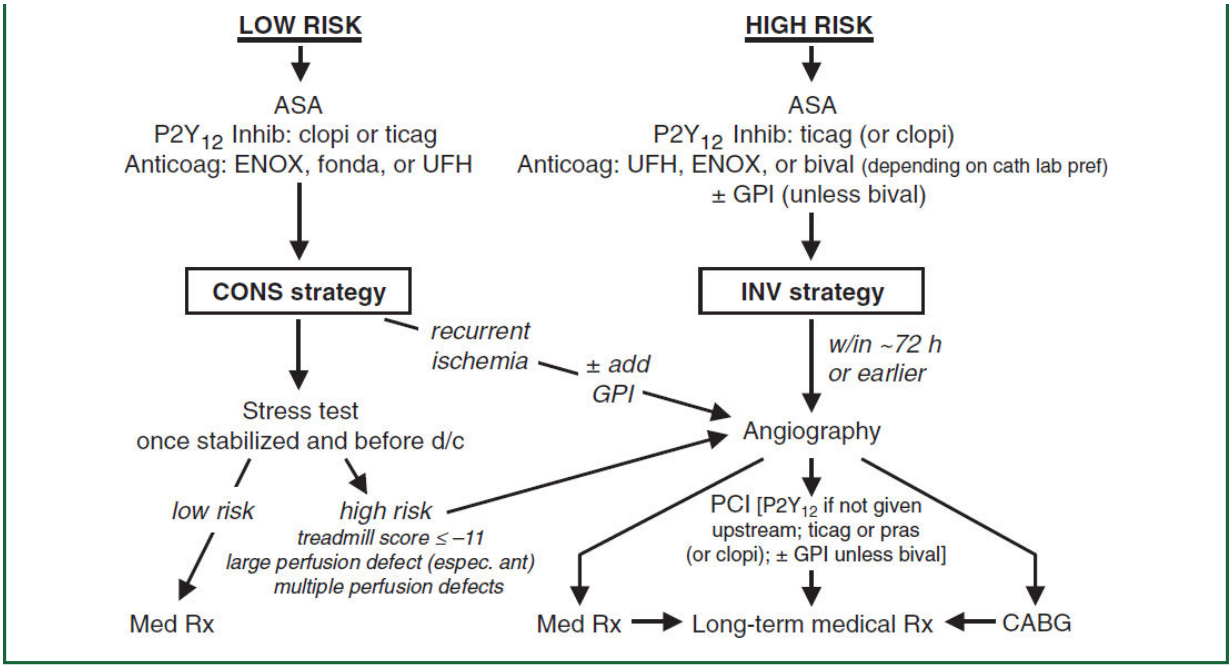
Coronary angiography (*Circ* 2014;130:e344)

- **Immediate/urgent coronary angiography** (w/in 2 h) if refractory/recurrent angina or hemodynamic or electrical instability
- **Routine angiography** (aka "invasive strategy") = coronary angiography for all
  - *Early (w/in 24 h) if:* ⊕ Tn, ST Δ, GRACE risk score >140 (*NEJM* 2009;360:2165; *Circ* 2018;138:2741)
  - *Delayed (ie, w/in 72 h) acceptable if w/o above features but w/:* diabetes, EF <40%, GFR <60, post-MI angina, TRS ≥3, GRACE score 109–140, PCI w/in 6 mo, prior CABG
  - 32% ↓ rehosp for ACS, nonsignif 16% ↓ MI, no Δ in mort. c/w select angio (*JAMA* 2008;300:71)
  - ↑ peri-PCI MI counterbalanced by ↓↓ in spont. MI. Mortality benefit seen in some studies, likely only if cons. strategy w/ low rate of angio.
- **Selective angiography** ("conservative strategy"): med Rx w/ pre-d/c stress test; angio only if recurrent ischemia or strongly ⊕ ETT. *Indicated for:* low TIMI Risk Score, Pt or physician pref in absence of high-risk features, or low-risk women (*JAMA* 2008;300:71).

TIMI Risk Score (TRS) for UA/NSTEMI (*JAMA* 2000;284:835)			
Calculation of Risk Score		**Application of Risk Score**	
Characteristic	**Point**	**Score**	**D/MI/UR by 14 d**
Historical		0–1	5%
Age ≥65 y	1	2	8%
≥3 Risk factors for CAD	1	3	13%
Known CAD (stenosis ≥50%)	1	4	20%
ASA use in past 7 d	1	5	26%
Presentation		6–7	41%
Severe angina (≥2 episodes w/in 24 h)	1	Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa inhibitors and early angiography (*JACC* 2003;41:89S)	
ST deviation ≥0.5 mm	1		
⊕ cardiac marker (troponin, CK-MB)	1		
RISK SCORE = Total points	**(0–7)**		

STEMI (*Circ* 2013;127:529; *EHJ* 2018;39:119)

Figure 1-2 Approach to UA/NSTEMI



Requisite STE (at J point)

- ≥2 contiguous leads w/ ≥1 mm (except for V_2–V_3: ≥2 mm in ♂ and ≥1.5 mm in ♀), *or*
- New or presumed new LBBB w/ compelling H&P, *or*
- True posterior MI: ST depression V_1–V_3 ± tall Rw w/ STE on posterior leads (V_7–V_9)

Reperfusion ("time is muscle")

- In PCI-capable hospital, goal should be **primary PCI w/in 90 min** of 1st medical contact
- In non–PCI-capable hospital, consider *transfer* to PCI-capable hospital (see below), o/w **fibrinolytic therapy** w/in 30 min of hospital presentation
- Do not let decision regarding *method* of reperfusion delay *time* to reperfusion

Primary PCI (*JACC* 2013;61:e78 & 2016;67:1235)

- Definition: immediate PCI upon arrival to hospital or transfer for immediate PCI
- **Indic: STE** + sx onset w/in <12 h; ongoing ischemia 12–24 h after sx onset; shock
- Superior to lysis: 27% ↓ death, 65% ↓ reMI, 54% ↓ stroke, 95% ↓ ICH (*Lancet* 2003;361:13)
- *Transfer* to center for 1° PCI superior to lysis (*NEJM* 2003;349:733), see below
- PCI of non-culprit lesions (stenoses ≥70% or FFR ≤0.80 if 50–69%) early after event (during initial PCI, prior to or early after d/c) ↓ recurrent MACE, primarily recurrent MI vs. culprit alone (*NEJM* 2019;381:1411-21); may harm if cardiogenic shock (*NEJM* 2018;379:1699)

Fibrinolysis vs. Hospital Transfer for Primary PCI: Assess Time and Risk
1. **Time required for transport to skilled PCI lab:** door-to-balloon <120 min & [door-to-balloon]–[door-to-needle] <1 h favors transfer for PCI
2. **Risk from STEMI:** high-risk Pts (eg, shock) fare better with mechanical reperfusion
3. **Time to presentation:** efficacy of lytics ↓ w/ ↑ time from sx onset, espec >3 h
4. **Risk of fibrinolysis:** if high risk of ICH or bleeding, PCI safer option

Adapted from ACC/AHA 2013 STEMI Guidelines (*Circ* 2013;127:529)

Fibrinolysis

- Indic: STE/LBBB + sx <12 h (& >120 min before PCI can be done); benefit if sx >12 h less clear; reasonable if persist. sx & STE, hemodynamic instability or large territory at risk
- Mortality ↓ ~20% in anterior MI or LBBB and ~10% in IMI c/w Ø reperfusion Rx
- Prehospital lysis (ie, ambulance): further 17% ↓ in mortality (*JAMA* 2000;283:2686)
- ~1% risk of ICH; high risk incl elderly (~2% if >75 y), ♀, low wt. ? PCI more attractive

Contraindications to Fibrinolysis	
Absolute Contraindications	**Relative Contraindications**
• Any prior ICH • Intracranial neoplasm, aneurysm, AVM • Ischemic stroke or closed head trauma w/in 3 mo; head/spinal surg. w/in 2 mo • Active internal bleeding or known bleeding diathesis • Suspected aortic dissection • Severe uncontrollable HTN • For SK, SK Rx w/in 6 mo	• H/o severe HTN, SBP >180 or DBP >110 on presentation (? absolute if low-risk MI) • Ischemic stroke >3 mo prior • CPR >10 min; trauma/major surg. w/in 3 wk • Internal bleed w/in 2–4 wk; active PUD • Noncompressible vascular punctures • Pregnancy • Current use of anticoagulants • For SK, prior SK exposure

Nonprimary PCI

- Rescue PCI if shock, unstable, failed reperfusion, or persistent sx (*NEJM* 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/revasc (*Lancet* 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia, & HF compared to w/in 2 wk (*NEJM* 2009;360:2705);
  ∴ *if lysed at non-PCI-capable hosp., consider transfer to PCI-capable hosp.. ASAP espec if high-risk (eg, ant. MI, IMI w/ ↓ EF or RV infarct, extensive STE/LBBB, HF, ↓ BP or ↑ HR)*
- *Late* PCI (median day 8) of occluded infarct-related artery: no benefit (*NEJM* 2006;355:2395)

Antiplatelet Therapy	
Aspirin 162–325 mg × 1 (crushed/chewed) then 81 mg qd	23% ↓ in death (*Lancet* 1988;ii:349) Should not be stopped if CABG required
P2Y$_{12}$ inhibitor Give ASAP (do not wait for angio) b/c onset inhib delayed in STEMI Pts Ticagrelor or prasugrel (if PCI) as detailed above Clopidogrel: 600 mg pre-PCI; 300 mg if lysis (no LD if >75 y) → 75 mg qd	*PCI:* prasugrel and ticagrelor ↓ CV events c/w clopi (*Lancet* 2009;373:723 & *Circ* 2010;122:2131) Prehospital ticagrelor may be safe & ? ↓ rate of stent thrombosis (*NEJM* 2014;371:1016) *Lysis:* clopidogrel 41% ↑ in patency, 7% ↓ mort, no Δ major bleed or ICH (*NEJM* 2005;352:1179; *Lancet* 2005;366:1607); no data for pras or ticag w/ lytic
GP IIb/IIIa inhibitors abciximab, eptifibatide, tirofiban	*Lysis:* no indication (*Lancet* 2001;357:1905) *Peri-PCI:* 60% ↓ D/MI/UR (*NEJM* 2001;344:1895)

(*Circ* 2013;127:529; *NEJM* 2021;384:452; *JAMA* 2021;325:1545)

Anticoagulant Therapy (choose one)	
UFH 60 U/kg IVB (max 4000 U) 12 U/kg/h (max 1000 U/h initially)	No demonstrated mortality benefit ↑ patency with fibrin-specific lytics Titrate to aPTT 1.5–2× control (~50–70 sec)

Anticoagulant Therapy (choose one)	
Enoxaparin *Lysis:* 30 mg IVB → 1 mg/kg SC bid (adjust for age >75 & CrCl) *PCI:* 0.5 mg/kg IVB	*Lysis:* 17% ↓ D/MI w/ ENOX × 7 d vs. UFH × 2 d (*NEJM* 2006;354:1477) *PCI:* ↓ D/MI/revasc and ≈ bleeding vs. UFH (*Lancet* 2011;378:693)
Bivalirudin 0.75 mg/kg IVB → 1.75 mg/kg/hr IV	*PCI:* similar bleeding, ± ↑ MI, ↑ stent thromb, ↓ mortality in some but not all trials (*Lancet* 2014;384:599; *JAMA* 2015;313:1336; *NEJM* 2015;373:997)

Fondaparinux can be used (if CrCl >30 mL/min) in setting of lysis, where superior to UFH w/ less bleeding (*JAMA* 2006;295:1519). Adapted from ACC/AHA 2013 STEMI Guidelines (*Circ* 2013;127:529; *Lancet* 2013;382:633).

LV failure (occurs in ~25%)

- Diurese to achieve PCWP ~14 → ↓ pulmonary edema, ↓ myocardial O_2 demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O_2 demand. Can use IV NTG or nitroprusside (although risk of coronary steal) → short-acting ACEI.
- Inotropes if HF despite diuresis & ↓ afterload; use dopamine, dobutamine, or milrinone
- **Cardiogenic shock** (~7%) = MAP <60 mmHg, CI <2.2 L/min/m^2, PCWP >18 mmHg.
  If not done already, coronary revasc (*NEJM* 1999;341:625)
  Support w/ inotropes or mechanical circulatory support to keep CI >2
  - **Intraaortic balloon pump (IABP)** counterpulsation offers ~0.5 L/min CO and ↑ coronary perfusion, but no survival benefit if early revasc (*NEJM* 2012;367:1287)
  - **Axial flow pumps (eg, Impella)** offer up to 3–5 L/min CO, but no data that improves clinical outcomes (*JACC* 2017;69:278)

IMI complications (*Circ* 1990;81:401; *NEJM* 1994;330:1211; *JACC* 2003;41:1273)

- **Heart block:** ~20%, occurs in part because RCA typically supplies AV node
  40% on present., 20% w/in 24 h, rest by 72 h; high-grade AVB can develop abruptly
  Rx: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp pacing wire
- **RV infarct:** proximal RCA occlusion → ↓ flow to RV marginals
  Angiographically present in 30–50% of cases, but only ~½ clinically significant
  HoTN; ↑ JVP, ⊕ Kussmaul's; ≥1 mm STE in V_4R; RA/PCWP ≥0.8; RV dysfxn on TTE
  Rx: optimize preload (RA goal 10–14 mmHg; *BHJ* 1990;63:98); ↑ contractility (dobutamine); maintain AV synchrony (pacing as necessary); reperfusion (*NEJM* 1998;338:933); mechanical support (IABP or RVAD); pulmonary vasodilators (eg, inhaled NO)

Mechanical complications (incid. <1% for each; typically occur a few days post-MI)

- **Free wall rupture:** ↑ risk w/ lysis, large MI, ↑ age, ♀, HTN; p/w PEA or hypoTN, pericardial sx, tamponade; Rx: volume resusc., ? pericardiocentesis, inotropes, **surgery**
- **VSD:** large MI in elderly; AMI → apical VSD, IMI → basal septum; 90% w/ harsh murmur ± thrill (*NEJM* 2002;347:1426); Rx: diuretics, vasodil., inotropes, IABP, **surgery**, perc. closure
- **Papillary muscle rupture:** more common after IMI (PM pap m. supplied by PDA alone) than AMI (AL supplied by OMs & diags); 50% w/ new murmur; ↑ *v* wave in PCWP tracing; asymmetric pulmonary edema on CXR. Rx: diuretics, vasodilators, IABP, **surgery**.

Arrhythmias post-MI (treat all per ACLS protocols if unstable or symptomatic)

- AF (10–16% incidence): βB or amio, ± digoxin (particularly if HF), heparin
- **VT/VF:** lido or amio × 6–24 h, then reassess; ↑ βB as tol., replete K & Mg, r/o ischemia; VT <48 h post-MI does *not* worsen prognosis; >48 h, consider ICD (see below)
- Accelerated idioventricular rhythm (AIVR): slow ventricular rhythm (<120 bpm), often after reperfusion; typically asx, gradual onset/offset, and does not require treatment
- Backup transcutaneous *or* transvenous pacing if: 2° AVB type II; BBB + AVB
- **Transvenous pacing** if: 3° AVB; new BBB + 2° AVB type II; alternating LBBB/RBBB

Other Post-MI Complications

Complication	Clinical Features	Treatment
LV thrombus	~30% incid. (espec lg antero-apical MI)	AC×3-6 mo (? warfarin pref)
Ventricular aneurysm	Noncontractile outpouching of LV; 8–15% incid. (espec ant); persist STE	Surgery or perc repair if HF, thromboemboli, arrhythmia
Ventricular pseudoaneurysm	Rupture (narrow neck) → sealed by thrombus and pericardium (esp in inf).	Urgent surgery (or percutaneous repair)
Pericarditis	10–20% incid.; 1–4 d post-MI ⊕ pericardial rub; ECG Δs rare	High-dose ASA, colchicine, narcotics; minimize anticoag
Dressler's syndrome	<4% incid.; 2–10 wk post-MI fever, pericarditis, pleuritis	High-dose aspirin, NSAIDs

CHECKLIST AND LONG-TERM POST-ACS MANAGEMENT

Risk stratification

- Stress test if anatomy undefined; consider stress if signif residual CAD post-PCI of culprit
- Assess LVEF prior to d/c; EF ↑ ~6% in STEMI over 6 mo (*JACC* 2007;50:149)

Antiplatelet therapy

- **Aspirin:** 81 mg daily (no clear benefit to higher doses)
- **$P2Y_{12}$ inhibitor:** ticagrelor or prasugrel preferred over clopi. In landmark analyses, benefit over clopidogrel both early & late. De-escalation (ticag → clopi or pras 10 → 5 mg) after 1 mo ↓ bleeding w/o clear ↑ MACE, but wide CIs (*Lancet* 2020;396:1079 & 2021;398:1305).
- Duration controversial. Traditionally ASA lifelong and $P2Y_{12}$ inhib for 12 mos. *Prolonged P2Y12 inhib* >12 mos → ↓ MACE but ↑ bleeding (*NEJM* 2014;371:2155 & 2015;372:1791). Consider if high ischemic and low bleeding risk. Shorter duration (eg, 3–6 mo) if converse or if require major surgery. *D/c ASA* after 1–3 mos and continuing $P2Y_{12}$ inhib monoRx (preferably ticagrelor) ↓ bleeding with no ↑ MACE (*Circ* 2020;142:538).

Anticoagulation

- If need therapeutic a/c (eg, AF) in addition to anti-plt Rx, consider full-dose apixa + $P2Y_{12}$ (typically clopi) and d/c ASA at time of hospital d/c (*NEJM* 2019;380:1509)
- In Pts w/o indic. for anticoag, once DAPT completed, rivaroxaban 2.5 bid + ASA ↓ MACE & CV death and ↑ bleeding vs. ASA monoRx (*NEJM* 2017;377:1319)

Other CV drugs

- **β-blocker:** 23% ↓ mortality after MI (benefit beyond 3 yrs less clear)
- **ACEI/ARB:** lifelong if HF, ↓ EF, HTN, DM; 4–6 wk or at least until hosp. d/c in all STEMI. Trend toward ARNI better than ACEI in post-MI Pts w/ ↓ EF (*NEJM* 2021;385:1845).
  ? long-term benefit of ACEI/ARB in CAD w/o HF (*NEJM* 2000;342:145)
- **Aldosterone antag:** 15% ↓ mort. if EF <40% & either s/s of HF or DM (*NEJM* 2003;348:1309)
- Nitrates: standing if symptomatic; SL NTG prn for all
- Ranolazine: ↓ recurrent ischemia, no impact on CVD/MI (*JAMA* 2007;297:1775)
- Low dose colchicine ↓ CV events post MI but ? ↑ PNA (*NEJM* 2019; 381:2497)

Risk factors and lifestyle modifications (*Circ* 2019;139:e1082 & *EHJ* 2020;41:111)

- **LDL-C**: goal <70 mg/dL (U.S) or <55 (Europe) or even <40 if recurrent events
  Statin: high-intensity (eg, atorva 80 mg, PROVE-IT TIMI 22, *NEJM* 2004;350:1495)
  Ezetimibe: ↓ CV events when added to statin (IMPROVE-IT, *NEJM* 2015;372:1500)
  PCSK9 inhibitor: ↓ CV events when added to statin (*NEJM* 2017;376:1713; 2018;379:2097)
- **BP** <140/90 and <130/80; **quit smoking**
- If diabetic, GLP1-RA ↓ MACE & SGLT2i ↓ hospitalization for HF (*Lancet D&E* 2019;7:776 & *Lancet* 2019;393:31); further tailor Hb_{A1c} goal based on Pt (avoid TZDs and saxa if HF)
- Exercise (30–60′ 5–7×/wk) 1–2 wk after revasc; cardiac rehab; BMI goal 18.5–24.9 kg/m^2
- Influenza & *S. pneumo* vaccines (*Circ* 2021;144:14764 *NEJM* 2018;378:345); ✓ for depression

ICD (*Circ* 2018;138:e272)

- Sust. VT/VF >2 d post-MI w/o revers. isch; ? ↓ death w/ *wearable* defib (*NEJM* 2018;379:1205)
- 1° prevention of SCD if post-MI EF ≤30–40% (NYHA II–III) or ≤30–35% (NYHA I); wait 40 d after MI (*NEJM* 2004;351:2481 & 2009;361:1427)

PA CATHETER AND TAILORED THERAPY

Rationale

- Cardiac output (CO) = SV × HR; optimize SV (and thereby CO) by manipulating preload/ LVEDV (w/ IVF, diuretics), contractility (w/ inotropes), & afterload (w/ vasodilators)
- Balloon at catheter tip inflated → floats into "wedge" position. Column of blood extends from tip of catheter, through pulm venous circulation to a point just prox to LA. Under conditions of no flow, PCWP ≈ LA pressure ≈ LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:
  (1) Catheter tip not in West lung zone 3 (and ? PCWP = alveolar pressure ≠ LA pressure); clues include lack of *a* & *v* waves and if PA diastolic pressure < PCWP
  (2) PCWP >LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)
  (3) Mean LA pressure >LVEDP (eg, MR, MS)
  (4) Δ LVEDP-LVEDV relationship (ie, abnl compliance, ∴ "nl" LVEDP may not be optimal)

Indications (*NEJM* 2013;369:e35; *Circ* 2017;136:e268)

- **Diagnosis and evaluation**
  Ddx of shock (cardiogenic vs. distributive; espec if trial of IVF failed or is high risk) and of pulmonary edema (cardiogenic vs. not; espec if trial of diuretic failed or is high risk)
  Evaluation of CO, intracardiac shunt, pulm HTN, MR, tamponade, cardiorenal syndrome
  Evaluation of unexplained dyspnea (PAC during provocation w/ exercise, vasodilator)
- **Therapeutics** (*Circ* 2017;136:e232)
  Tailored therapy to optimize PCWP, SV, $S_{MV}O_2$, RAP, PVR in heart failure or shock
  Guide to vasodilator therapy (eg, inhaled NO, nifedipine) in PHT, RV infarction
  Guide periop mgmt in some high-risk Pts, candidacy for mech circ support & transplant
- **Contraindications**
  Absolute: right-sided endocarditis, thrombus/mass or mechanical valve; proximal PE
  Relative: coagulopathy (reverse), recent PPM or ICD (place under fluoroscopy), LBBB (~5% risk of RBBB → CHB, place under fluoro), bioprosthetic R-sided valve

Efficacy concerns (*NEJM* 2006;354:2213; *JAMA* 2005;294:1664)

- No benefit to routine PAC use in high-risk surgery (*JACC* 2014;62:e77), sepsis, ARDS
- No benefit in decompensated HF (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ~½ of *clinical* CO & PCWP estimates incorrect; CVP & PCWP not well correl.; ∴ use PAC to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic

shock

Placement (*NEJM* 2013;369:e35)

- Insertion site: **R IJ** or **L subclavian veins** preferred for "anatomic" flotation into PA
- **Inflate** balloon (max 1.5 cc, mindful of resistance) when **advancing** and to **measure PCWP**
- **Deflate** the balloon when **withdrawing** and at all other times
- CXR should be obtained after placement to assess for catheter position and PTX
- If catheter cannot be floated (i.e., severe TR, RV dilatation), consider fluoroscopic guidance

Complications

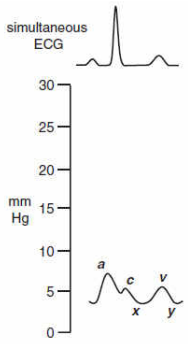
- **Central venous access:** pneumo/hemothorax (~1%), arterial puncture (if inadvertent cannulation w/ dilation → surgical/endovasc eval), air embolism, thoracic duct injury
- **Advancement:** atrial or ventricular arrhythmias (3% VT; 20% NSVT and >50% PVC), RBBB (5%), catheter knotting, cardiac perforation/tamponade, PA rupture
- **Maintenance:** infection (espec if catheter >3 d old), thrombus, pulm infarction (≤1%), valve/chordae damage, PA rupture/pseudoaneurysm (espec w/ PHT), balloon rupture

Intracardiac pressures

- Transmural pressure (≈ preload) = measured intracardiac pressure – intrathoracic pressure
- Intrathoracic pressure (usually slightly ⊖) is transmitted to vessels and heart
- **Always measure intracardiac pressure at end-expiration**, when intrathoracic pressure closest to 0 ("high point" in spont. breathing Pts; "low point" in Pts on ⊕ pressure vent.)
- If ↑ intrathoracic pressure (eg, PEEP), measured PCWP *overestimates* true transmural pressures. Can approx by subtracting ~½ PEEP (× ¾ to convert cm H_2O to mmHg).
- PCWP: LV preload best estimated at *a* wave; risk of pulm edema driven by avg PCWP

Cardiac output

- **Thermodilution:** saline injected in RA or intermittent heating of prox thermal filament in some PA lines ("continuous CO"). Δ in temp over time measured at thermistor (in PA) used to calc CO. Inaccurate if ↓ CO, severe TR, or shunt.
- **Fick method:** O_2 consumption (L/min) = CO (L/min) × Δ arteriovenous O_2 content ∴ **CO = $\dot{V}O_2$/C(a-v)O_2**
  - $\dot{V}O_2$ ideally measured (esp. if ↑ metab demands), but freq estimated (125 mL/min/m^2)
  - C(a-v)O_2 = [10 × 1.36 mL O_2/g of Hb × Hb g/dL × (S_aO_2 – $S_{MV}O_2$)]. *$S_{MV}O_2$ is key var that Δs.*
  - If $S_{MV}O_2$ >80%, consider if the PAC is "wedged" (ie, pulm vein sat), L→R shunt, impaired O_2 utilization (severe sepsis, cyanide, carbon monoxide), ↑↑ CO or FiO_2.

PA Catheter Waveforms				
Location	**RA**	**RV**	**PA**	**PCWP**
Distance	~20 cm	~30 cm	~40 cm	~50 cm
Normal Pressure (mmHg)	mean ≤6	syst 15–30 diast 1–8	syst 15–30 mean 9–18 diast 6–12	mean ≥12
Waves				
Comment	*a* = atrial contraction, occurs in PR interval *c* = bulging of TV back into RA at start of systole *x* = atrial relaxation and descent of base of heart *v* = blood entering RA, occurs mid T wave *y* = blood exiting RA after TV opens at start of diastole	RVEDP occurs right before upstroke and ≥mean RA pressure unless there is TS or TR	Waveform should contain notch (closure of pulmonic valve). Peak *during* T wave. PA systolic = RV systolic unless there is a gradient (eg, PS). PA diastolic ≈ PCWP unless ↑ trans-pulm gradient (eg, ↑ PVR).	Similar to RA except *dampened* and *delayed*. *a* wave *after* QRS, ± distinct *c* wave, *v* wave *after* T (helps distinguish PCWP w/ large *v* waves 2° MR from PA).

PCWP waveform abnormalities: large *a* wave → ? mitral stenosis; large *v* wave → ? mitral regurgitation; blunted *y* descent → ? tamponade; steep *x* & *y* descents → ? constriction.

Hemodynamic Profiles of Various Forms of Shock (*NEJM* 2013;369:1726)				
Type of Shock	**RA**	**PCWP**	**CO**	**SVR**
Hypovolemic	↓	↓	↓	↑
Cardiogenic	nl or ↑	↑	↓	↑
RV infarct/massive PE	↑	nl or ↓	↓	↑
Tamponade	↑	↑	↓	↑
Distributive	variable	variable	usually ↑ (can be ↓ in sepsis)	↓

Surrogates: RA ≈ JVP (1 mmHg = 1.36 cm H_2O); pulmonary edema on CXR implies ↑ PCWP; UOP ∝ CO (barring AKI); delayed capillary refill (ie, >2–3 sec) implies ↑ SVR

Tailored therapy in cardiogenic shock (*Circ* 2009;119:e391)

- **Goals:** optimize both MAP and CO while ↓ risk of pulmonary edema
  - MAP = CO × SVR; CO = HR × SV (which depends on preload, afterload, and contractility)
  - pulmonary edema when PCWP >20–25 (↑ levels may be tolerated in chronic HF/MS)
  - hepatic and renal congestion (↓ GFR) occur when CVP/RAP >15 mmHg
- **Optimize preload** = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (*NEJM* 1973;289:1263)
  - goal **PCWP ~14–18 in acute MI, □14 in acute decompensated HF**

optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve
↑ by giving crystalloid (albumin w/o clinical benefit over NS; PRBC if significant anemia)
↓ by diuresis (qv), ultrafiltration or dialysis if refractory to diuretics or ESRD

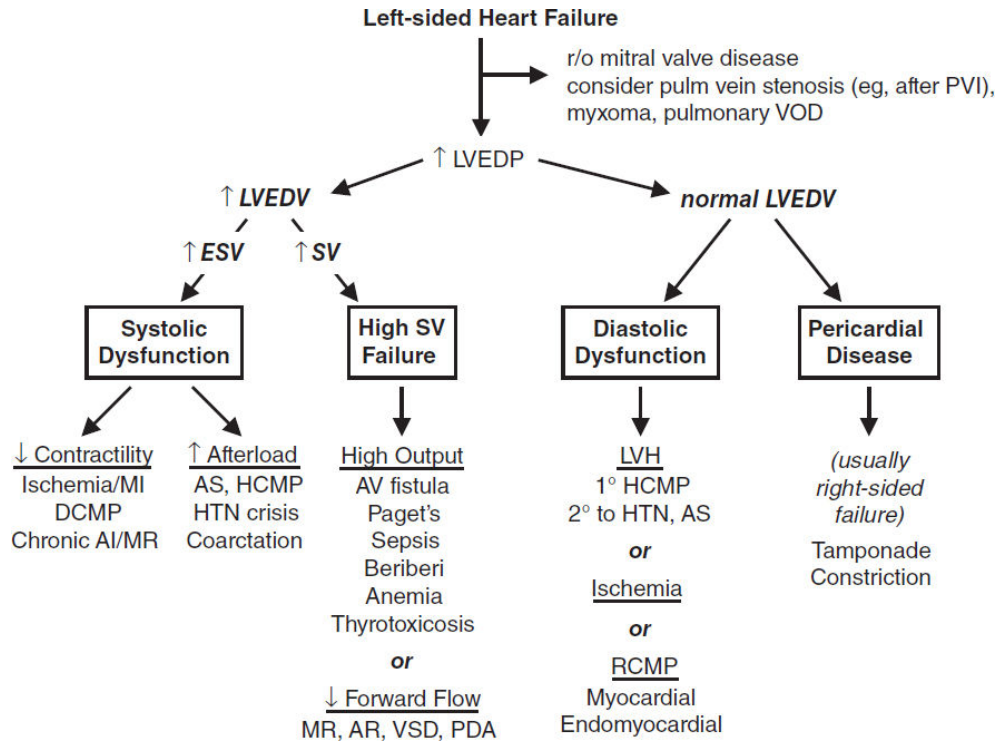
- **Optimize afterload** ≈ wall stress during LV ejection = [(~SBP × radius) / (2 × wall thick.)] and ∴ ∝ MAP and ∝ SVR = (MAP – CVP / CO); goals: **MAP >60**, **SVR 800–1200**
  MAP >60 (& ∴ SVR ↑): vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors
  MAP <60 (& ∴ SVR low/nl, ie, inappropriate vasoplegia): start with inopressor (eg, norepinephrine [α > β], dopamine [β → α w/ ↑ doses], epi [β > α at low doses]); better outcomes w/ norepi than dopa even in cardiogenic shock (*NEJM* 2010;362:779)
- **Optimize contractility** ∝ CO for given preload & afterload; **goal CI = (CO / BSA) >2.2**
  if too low despite optimal preload & vasodilators (as MAP permits):
  ⊕ *inotropes:* eg, dobutamine (mod inotrope & mild vasodilator) or milrinone (strong inotrope & vasodilator, incl pulm), both proarrhythmic, or epi (strong inotrope & pressor)
  mech circulatory support (L/min): IABP (0.5), Impella (3.7–5.5), TandemHeart (5), VAD (L-sided, R-sided or both; temp or perm; 10) or ECMO (6) (*JACC* 2021;77:1243)

HEART FAILURE

Definitions (*Braunwald's Heart Disease*, 12th ed., 2022)

- Failure of heart to pump blood forward at rate sufficient to meet metabolic demands of peripheral tissues, or ability to do so only at abnormally high cardiac filling pressures
- Low output (↓ cardiac output) vs. high output (↑ stroke volume ± ↑ cardiac output)
- Left-sided (pulmonary edema) vs. right-sided (↑ JVP, hepatomegaly, peripheral edema)
- Backward (↑ filling pressures, congestion) vs. forward (impaired systemic perfusion)
- Systolic (inability to expel sufficient blood) vs. diastolic (failure to relax and fill normally)
- Reduced (HFrEF, EF <40%), mildly reduced (HFmrEF, EF 40–49%), & preserved (HFpEF, EF >50%); combination of systolic and diastolic dysfxn may occur regardless of EF

Figure 1-3 Approach to left-sided heart failure



History

- Low output: fatigue, weakness, exercise intolerance, Δ MS, anorexia
- Congestive: left-sided → dyspnea, orthopnea, paroxysmal nocturnal dyspnea
  right-sided → peripheral edema, RUQ discomfort, bloating, satiety

Functional classification (New York Heart Association class)

- Class I: no sx w/ ordinary activity; class II: sx w/ ordinary activity; class III: sx w/ minimal activity; class IV: sx at rest

Physical exam ("2-minute" hemodynamic profile; *JAMA* 1996;275:630 & 2002;287:628)

- **Congestion ("dry" vs. "wet"):** ↑ JVP (~80% of the time JVP >10 → PCWP >22)
  - ⊕ hepatojugular reflux: ≥3 cm ↑ in JVP for ≥10–15 sec w/ abdominal pressure Se/Sp 73/87% for RA >8 and Se/Sp 55/83% for PCWP >15 (*AJC* 1990;66:1002)
  - Abnl Valsalva response: square wave (↑ SBP w/ strain), no overshoot (no ↑ BP after strain)
  - S_3 (in Pts w/ HF → ~40% ↑ risk of HF hosp. or pump failure death; *NEJM* 2001;345:574)
  - Rales, dullness at base 2° pleural effus. (*often absent* in chronic HF due to lymphatic compensation) ± hepatomegaly, ascites and jaundice, peripheral edema
- **Perfusion ("warm" vs. "cold")**
  - narrow pulse pressure (<25% of SBP) → CI <2.2 (91% Se, 83% Sp; *JAMA* 1989;261:884);
  - soft S_1 (↓ dP/dt), pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
- ± Other: Cheyne-Stokes resp., abnl PMI (diffuse, sustained or lifting depending on cause of HF), S_4 (diast. dysfxn), murmur (valvular dis., ↑ MV annulus, displaced papillary muscles)

Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions ± cardiomegaly, cephalization, Kerley B-lines; lung U/S better than CXR (PPV & NPV 92% vs. 77%; *Chest* 2015;148:202)
- BNP/NT-proBNP can help exclude HF; levels ↑ w/ age, renal dysfxn, AF; ↓ w/ obesity Se ≥95%, Sp: ~50%, PPV ~65%, NPV ≥ 94% for HF in Pts p/w SOB (*BMJ* 2015;350:h910)
- Evidence of ↓ organ perfusion: ↑ Cr, ↓ Na, abnl LFTs
- Echo (see inserts): ↓ EF & ↑ chamber size → systolic dysfxn; hypertrophy, abnl MV inflow, abnl tissue Doppler → ? diastolic dysfxn; abnl valves or pericardium; ↑ estimated RVSP
- PA catheterization: ↑ PCWP, ↓ CO, and ↑ SVR (in low-output failure)

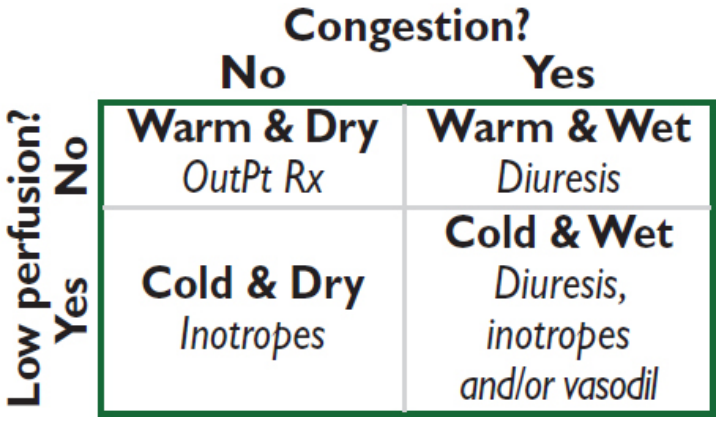
Evaluation for the potential causes of heart failure

- **ECG:** evidence for CAD, LVH, LAE, heart block or low voltage (? infiltrative CMP/DCM)
- **TTE:** LV & RV size & fxn, valve abnl (cause or consequence?), infiltrative or pericardial dis.
- **Cardiac MRI:** distinguishes ischemic vs. nonischemic and can help determine etiol. of latter
- **Coronary angio** (or noninvasive imaging, eg, CT angio); if no CAD, w/u for NICM

Precipitants of acute heart failure

- **Dietary indiscretion or medical nonadherence** (~40% of cases)
- **Myocardial ischemia or infarction** (~10–15% of cases); myocarditis
- **Renal failure** (acute, progression of CKD, or insufficient dialysis) → ↑ preload
- **Hypertensive crisis (incl. from RAS), worsening AS** → ↑ left-sided afterload

- **Drugs** (βB, CCB, NSAIDs, TZDs), **chemo** (anthracyclines, trastuzumab), or **toxins** (EtOH)
- **Arrhythmias; acute valvular dysfxn** (eg, endocarditis), espec mitral or aortic regurgitation
- COPD/PE → ↑ right-sided afterload; extreme stress; anemia; systemic infxn; thyroid dis.



Rx of acute decompens. HF (*NEJM* 2017;377:1964)
- Assess congestion & adequacy of perfusion
- For **congestion: "LMNOP"**
  Lasix IV; 1–2.5× usual total daily PO dose Ø clear diff between gtt vs. q12h IV
  Morphine (↓ sx, venodilator, ↓ afterload)
  Nitrates (venodilator)
  Oxygen ± noninvasive ventilation
  Position (sitting up & legs dangling over side of bed → ↓ preload)
- For **low perfusion**, see below
- Adjustment of home oral meds: prefer to continue, except:
  ACEI/ARB/ARNI: hold or ↓ dose if HoTN; Δ to hydralazine & nitrates w/ AKI
  βB: hold if evidence of hypoperfusion or HoTN

Treatment of acute advanced heart failure (*Circ* 2013;128:e240)
- Consider PAC if not resp to Rx, unsure re: vol status, HoTN, hypoperfusion, need inotropes
- Tailored Rx w/ PAC (qv); goals of MAP >60, CI >2.2 (MVO_2 >60%), SVR <800, PCWP <18
- **IV vasodilators:** NTG, nitroprusside (risk of coronary steal if CAD)
- **Inotropes** (properties in addition to ↑ inotropy listed below)
  dobutamine: vasodilation at doses ≤5 μg/kg/min; mild ↓ PVR; desensitization over time
  dopamine: splanchnic vasodil. → ↑ GFR & natriuresis; vasoconstrictor at ≥5 μg/kg/min
  milrinone: prominent systemic & pulmonary vasodilation; ↓ dose by 50% in renal failure
- **Mechanical circulatory support** (also see "Tailored Therapy;" *JACC* 2015;65:e7 & 2542)
  Temporary: bridge to recovery, transplant, or durable MCS; periprocedural support

Intra-aortic balloon pump (IABP): inflates in diastole & deflates in systole to ↓ impedance to LV ejection, ↓ myocardial O_2 demand & ↑ coronary perfusion; +0.5 L/min CO

Axial flow pumps (eg, Impella): Archimedes screw principle in LV; +3.7–5.5 L/min

Extracorporeal centrifugal pumps: TandemHeart (+5 L/min, percutaneous) & CentriMag (10 L/min, surgical)

Extracorporeal membrane oxygenation (ECMO): 6 L/min (*JACC HF* 2018;6:503)

Durable: surgically placed LVAD ± RVAD as bridge to sufficient recovery (in 5–50% of niCMP; *JACC* 2017;69:1924), to transplant or as destination Rx (>50% ↓ 1-y mort. vs. med Rx; *NEJM* 2001;345:1435 & 2009;361:2241). Current preferred option is fully magnetically levitated centrifugal flow pump (HeartMate 3), ↓ stroke or re-op vs. axial flow models (*NEJM* 2019;380:1618).

• Cardiac transplantation: ~2200/yr in U.S. <10% mort. in 1st y, median survival ~13 y

Recommended Chronic Therapy by HF Stage (*JACC* 2021;77:772)		
Stage (not NYHA Class)		**Therapy**
A	At risk for HF (eg, HTN); but asx & w/o struct. dis.	Rx HTN, lipids, DM; stop smoking, EtOH; ↑ exercise ACEI/ARB if HTN/DM/CAD/PAD
B	⊕ Struct. heart dis. (eg, CMP, LVH), but asx	As per stage A + ACEI/ARB + βB if MI/CAD or ↓ EF. ? ICD.
C	⊕ Struct. heart dis. ⊕ Any h/o Sx of HF	As per stage A + diuretics, ↓ Na. If ↓ EF: ARNI, ACEI or ARB; βB; aldo antag; SGLT2i; ICD; ? CRT; ± nitrate/hydral; ± dig. If preserved EF: ? ARNI; ? aldo antag; SGLT2i
D	Refractory HF requiring specialized interventions	All measures for stages A–C. Consider IV inotropes, VAD, transplant, end-of-life care (4-y mortality >50%)

• Utility of BNP-guided Rx (inPt and outPt) remains debated (*Eur Heart J* 2014;35:16)

• Implantable PA pressure sensor in sx Pts: ~19–37% ↓ risk of hosp (*Lancet* 2016;387:453 & 2021;398:991)

Treatment of Chronic HF with Reduced EF (*Circ* 2017;136:e137; *JACC* 2021;77:772)	
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
RASi Choose one of **ARNI** (ARB + neprilysin inhib), **ACEI** or **ARB** 36-hr washout when transitioning ACEI to ARNI	*ARNI preferred RASi in NYHA II–IV*. Neutral endopeptidase (NEP, aka neprilysin) degrades natriuretic peptides, bradykinin & angiotensins. Valsartan + sacubitril (NEPi) ↓ CV mort & HF hosp c/w ACEi; ↑ HoTN, AKI (*NEJM* 2014;371:993 & 2019;380:539). Contraindicated if h/o angioedema. *ACEI:* if unable to tolerate or afford ARNI. ↓ mortality vs. placebo. High-dose more effic. than low. Watch for ↑ Cr, ↑ K (ameliorate by low-K diet, diuretics, K binders), cough, angioedema. ARB: consider if cannot tolerate ACEI (eg, b/c cough) as noninferior
β-blocker (data for carvedilol, metoprolol, bisoprolol)	*Add in concert w/ RASi* 35% ↓ mort. & 40% ↓ rehosp. in NYHA II–IV (*JAMA* 2002;287:883) EF will transiently ↓, then ↑. Contraindicated in ADHF. Carvedilol superior to low-dose metop in 1 trial (*Lancet* 2003;362:7), but meta-analysis suggests no diff between βB (*BMJ* 2013;346:f55).
Aldosterone antagonists	*Add after RASi and* b*B if adeq. renal fxn and w/o hyperkalemia* 25–30% ↓ mort. in NYHA II–IV & EF ≤35% (*NEJM* 2011;364:11) 15% ↓ mort. in HF post-MI, EF ≤40% (*EPHESUS, NEJM* 2003;348:1309) Watch for ↑ K. Do not use if GFR <30 or K ≥5
SGLT2i	~25% ↓ death or HF hospitalization in NYHA II–IV (*DAPA-HF, NEJM* 2019; 381:1995, *EMPEROR-Reduced; NEJM* 2020;383:1413).

Treatment of Chronic HF with Reduced EF (*Circ* 2017;136:e137; *JACC* 2021;77:772)	
Hydralazine + nitrates	*Consider if cannot tolerate ACEI/ARB or in black Pts w/ class III/IV* 25% ↓ mort. (*NEJM* 1986;314:1547); infer. to ACEI (*NEJM* 1991;325:303) 40% ↓ mort. in blacks on standard Rx (A-HEFT, *NEJM* 2004;351:2049)
Ivabradine (I_f blocker w/o ⊖ ino)	*Reasonable if EF ≤35%, NYHA II or III, HR ≥70, NSR on max* b*B.* 18% ↓ CV mort or HF hosp (*Lancet* 2010;376:875)
Digoxin	23% ↓ HF hosp., no Δ mort (*NEJM* 1997;336:525); ? ↑ mort w/ ↑ levels (*NEJM* 2002;347:1403); optimal 0.5–0.8 ng/mL (*JAMA* 2003;289:871)
Vericiguat	10% ↓ CV mort or HF hosp in NYHA II–IV (*NEJM* 2020;382:1883)
Cardiac resynch therapy (CRT, qv)	*Consider if EF ≤35%, LBBB (QRS ≥130 ms) and symptomatic HF* 36% ↓ mort. & ↑ EF in NYHA III–IV (CARE-HF, *NEJM* 2005;352:1539) 41% ↓ mort. if EF ≤30%, LBBB and NYHA I/II (*NEJM* 2014;370:1694)
ICD (see "Cardiac Rhythm Mgmt Devices")	*For 1° prevention if EF ≤30–35% or 2° prevention; not if NYHA IV* ↓ mort. in ischemic CMP but perhaps only SCD in modern era in niCMP (*NEJM* 2005;352:225 & 2016;375:1221)
Iron supplementation	*? IV (not PO) if NYHA II/III, EF ≤40%, Fe-defic* (ferritin <100 or 100– 300 & TSAT <20%). ~20% ↓ HF hosp. (*Lancet* 2020;396:1895).
Anticoagulation	*If AF, VTE, LV thrombus*, ± *if large akinetic LV segments.*
Heart rhythm	If AF & NYHA II–IV w/ EF <35%, catheter ablation ↓ D/HF hosp vs. med Rx (rate or rhythm; *NEJM* 2018;378:417)
BP	Goal <130/80 (*JACC* 2018;71:127)
Diet, exercise	? Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
Meds to avoid	NSAIDs, nondihydropyridine CCB, TZDs

(*Circ* 2013;128:e240 & 2016;134:e282; *EHJ* 2016;37:2129)

Heart failure with preserved EF (HFpEF; "Diastolic HF") (*JACC* 2022;epub)

- Epidemiology: ~½ of Pts w/ HF have normal (EF ≥50%); risk factors for HFpEF incl ↑ age, ♀, DM, AF. Mort ≈ to those w/ HFrEF.
- Etiologies (impaired relaxation and/or ↑ passive stiffness): ischemia, prior MI, LVH, HCMP, infiltrative CMP, RCMP, aging, hypothyroidism
- Precipitants of pulmonary edema: *volume overload* (poor compliance of LV → sensitive to small ↑ in volume); *ischemia* (↓ relaxation); *tachycardia* (↓ filling time in diastole), *AF* (loss of atrial boost to LV filling); *HTN* (↑ afterload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic fxn. Dx supported by evidence of diast dysfxn:
  (1) echo: impaired relaxation using tissue Doppler (eg, e′ <9 cm/s), high filling pressures ± impaired relaxation (eg, E/e′ ≥15), large left atrium
  (2) exercise-induced ↑ PCWP ± inadequate ↑ stroke volume or CO
- Treatment: **diuresis**, Rx HTN, tachycardia, and ischemia
  SGLT2i ↓ CV death or HF hosp (*NEJM* 2021;385:1451; DELIVER)
  Nonsignficiant trends toward benefit for ARB vs. placebo. **ARNI** ↓ CV death or hosp for HF in HFpEF Pts w/ LVEF <60% (*NEJM* 2019; 381:1609)
  Spironolactone likely ↓ HF hospitalization (*NEJM* 2014;370:1383; *Circ* 2015;131:34)

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

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DILATED CARDIOMYOPATHY (DCM)

Definition and epidemiology (*JACC* 2016;67:2996; *Lancet* 2017;390:400)

- **LV or biventricular dilatation and global** ↓ contractility ± ↓ wall thickness in the absence of ischemia/infarct, valvular disease or HTN. Pts w/ prior MI complicated by LV dilation and ↓ EF are often termed "ischemic CMP."

Etiologies (*JACC* 2021;77:2551; can also be prior myocarditis, vide infra)

- **Familial/genetic** (>35%): Pt & ≥2 closely related family members w/ unexplained DCM; ~30 genes identified to date, encoding structural & nuclear proteins (eg, titin)
- **Idiopathic** (<20%): ? undx infectious, EtOH, or genetic cause; ¼ w/ e/o DCM in relative
- **Toxic:** alcohol (~20%) typ. 7–8 drinks/d × >5 y, but variable; cocaine; XRT (usu RCMP);
  anthracyclines (risk ↑ >550 mg/m^2, may manifest late), CYC, trastuzumab, TKIs.
- **Infiltrative** (5%): typically RCMP (qv), but can be DCMP with thickened walls; amyloidosis, sarcoidosis, hemochromatosis, tumor
- **Peripartum** (onset last mo → 5 mo postpartum; *JACC* 2020;75:207): ~1:2000; ↑ risk w/ multip, ↑ age, Afr Am; stnd HF Rx (if preg, no ACEI or spironolact.); ~30% recur w/ next preg
- **Stress-induced** (Takotsubo = apical ballooning): typically postmenopausal ♀; mimics MI (chest pain, ± STE & ↑ Tn; deep TWI & ↑ QT); mid/apex dyskinesis; ? Rx w/ βB, ACEI; usu. improves over wks (*JAMA* 2011;306:277). In-hosp morb/mort similar to ACS (*NEJM* 2015;373:929).
- **Tachycardia** (*JACC* 2019;73:2328): likelihood ∝ rate/duration; often resolves w/ rate cntl
- **Arrhythmogenic right ventricular cardiomyopathy** (ACM/ARVC): fibrofatty replacement of RV → dilation (dx w/ MRI); ECG: ± RBBB, TWI V_1–V_3, ε wave; VT risk (*NEJM* 2017;376:61)
- **LV noncompaction** (*Lancet* 2015;386:813): prominent trabeculae, arrhythmias, cardioemboli
- **Metab/other:** hypothyroid, acromegaly, pheo, OSA, Vit B_1, selenium or carnitine defic.

Clinical manifestations

- **Heart failure:** both congestive & poor forward flow sx; signs of L- & R-sided HF
  diffuse, **laterally displaced PMI**, **S3**, ± MR or TR (annular dilat., displaced pap. muscle)
- Embolic events (~10%), supraventricular/ventricular arrhythmias, & palpitations

Diagnostic studies and workup (*JACC* 2016;67:2996)

- ECG: may see PRWP, Q waves, or BBB; low-voltage; AF (20%); may be normal
- Echocardiogram: LV dilatation, ↓ EF, *regional or global* LV HK ± RV HK, ± mural thrombi
- Cardiac MRI: high Se for myocarditis or infiltration; extent of scar correlated w/ mortality
- Labs: TFTs, Fe panel, HIV, SPEP, ANA; viral sero *not* recommended; others per suspicion
- Family hx (20–35% w/ familial dis.), genetic counseling ± genetic testing (*JAMA* 2009;302:2471)
- Coronary CT angiography (or invasive) to r/o CAD if risk factors, h/o angina, Qw MI
- Endomyocardial biopsy: consider if fulminant myocarditis or suspect infiltrative disease

Treatment (see "Heart Failure" for standard HF Rx)
- Possibility of reversibility of CMP may temper implantation of devices
- Prognosis differs by etiology (*NEJM* 2000;342:1077): postpartum (best), ischemic/GCM (worst)

MYOCARDITIS

Etiologies
- **Infectious** (*Lancet* 2012;379:738; *JACC* 2012;59:779)
  - Viruses (parvoB19, Coxsackie, adeno, HIV, SARS-CoV-2/vaccine, etc.)
  - Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB)
  - Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (*Lancet* 2018;391:82)
- **Autoimmune**
  - Idiopathic giant cell myocarditis (GCM): avg age 42, fulminant, AVB/VT (*Circ HF* 2013;6:15)
  - Eosinophilic (variable peripheral eos): hypersensitivity (mild HF but at risk for SCD) or acute necrotizing eosinophilic myocarditis (ANEM; STE, effusion, severe HF)
  - Collagen vasc. dis. (pericarditis >myocarditis): PM, SLE, scleroderma, PAN, RA, EGPA

Clinical manifestations
- Highly variable, ranging from incidental dx based on labs/imaging to fulminant HF w/ shock
- Can present as ACS-like syndrome (chest pain, ECG Δs, ↑ Tn), acute HF, arrhythmias

Diagnostic studies and workup
- Echo: systolic dysfxn (typically global but can be regional); ± ↑ LV wall thickness due to edema; LV size may be small in fulminant and dilated in chronic; ± pericardial effusion
- Cardiac MRI: can show hyperemia, edema, and scar (*JACC* 2009;53:1475)
- Endomyocardial biopsy: useful in GCM & eosinophilic; ∴ consider if rapidly progressive HF, high-grade AVB or sustained VT, suspected allergic rxn or eosinophilia

Treatment
- Standard HF Rx if LV dysfxn (but do not start if e/o shock); temporary MCS as needed

• Immunosuppression: for GCM (high-dose steroids + CsA or tacrolimus ± AZA), collagen vascular disease, peripartum (? IVIg), & eosinophilic; no proven benefit if viral

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HYPERTROPHIC CARDIOMYOPATHY (HCM)

Definition, epidemiology, pathology (*Circ Res* 2017;121:749)

• LV (usually ≥15 mm) and/or RV hypertrophy disproportionate to hemodynamic load
• Due to gene mutations affecting proteins of or related to sarcomere; prev.: ~1/200-500
• Myocardial fiber disarray with hypertrophy, which creates arrhythmogenic substrate
• Many morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical
• Ddx: LVH 2° to HTN, AS, elite athletes (wall usually <13 mm & symmetric and nl/↑ rates of tissue Doppler diastolic relaxation; *Circ* 2011;123:2723), Fabry dis. (↑ Cr, skin findings)

Pathophysiology

• LV outflow tract obstruction (LVOTO) in ≥70%: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable, or nonexistent) and papillary muscle displacement. Gradient (∇) worse w/ ↑ contractility (digoxin, β- agonists, exercise, PVCs), ↓ preload (eg, Valsalva maneuver) or ↓ afterload.
• Mitral regurgitation: due to SAM (mid-to-late, post.-directed regurg. jet) and/or abnl mitral leaflets and papillary muscles (pansystolic, ant.-directed regurg. jet)
• Diastolic dysfunction: ↑ chamber stiffness + impaired relaxation
• Ischemia: small vessel dis., perforating artery compression (bridging), ↓ coronary perfusion

Clinical manifestations (70% are asymptomatic at dx)

• **Dyspnea** (90%): due to ↑ LVEDP, MR, and diastolic dysfunction
• **Angina** (25%) even w/o epicardial CAD; microvasc. dysfxn (*NEJM* 2003;349:1027)
• **Arrhythmias** (AF in 20–25%; VT/VF): palpitations, syncope, sudden cardiac death

Physical exam

• Sustained PMI, S_2 paradoxically split if severe outflow obstruction, ⊕ S_4 (occ. palpable)
• **Systolic murmur:** crescendo-decrescendo; LLSB; ↑ **w/ Valsalva** & standing (↓ preload)
• ± mid-to-late or holosystolic murmur of MR at apex
• Bifid (biphasic) carotid pulse (brisk rise, decline, then 2nd rise); JVP w/ prominent *a* wave
• Contrast to AS, which has murmur that ↓ w/ Valsalva and ↓ carotid pulses

Diagnostic studies (*EHJ* 2014;35:2733)

• ECG: LVH, anterolateral TWI and inferior pseudo-Qw, ± apical giant TWI (apical variant)
• **Echo:** any LV wall segment ≥15 mm (or ? even ≥13 if ⊕ HFx), often but not necessarily involving septum; other findings include dynamic outflow obstruction,

SAM, MR
- MRI: hypertrophy + patchy delayed enhancement (useful for dx & prog) (*Circ* 2015;132:292)
- Cardiac cath: subaortic pressure ∇; *Brockenbrough sign* = ↓ pulse pressure post-PVC (in contrast to AS, in which pulse pressure ↑ post-PVC); spike & dome Ao pressure pattern
- Consider genotyping for family screening; pathogenic variant ID'd in <½ (*Circ* 2020;142:e558)

Treatment (*Circ* 2020;142:e558; *Lancet* 2021;398:2102; *JACC* 2022;79:390)
- Heart failure
  - ⊖ **inotropes/chronotropes:** β-blockers (*JACC* 2021;78:2505), CCB (verapamil), disopyramide
  - Careful use of diuretics, because may further ↓ preload. If LVOTO, *avoid vasodilators*. Avoid digoxin b/c ↑ contractility and ∴ outflow obstruction.
  - If sx refractory to drug Rx + *obstructive* physio. (∇ ≥30 mmHg at rest or w/ provocation):
  - (a) Surgical myectomy: long-term ↓ symptoms in 90% (*Circ* 2014;130:1617)
  - (b) Alcohol septal ablation (*JACC* 2018;72:3095): ∇ ↓ by ~80%, only 5–20% remain w/ NYHA III–IV sx; 14% require repeat ablation or myectomy. Good alternative for older Pts, multiple comorbidities. Complic: transient (& occ. delayed) 3° AVB w/ 10–20% req. PPM; VT due to scar formation.
  - Mavacamten (cardiac myosin inhibitor) ↓ HF sxs & LVOT ∇ (*Lancet* 2020;396,750)
  - If refractory to drug therapy and there is *nonobstructive* pathophysiology: transplant
- Acute HF: can be precip. by dehydration or tachycardia; Rx w/ fluids, βB, phenylephrine
- AF: rate control w/ βB, maintain SR w/ disopyramide or amio; low threshold to anticoag
- ICD if VT/VF. Reasonable for 1° prevention if ≥1 risk factor: ⊕ FHx SCD, unexplained syncope, LV wall ≥30 mm, LV aneurysm or EF <50%; consider if NSVT, failure of SBP to ↑ or fall from peak ≥20 mmHg w/ exercise, ? extensive MRI delayed enhancement. EPS *not* useful. HCM Risk-SCD Score (https://doc2do.com/hcm/webHCM.html).
- Counsel to avoid dehydration, extreme exertion
- 1st-degree relatives: screen w/ TTE q12–18m as teen or athlete then q5y as adult, ECG (because timing of HCMP onset variable). Genetic testing if known mutation.

RESTRICTIVE & INFILTRATIVE CMP

Definition (*JACC* 2018;71:1130 & 1149)
- Restrictive CMP: ↓ ventricular filling with ↓ compliance in nonhypertrophied, nondilated ventricles; nl/↓ diastolic volumes, nl or near-nl EF; must r/o pericardial disease
- Infiltrative CMP: myocardial deposition; ± ↑ wall thickness; may present as RCM or DCM

Etiologies (*JACC* 2018;71:1130 & 1149)
- **Amyloidosis**: age at presentation ~60 y; ♂:♀ = 3:2

AL (eg, MM, etc.); familial (transthyretin, ATTR-m); senile (ATTR-wt)
ECG: ↓ QRS amplitude (50%), pseudoinfarction pattern (Qw), AVB (10–20%), hemiblock (20%), BBB (5–20%)
Echo: biventricular wall thickening (*yet w/ low voltage on ECG*), granular sparkling (30%), biatrial enlargement (40%), valve thickening, small effusions
Normal ECG voltage & septal thickness has NPV ~90%
Cardiac MRI: distinct late gadolinium enhancement pattern (*JACC* 2008;51:1022)

- **Sarcoidosis** (can also be DCM): presents at age ~30 y; ↑ in blacks, N. Europe, ♀
  Cardiac involvement in 25–58% of sarcoid, many not overt; cardiac w/o systemic in 10%
  ECG: AVB (75%), RBBB (20–60%), VT; PET: ↑ FDG uptake in affected area
  Echo: regional WMA (particularly basal septum) w/ thinning or mild hypertrophy
  Cardiac MRI: T2 early gad (edema); fibrosis/scar in basal septum; LGE prognostic
- **Other myocardial processes**
  Hemochromatosis: often middle-aged men (espec N. European); 15% w/ cardiac sx
  Diabetes; radiation (also accelerated athero, valvular disease, constrictive pericarditis)
  Autoimmune (scleroderma, polymyositis-dermatomyositis)
- **Endomyocardial diseases**: carcinoid heart disease (R-sided HF w/ TR/TS, PR/PS); Löffler's endocarditis (↑ eos; mural thrombi that can embolize; fibrosis); endomyocardial fibrosis (tropical climates; resembles Löffler's but w/o eos)
- **Storage diseases**: Fabry (glycosphingolipids); Gaucher (glucocerebrosidase)

Pathophysiology

- ↓ myocardial compliance → nl EDV but ↑ EDP → ↑ systemic & pulm. venous pressures
- ↓ ventricular cavity size → ↓ SV and ↓ CO

Clinical manifestations (*JACC* 2018;71:1130 & 1149)

- **Right-sided >left-sided heart failure** with peripheral edema >pulmonary edema
- **Diuretic "refractoriness"; thromboembolic events**
- Poorly tolerated tachyarrhythmias; VT → syncope/sudden cardiac death

Physical exam

- ↑ JVP, ± Kussmaul's sign (JVP not ↓ w/ inspir., classically seen in *constrict. pericarditis*)
- Cardiac: ± S_3 and S_4, ± murmurs of MR and TR
- Congestive hepatomegaly, ± ascites and jaundice, peripheral edema

Diagnostic studies

- CXR: normal ventricular chamber size, enlarged atria, ± pulmonary congestion
- ECG: low voltage, pseudoinfarction pattern (Qw), ± arrhythmias
- Echo: ± symmetric wall thickening, biatrial enlarge., ± mural thrombi, ± cavity oblit. w/ diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio; ↓ mitral annular velocity (e′) on tissue Doppler, ↑ E/e′ ratio
- Cardiac MRI/PET: may reveal inflammation or evidence of infiltration (but nonspecific)
- Amyloid (qv) workup: ✓ for plasma cell dyscrasia (immunofix. & serum free light chains). If ⊕ → fat pad bx. If ⊖ → PYP SPECT for TTR evaluation (not AL).

- Endomyocardial biopsy if suspect amyloid (Se ~100%) & noninvasive tests non-dx. Se low for sarcoidosis b/c patchy disease infiltrative process.
- Cardiac catheterization
  - Atria: **M's** or **W's** (prominent *x* and *y* descents)
  - Ventricles: **dip & plateau** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  - **Concordance** of LV–RV pressure peaks w/ respiration (vs. discordance in constriction)
- Restrictive cardiomyopathy vs. constrictive pericarditis: see "Pericardial Disease"

Treatment (in addition to Rx'ing underlying disease)

- Gentle diuresis. May not tolerate CCB or other vasodilators.
- Control HR (but can ↓ CO); maintain SR (helps filling). Digoxin ↑ arrhythmias in amyloid.
- Anticoagulation (particularly with AF or low CO)
- Transplantation for refractory cases
- AL amyloid: Rx targeted at plasma cell dyscrasia
- ATTR amyloid: tafamidis (TTR binder) ↓ death and CV hosp, ↑QoL (*NEJM* 2018;379:1007)
- Sarcoid: consider steroids/immunomodulators if FDG PET ⊕ for inflammation + AVB, VT or LV dysfxn; ↑ risk for VT; unique indications for ICD placement (*Circ* 2018;138:e272)

VALVULAR HEART DISEASE

AORTIC STENOSIS (AS)

Etiology

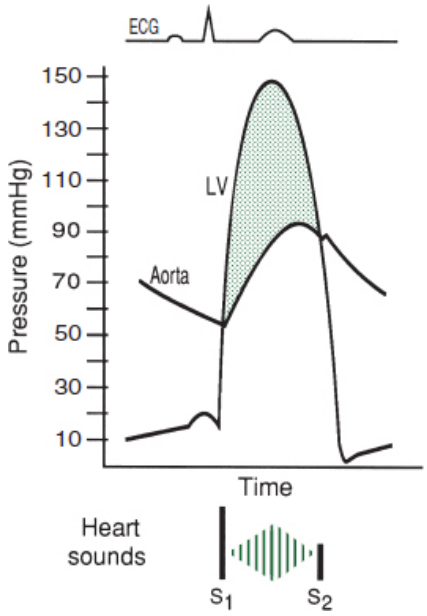
- **Calcific:** predominant cause in Pts >70 y; risk factors: HTN, ↑ LDL-C, ↑ Lp(a), ESRD
- **Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- **Rheumatic heart disease** (AS usually accompanied by AR and MV disease)
- AS mimickers: subvalvular (HCMP, subaortic membrane) or supravalvular stenosis

Clinical manifestations (usually indicates AVA <1 cm^2 or concomitant CAD)

- **Angina:** ↑ O_2 demand (hypertrophy) + ↓ O_2 supply (↓ cor perfusion pressure) ± CAD
- **Syncope** (*exertional*): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- **Heart failure:** outflow obstruct + diastolic dysfxn → pulm. edema, esp. if ↑ HR/AF (↓ LV fill.)
- Acquired vWF disease (~20% of sev. AS): destruction of vWF; GI angiodysplasia
- Natural hx: usually slowly progressive (AVA ↓ ~0.1 cm^2/y, but varies; *Circ* 1997;95:2262), until sx develop; mean survival based on sx: angina = 5 y; syncope = 3 y; CHF = 2 y

Physical exam

- **Midsystolic crescendo-decrescendo** murmur at **RUSB**, harsh, high-pitched, radiates to carotids, apex (holosystolic = Gallavardin effect), ↑ w/ passive leg raise, ↓ w/ standing & Valsalva. Dynamic outflow obstruction (HCM) is the reverse.
- Ejection click after S_1 sometimes heard with *bicuspid* AoV
- Signs of severity: *late-peaking* murmur, paradoxically split S_2 or inaudible A_2, small and delayed carotid pulse ("*pulsus parvus et tardus*"), LV heave, ⊕ S_4 (occasionally palpable)



Pathophys Heart Dis., 7th ed., 2021, for this et al.

Diagnostic studies

- ECG: may see LVH, LAE, LBBB, AF (in late disease)
- CXR: cardiomegaly, AoV calcification, poststenotic dilation of ascending Ao, pulmonary congestion
- **Echo:** valve morph., jet velocity → estimate pressure gradient (∇) & calculate AVA, dimensionless index (DI); LVEF
- **Cardiac cath:** usually to *r/o CAD* (in ~½ of calcific AS); for hemodyn. if disparity between exam & echo: ✓ pressure gradient (∇) across AoV, calc AVA (underestim. if mod/sev AR)
- **Dobutamine challenge** (echo or cath): if low EF and mean ∇ <40, use to differentiate:
  Afterload mismatch: 20% ↑ SV & ∇, no Δ AVA (implies contractile reserve, ↑ EF post-AVR)
  Pseudostenosis: 20% ↑ SV, no Δ in ∇, ↑ AVA (implies low AVA *artifact* of LV dysfxn)
  Limited contractile reserve: no Δ SV, ∇ or AVA (implies EF prob. will not improve w/ AVR)

Classification of Aortic Stenosis (*Circ* 2021;143:e72)							
Stage	**Sx**	**Severity**	**Max Jet Vel ($^m/_s$)**	**Mean ∇ (mmHg)**	**AVA (cm^2)[a]**	**LVEF**	**DI**
n/a	N	Normal	1	0	3–4	nl	n/a
A	N	At risk	<2	<10	3–4	nl	n/a
B	N	Mild	2–2.9	<20	>1.5	nl	>0.5
		Moderate	3–3.9	20–39	1–1.5	nl	0.25–0.5
C1	N	Severe	≥4	≥40	≤1.0	nl	<0.25
		Very severe	≥5	≥60	≤0.8	nl	
C2		Severe + ↓ EF	≥4	≥40	≤1.0	↓	
D1	Y	Severe	≥4	≥40	≤1.0	nl	<0.25
D2		Severe + low flow/∇ + ↓ EF[b]	<4	<40	≤1.0	↓	
D3		Severe + low flow/∇ + nl EF[c]	<4	<40	≤1.0	nl	

[a]AVA indexed to BSA <0.6 cm^2/m^2 also severe (use for smaller Pts); [b]DSE → max jet vel ≥4 & AVA ≤1.0; [c]Small LV w/ ↓ stroke vol (LVSVi <35 mL/m^2), severe LVH with marked diastolic dysfunction, consider cardiac amyloid

Valve replacement (*Circ* 2021;143:e72)

- Based on *symptoms:* once they develop → AVR needed
- *Indicated in:* **sx severe** (stage D1; D2; D3 if AS felt to be cause of sx); **asx severe + EF <50%** (stage C2); or severe (stage C1) *and* undergoing other cardiac surgery
- *Reasonable if:* **asx severe** (C1) *but* either **sx or ↓ BP w/ exercise** (can *carefully* exercise asx AS to uncover sx; do *not* exercise sx AS), **very severe,** ↑ BNP, rapid progression
- Growing data to support AVR in **asx severe** AS (*NEJM* 2020;382:111; *Circ* 2021;143:e72)
- Type of valve: mechanical reasonable if Pt <50 yrs, bioprosthetic if >65 yrs or cannot tolerate long-term anticoagulation; individualize if 50–65 yrs
- Transcatheter AoV implantation (TAVI, see below) attractive alternative to surgery
- Medical (if not AVR candidate or to temporize): careful diuresis prn, control HTN, maintain
  SR; digoxin if ↓ EF & HF or if AF; *avoid* venodilators (nitrates) & ⊖ inotropes (βB/CCB) if
  severe AS; avoid vigorous physical exertion once AS mod–severe
  ? nitroprusside (w/ PAC) in HF w/ sev. AS, ↓ EF/CO, & HTN (*Circ* 2013;128:1349)
- IABP: stabilization, bridge to surgery
- Balloon valvotomy (now rare): ↑ AVA, *but* risk CVA/AR & restenosis; ∴ bridge or palliation

TAVI (transcatheter AoV implantation) (*JAMA* 2021;325:2480; *Circ* 2021;143:e72)

- Valves: balloon-expandable or self-expanding.
- Most commonly deployed retrograde via perc. transfemoral access (best outcomes)
- Peri- & postprocedural complic.: CHB ~15% at 30d, more common if preexisting RBBB (*JACC* 2020;76:2391); annular rupture or coronary occlusion (both rare); stroke; local vascular; paravalvular leaks
- Postprocedural antithrombotic Rx: ASA 75–100 mg/d superior to DAPT (*NEJM* 2020;383:1447). In Pts *with indication for OAC*: OAC alone superior to OAC + $P2Y_{12}$

(*NEJM* 2020;382:1696; *Circ* 2021;143:e72); apixaban & edoxaban appear comparable to warfarin (ATLANTIS, ACC 2021; *NEJM* 2021;385:2150)

- Outcomes w/ TAVI: In *nonoperative Pts* (ie, vs. med Rx): ↓ mortality but still ~72% 5 y mortality in TAVI reflective of comorbidities (*NEJM* 2012;366:1696; *Lancet* 2015;385:2485). TAVI noninferior to SAVR in terms of risk of death or disabling stroke for high, intermediate, and low surgical risk Pts (*NEJM* 2014;370:1790; 2020;382:799; 2019;380:1695 & 2019;380:1706; *JACC* 2021;77:1149).

AORTIC REGURGITATION (AR)

Etiology (*Circ* 2006;114:422)

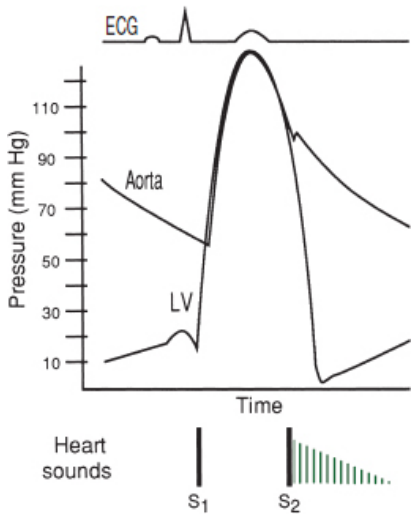
- **Valve disease** (43%): **rheumatic** (usually mixed AS/AR + MV disease); **bicuspid AoV** (natural hx: ⅓→ normal, ⅓→ AS, ⅙→ AR, ⅙→ endocarditis → AR); **infective endocarditis;** valvulitis (RA, SLE, certain anorectics & serotonergics, XRT)
- **Root disease** (57%): **HTN**, aortic aneurysm/dissection, annuloaortic ectasia (ie, Marfan), **aortic inflammation** (GCA, Takayasu's, ankylosing spond., reactive arthritis, syphilis)

Clinical manifestations

- Acute: sudden ↓ forward SV and ↑ LVEDP (noncompliant ventricle) → pulmonary edema ± hypotension and cardiogenic shock
- Chronic: clinically silent while LV dilates (to ↑ compliance to keep LVEDP low) more than it hypertrophies → chronic volume overload → LV decompensation → CHF
- Natural hx: *variable* progression (unlike AS, can be fast or slow); once decompensation begins, prognosis poor w/o AVR (mortality ~10%/y)

Physical exam

- **Early diastolic decrescendo murmur at LSB** (RSB if dilated Ao root); ↑ w/ sitting forward, expir, handgrip; severity of AR ∝ duration of murmur (except in acute and severe late); *Austin Flint murmur:* mid-to-late diastolic rumble at apex (AR jet interfering w/ mitral inflow)
- **Wide pulse pressure** due to ↑ stroke volume, hyper-dynamic pulse; pulse pressure narrows in late AR with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- PMI diffuse and laterally displaced; soft S_1 (early closure of MV); ± S_3 (≠ ↓ EF but rather just volume overload in AR)



Classic Eponymous Signs in Chronic AR (*South Med J* 1981;74:459)	
Sign	**Description**
Corrigan's pulse	"water hammer" pulse (ie, rapid rise/fall or distention/collapse)
Hill's sign	(popliteal SBP – brachial SBP) >60 mmHg
Duroziez's sign	to-and-fro murmur heard over femoral artery w/ light compression
Pistol shot sounds	pistol shot sound heard over femoral artery
Traube's sound	double sound heard over femoral artery when compressed distally
de Musset's sign	head-bobbing with each heartbeat (low Se)
Müller's sign	systolic pulsations of the uvula
Quincke's pulses	subungual capillary pulsations (low Sp)

Diagnostic studies

- ECG: can see LVH, LAD, abnl repol; CXR: cardiomegaly ± ascending Ao dilatation
- **Echo:** severity of AR (severe = regurg jet width ≥65% LVOT, regurg fraction ≥50%, effective regurg orifice ≥0.3 cm^2, holodiastolic flow reversal in descend. Ao; moderate = jet width 25–64%, regurg fraction 30–49%, regurg orifice 0.1–0.29 cm^2); LV size & fxn

Treatment (*Lancet* 2016;387:1312; *Circ* 2021;143:e72)

- Acute decompensation (consider endocarditis as possible acute precipitant): *surgery* usually urgently needed for acute severe AR, which is poorly tolerated by LV IV afterload reduction (nitroprusside) and inotropic support (dobutamine) ± chronotropic support (↑ HR → ↓ diastole → ↓ time for regurgitation) pure vasoconstrictors and IABP contraindicated
- In chronic AR, management decisions based on *LV size and fxn* (and before sx occur); low diastolic BP and high resting HR associated with mortality (*JACC* 2020;75:29)
- **Surgery** (AVR, replacement or repair if possible):
  Severe and **sx** (if equivocal, consider stress test)
  Asx *and* either **EF ≤55%**, **LV dilation** [LVESD >50 mm or LVESDi (indexed to BSA) ≥ 25 mm/m^2 (*JACC* 2019;73:1741)], or **undergoing cardiac surg**
- Transcatheter AoV implantation (TAVI) being explored (*JACC* 2013;61:1577 & 2017;70:2752)

• Medical therapy: **vasodilators** (nifedipine, ACEI/ARB, hydralazine) if severe AR w/ sx or LV dysfxn & not operative candidate or to improve hemodynamics before AVR.

MITRAL REGURGITATION (MR)

Etiology (*NEJM* 2010;363:156 & 2020;383:1458)

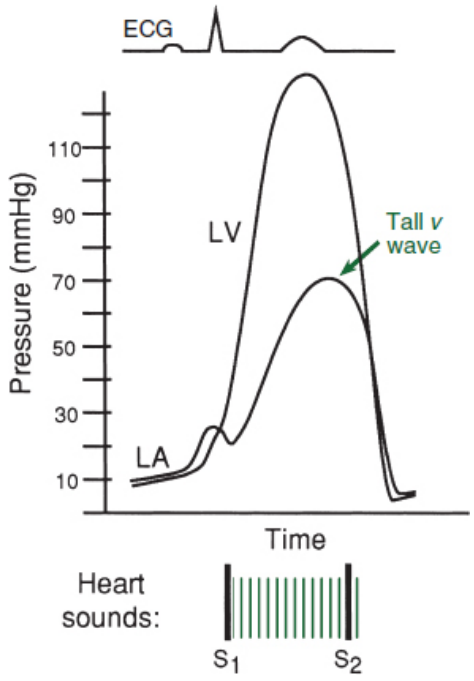
• **Primary** (degeneration of valve apparatus)
  Leaflet abnl: myxomatous (MVP), endocarditis, calcific, RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs (phen-fen), XRT
  Chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma
  Papillary muscle dysfxn b/c of ischemia or *rupture* during MI [usu. posteromedial papillary m. (supplied predominantly by PDA) vs. anterolateral (suppl. by diags & OMs)]
• **Secondary (functional):** inferoapical papillary muscle displacement due to ischemic LV remodeling or DCM; HCM (*JACC* 2015;65:1231)

Clinical manifestations

• Acute: **pulmonary edema**, hypotension, cardiogenic shock (*NEJM* 2004;351:1627)
• Chronic: typically asx for yrs, then as LV fails → progressive DOE, fatigue, AF, PHT
• Prognosis: 5-y survival w/ medical therapy is 80% if asx, but only 45% if sx

Physical exam

• **High-pitched, blowing, holosystolic murmur at apex;** radiates to axilla; ± thrill; ↑ w/ handgrip (Se 68%, Sp 92%),
  ↓ w/ Valsalva (Se 93%)
  ant. leaflet abnl → post. jet heard at spine
  post. leaflet abnl → ant. jet heard at sternum
• ± diastolic rumble b/c ↑ flow across valve
• Lat. displ. hyperdynamic PMI, obscured S_1, widely split S_2 (A_2 early b/c ↓ LV afterload, P_2 late if PHT); ± S_3
• Carotid upstroke brisk (vs. diminished and delayed in AS)



Diagnostic studies (*Circ* 2021;143:e72)

- ECG: may see LAE, LVH, ± atrial fibrillation
- CXR: dilated LA, dilated LV, ± pulmonary congestion
- **Echo:** MV anatomy (ie, etiol); MR severity: jet area, jet width at origin (vena contracta) or effective regurgitant orifice (ERO; predicts survival); LV fxn (EF should be *supranormal* if compensated, ∴ EF <60% w/ sev. MR = LV dysfxn)
- TEE or cardiac MR if TTE not sufficiently informative
- Cardiac cath: prominent PCWP *c-v* waves (not spec. for MR), LVgram for MR severity & EF

Grading of Primary Mitral Regurgitation						
Severity	**Regurg. Fraction**	**Jet Area** (% of LA)	**Vena contracta** (cm)	**ERO** (cm^2)	**Pulm vein systolic flow**[a]	**Angio**[b]
Mild	<30%	<20	<0.3	<0.2	nl	1+
Moderate	30–49%	20–40	0.3–0.69	0.2–0.39	nl/blunting	2+
Severe[c]	≥50%	>40	≥0.70	≥0.40	reversal	3/4+

[a]Influenced by LV function, etc. [b]1+ = LA clears w/ each beat; 2+ = LA does not clear, faintly opac. after several beats; 3+ = LA & LV opac. equal. [c]For 2° MR, ERO ≥0.20 severe as underestimated & likely LV dysfxn.

Treatment (*Circ* 2021;143:e72)

- **Acute severe MR:** consider ischemia & endocarditis as precipitants; IV afterload reduction (nitroprusside), relieve congestion (diuresis & NTG), ± inotropes (dobuta), IABP, avoid vasoconstrictors; *surgery* usually needed b/c prognosis poor w/o (*JAMA* 2013;310:609)
- **Chronic severe *primary* MR: surgery** (repair [preferred if feasible] vs. replacement) if **sx; asx & either EF □60% or LVESD □40 mm**; reasonable if low surgical risk + high prob successful repair; consider transcatheter repair if not surg candidate
- For primary MR, surgery superior to percutaneous repair (*NEJM* 2011;364:1395)

- If undergoing surgery & AF, MAZE ↓ AF recurrence, Ø Δ stroke (*NEJM* 2015;372:1399); surgical LAA occlusion ↓ risk of stroke; nb, Pts remained on anticoag (*NEJM* 2021;384:2081)
- **Chronic sx severe *secondary* MR:** if on optimal GDMT, EF 20–50%, LVESD ≤70 mm, & PASP ≤70 mmHg**, transcatheter edge-to-edge repair** (TEER) may ↑ survival & ↓ HF hosp., but conflicting trial data (*NEJM* 2018:379;2297 & 2307; *JACC* 2021;77:1029 & 78:2326); consider MV surgery if EF≥50% or EF≤50% but not meeting criteria for repair
- Transcathether replacement (TMVR) remains under study (*JACC Intv* 2021;14:489)
- If sx & EF<60% but not operative candidate: Rx (βB, ACE/ARB ± MRA); ↓ preload w/ diuretics, NTG (espec. if ischemic MR) for sx relief ± ↓ ERO; maintain SR
- Asymptomatic: Ø proven benefit of medical therapy; βB ↑ LV fxn (*JACC* 2012;60:833)

Mitral Valve Prolapse (MVP)

Definition and Etiology
- Billowing of MV leaflet ≥2 mm above mitral annulus in parasternal long axis echo view
- Primary: sporadic or familial myxomatous proliferation of spongiosa of MV apparatus
- Secondary: trauma, endocarditis, congenital, CTD (eg, Marfan's, OI, Ehlers-Danlos)

Clinical manifestations (usually asymptomatic)
- MR, endocarditis, emboli, arrhythmias (rarely SCD from VT from papillary muscle)
- High-pitched, midsystolic click (earlier w/ ↓ preload) ± mid-to-late systolic murmur
- No Rx *per se* [endocarditis Ppx not rec. (*Circ* 2007;116:1736)]; Rx MR as above

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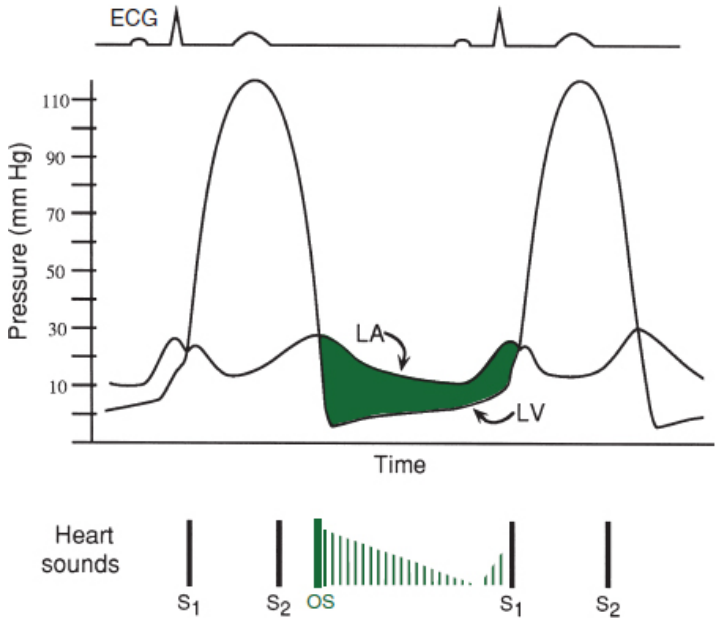
Mitral Stenosis (MS)

Etiology (*Lancet* 2012;379:953)
- **Rheumatic heart disease** (RHD): *fusion of commissures* → "fish-mouth" valve from autoimmune rxn to β strep infxn; seen largely in developing world (*Circ* 2020;142:e337)
- **Mitral annular calcification:** encroachment upon leaflets → fxnal MS; espec in ESRD
- Postsurgical repair or post-TEER w/ reduced mitral valve area (MVA)
- Congenital, infectious endocarditis w/ large lesion, myxoma near MV, thrombus
- Valvulitis (eg, SLE, amyloid, carcinoid) or infiltration (eg, mucopolysaccharidoses)

Clinical manifestations (*Lancet* 2009;374:1271)
- **Dyspnea and pulmonary edema** (if due to RHD, sx usually begin in 30s) precipitants: exercise, fever, anemia, volume overload (incl. pregnancy), tachycardia, AF
- **Atrial fibrillation:** onset often precipitates heart failure in Pts w/ MS
- **Embolic events:** commonly cerebral, espec in AF or endocarditis
- Pulmonary: hemoptysis, frequent bronchitis (due to congestion), PHT, RV failure
- Ortner's syndrome: hoarseness from LA compression of recurrent laryngeal nerve



Physical exam

- **Low-pitched mid-diastolic rumble at apex** w/ presystolic accentuation (if not in AF); best heard in L lat decubitus position during expiration, ↑ w/ exercise; severity proportional to *duration* (not intensity) of murmur; loud S_1
- **Opening snap** (high-pitched early diastolic sound at apex) from fused leaflet tips; MVA proportional to S_2–OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S_1 (unless MV calcified and immobile)

Diagnostic studies

- ECG: **LAE** ("P mitrale"), ± AF, ± RVH
- CXR: **dilated LA** (flat L heart border, R double density, displaced L mainstem bronchus)
- **Echo:** estimate pressure gradient (∇), RVSP, valve area, valve echo score (0–16, based on leaflet mobility & thick, subvalvular thick., Ca^{++}); exer. TTE (to assess Δ RVSP and ∇) if sx & severity of MS at rest discrepant; TEE to assess for LA thrombus before PMBC
- **Cardiac cath:** ∇, calculated MVA; LA tall *a* wave & blunted *y* descent; ↑ PA pressures

Grading of Mitral Stenosis

Stage	Mean ∇ (mmHg)	Pressure ½ Time	MVA (cm^2)	PA sys (mmHg)
Normal	0	n/a	4–6	<25
Mild-mod	<5	100–149	1.6–2	<30
Severe	5–9	150–219	1.1–1.5	30–50
Very severe	≥10	≥220	≤1	>50

Treatment (*Lancet* 2016;387:1324; *Circ* 2021;143:e72)

- Medical: Na restriction, cautious diuresis, βB, AF control, sx-limited physical stress
- Antibiotic Ppx recommended if h/o RHD w/ valvular disease for 10 y or until age 40

- Anticoag w/ warfarin (not DOAC) if: AF; prior embolism; LA clot
- Mechanical intervention indicated if **sx severe MS**; reasonable if asx severe MS but PASP >50 mmHg and morphology favorable for PMBC; consider PMBC if non-severe MS but exertional sx and hemodyn signif w/ exercise, or if asx severe MS and new-onset AF
- **Percutaneous mitral balloon commissurotomy** (PMBC): preferred Rx if RHD; ≈ MVR *if* valvuloplasty score <8, Ø if mod-severe MR or LA clot
- Surgical (MV repair if possible, o/w replacement) if PMBC contraindicated
- Calcific MS: surgical MVR if severe & highly sx; use of transcatheter aortic prosthesis experimental and w/ high rate of complications (*Circ CVI* 2020;13:e008425)
- Pregnancy: if NYHA class III/IV → PMBC, o/w medical Rx w/ low-dose diuretic & βB

TRICUSPID REGURGITATION (*Circ* 2014;129:2440; *Lancet* 2016;388:2431)

- Fxnl etiol (90%): RV dilation, PHT (may be 2° to L-sided dis.), large L → R shunts
- 1° etiol: myxomatous, IE, pacemaker leads, RHD, CTD, XRT, Ebstein's, carcinoid, tumors
- Holosystolic murmur, 3rd/4th ICS, ↑ w/ insp (Carvallo's sign); S_3; prominent *cv* wave in JVP
- Consider repair/replacement in severe TR (eg, ERO ≥0.40 cm^2) undergoing L-sided surgery, R heart failure or ? progressive RV dysfxn; emerging transcatheter Rx (*JACC* 2018;71:2935)

PROSTHETIC HEART VALVES

Mechanical

- Bileaflet (eg, St. Jude Medical); tilting disk; caged-ball
- Very durable (20–30 y), but thrombogenic and ∴ require anticoagulation consider if age <50 y or if anticoagulation already indicated (*JACC* 2010;55:2413)

Bioprosthetic

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Less durable, but min. thrombogenic; consider if >~65 y, lifespan <20 y, or Ø anticoag
- If 50–69 y, 2× reop but ½ bleeding or stroke vs. mech (*JAMA* 2014;312:1323 & 2015;313:1435)

Physical exam

- **Crisp sounds** ± soft murmur during forward flow (normal to have small ∇)

Anticoagulation & antiplatelet therapy (*Circ* 2021;143:e72)

- **Mechanical:** warfarin (not DOAC), INR 3 or 2.5 if low-risk mech AVR (none of following: prior thromboembolism, AF, EF <30–35%, hypercoagulable).
  If thrombosis, ↑ intensity (eg, INR 2–3 → 2.5–3.5; 2.5–3.5 → 3.5–4.5; or + ASA if not on)
- **Bioprosthetic:**
  Surgical: ASA (75–100 mg/d) or warfarin INR 2.5 ×3–6 mo, then ASA (75–100 mg/d). DOAC reasonable alternative to warfarin if indication for anticoag (*NEJM* 2020;383:2117).
  TAVI: ASA 75–100 mg/d. If need OAC, then no antiplt (vide supra).

Periprocedural "Bridging" of Anticoagulation in Pts with Mechanical Valve(s)	
AVR w/o risk factors	d/c warfarin 2–4 d before surg; restart 12–24 h after surg
MVR or AVR w/ risk factors	Preop: d/c warfarin, start UFH (preferred to LMWH) when INR <2 4–6 h preop: d/c UFH; postop: restart UFH & warfarin ASAP

JACC 2017;70:253. Procedures include noncardiac surgery, invasive procedures, and major dental work.

Correction of overanticoagulation (*Circ* 2021;143:e72)

- Risk from major bleeding must be weighed against risk of valve thrombosis
- Not bleeding: if INR 5–10, withhold warfarin
- Bleeding: PCC (or FFP); reversal agent for DOACs; ± low-dose (1 mg) vit K IV if on VKA

Endocarditis prophylaxis: for all prosthetic valves (see "Endocarditis")

Complications

- Structural failure (r/o endocarditis); mechanical valves: rare except for Bjork-Shiley; bioprosth: up to 30% rate w/in 10–15 y, mitral >aortic; consider TAVR (*JACC* 2017; 69:2253)
- Paravalvular leak (r/o endocarditis); small *central* jet of regurg is normal in mech. valves
- Obstruction from thrombosis (*JACC* 2013;62:1731) or pannus: ✓ TTE, TEE, CTA, or fluoro
  significantly symptomatic *pannus* ingrowth: remove w/ surgery
  thrombosis: surgery if sx or large L-sided mech valve obstruction; UFH ± low-dose lytic if small, not surgical candidate, or R-sided; OAC for sx bioprosthetic thrombosis
- Infective endocarditis ± valvular abscess and conduction system dis. (see "Endocarditis")
- Embolization (r/o endocarditis); risk highest 1st 90 d, ~1%/y w/ warfarin (vs. 2% w/ ASA, or 4% w/o meds); mech MVR 2× risk of embolic events vs. mech AVR (*Circ* 1994;89:635)
- Bleeding (from anticoag), hemolysis (espec w/ caged-ball valves or paravalvular leak)

PERICARDIAL DISEASE

Anatomy

• 2-layered (parietal & visceral) tissue sac surrounding heart & proximal great vessels

Disease states

• Inflammation (w/ or w/o fluid accumulation) → pericarditis
• Fluid accumulation → effusion ± tamponade
• Decrease in compliance (sequela of inflammation) → constrictive pericarditis
• Tamponade and constriction characterized by increased ventricular interdependence

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PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Acute Pericarditis (*JACC* 2020;75:76)	
Idiopathic (~90%)	Most presumed to be undiagnosed viral etiologies
Infectious (<5% can be confirmed infectious)	Viral: Coxsackie, Parvovirus B19, echo, adeno, EBV, VZV, HIV, influenza, SARS CoV-2 Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): *S. pneumo, N. meningitidis, S. aureus, Borrelia* (Lyme); TB Fungi: *Histo, Coccidio, Candida*; Parasite: *Entamoeba, Echino*
Neoplastic (<10%)	*Common:* metastatic (lung, breast, lymphoma, leukemia, RCC) *Rare:* primary cardiac & serosal tumors (mesothelioma)
Autoimmune	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, ANCA ⊕ (EGPA, GPA) Drug-induced: procainamide, hydralazine, inh, CsA
Uremia	~5–13% of Pts prior to HD; ~20% occurrence in chronic HD Pts
Cardiovascular	STEMI, late post-MI (Dressler's syndrome), but rare in modern era; prox AoD; chest trauma/postpericardiotomy; PCI or EP complication
Radiation	>40 Gy to mediastinum; acute or delayed; may be transudative
Effusion w/o pericarditis	HF (particularly R-sided as pericardial fluid drains into RA), cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis. Transudative.

Clinical manifestations (*NEJM* 2014;371:2410; *JACC* 2020;75:76)

• **Pericarditis:** retrosternal CP, pleuritic, positional (often ↓ by sitting forward), → trapezius; may be *absent* in TB, neoplastic, XRT, or uremic; ± fever; ± s/s of systemic etiologies
• **Effusion:** present in 50–65% of Pts w/ pericarditis; ranges from asx to tamponade
• **Definitions:** acute (<4–6 wks), incessant (persistent sx >4–6 wks), recurrent (after a symptom-free interval of 4–6 wks), chronic (lasting >3 mos)

Physical exam

• **Pericarditis:** multiphasic **friction rub** best heard at LLSB w/ diaphragm of stethoscope. Notoriously variable and evanescent leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, ventricular relaxation (*NEJM* 2012;367:e20).

- **Effusion:** distant heart sounds, dullness over left posterior lung field due to compressive atelectasis from pericardial effusion (Ewart's sign)

Diagnostic studies (*JAMA* 2015;314:1498; *EHJ* 2015;36:2921; *JACC* 2020;75:76)

- Need ≥2 of the following: chest pain (as noted above), friction rub, ECG findings, effusion
- **ECG:** may show diffuse STE (*concave up*) & PR depression (except in aVR: ST ↓ & PR ↑), TWI; classically and in contrast to STEMI, TWI do not occur until STs normalize
  Stages: (I) STE & PR ↓; (II) ST & PR normalize; (III) diffuse TWI; (IV) Tw normalize
  ECG may show evidence of large effusion w/ low-voltage & electrical alternans (beat-to-beat Δ in QRS amplitude and/or axis due to swinging heart)
- CXR: if lg effusion (>250 mL) → ↑ cardiac silhouette w/ "water-bottle" heart & epicardial halo
- **Echocardiogram:** presence, size, & location of *effusion;* presence of *tamponade physiology;* pericarditis itself w/o spec. abnl (∴ echo can be nl), although can see pericardial stranding (fibrin or tumor); can also detect LV/RV dysfxn (myocarditis?)
- CT: effusion (often larger by CT than by echo) ± calcif.; pericard. enhancement w/ contrast
- **MRI:** may reveal pericardial thickening/inflammation, as well as myocardial involvement
- ⊕ cTn in ~30%, indicative of concomitant myocarditis (*JACC* 2003;42:2144). Inflammatory biomarkers (ESR, CRP) elevated in 80% of presentations; CRP predicts recurrence.

Workup for effusion

- r/o infxn: usually apparent from Hx & CXR; ? value of ✓ acute and convalescent serologies
- r/o noninfectious etiologies: BUN, Cr, ANA, RF, HIV, screen for common malignancies
- Pericardiocentesis if suspect infxn or malignancy or large effusion (>2 cm) or recurrent
  ✓ cell counts, TP, LDH, glc, Gram stain & Cx, AFB, cytology
  ADA, PCR for MTb, and specific tumor markers as indicated by clinical suspicion
  "exudate": TP >3 g/dL, TP_{eff}/TP_{serum} >0.5, LDH_{eff}/LDH_{serum} >0.6 or glc <60 mg/dL; high Se (~90%) but *very low* Sp (~20%); overall low utility (*Chest* 1997;111:1213)
- Pericardial bx if suspicion for malignancy or TB; perform during every surgical drainage

Treatment of pericarditis (*JACC* 2020;75:76)

- High-dose **NSAID** (eg, ibuprofen 600–800 mg tid) or ASA (eg, 650–1000 mg tid) × 7–14 d then taper over wks; ASA preferred over NSAID in acute MI; consider PPI to ↓ risk of GIB
- **Add colchicine** 0.6 mg bid (qd if ≤70 kg) × 3 mo; 50% ↓ risk of refractory or recurrent pericarditis (*NEJM* 2013;369:1522). Amio, dilt, verap & atorva ↓ P-gp & ↑ risk of colchicine tox.
- Avoid steroids except for systemic autoimmune disorder, uremia, preg., NSAIDs contra- indicated. Appear to ↑ rate of pericarditis recurrence; risk lower w/ low-dose wt-based (ie, prednisone 0.2–0.5 mg/kg) with slow taper (*Circ* 2008;118:667 & 2011;123:1092).

- Avoid anticoagulants (although no convincing data that ↑ risk of hemorrhage/tamponade)
- Infectious effusion → pericardial drainage (preferably surgically) + systemic antibiotics
- Restrict activity until sx resolve/hsCRP ↓; athletes must also wait ~1–3 mos w/ nl TTE/ECG
- Acute idiopathic pericarditis self-limited in 70–90% of cases
- **Recurrent pericarditis** (*Circ* 2007;115:2739) risk factors: subacute, lg effusion/tamponade, T >38°C, no NSAID response after 7 d. Rx: colchicine 0.6 mg bid × 6 mo (*Lancet* 2014;383: 2232). IL-1 antagonists: anakinra (*JAMA* 2016;316:1906) or rilonacept (*NEJM* 2021;384:31).
- Recurrent effusions: consider pericardial window (percutaneous vs. surgical)

PERICARDIAL TAMPONADE

Etiology
- Any cause of pericarditis but espec **malignancy**, **infectious**, uremia, ascending AoD, myocardial rupture, periprocedural complication, trauma, post-cardiotomy
- Rapidly accumulating effusions most likely to cause tamponade b/c no time for pericardium to stretch (eg, to ↑ compliance) and accommodate ↑ intrapericardial fluid volume

Pathophysiology (*NEJM* 2003;349:684)
- ↑ intrapericardial pressure, compression of heart chambers, ↓ venous return → ↓ CO
- Diastolic pressures ↑ & equalize in all cardiac chambers → minimal flow of blood from RA to RV when TV opens → blunted *y* descent
- ↑ ventricular interdependence → pulsus paradoxus (pathologic exaggeration of nl physio) Inspiration → ↓ intrapericardial & RA pressures → ↑ venous return → ↑ RV size → septal shift to left. Also, ↑ pulmonary vascular compliance → ↓ pulm venous return. Result is ↓ LV filling → ↓ **LV stroke volume** & blood pressure & pulse pressure.

Clinical manifestations
- **Cardiogenic shock** (hypotension, fatigue) **without pulmonary edema**
- Dyspnea (seen in ~85%) may be due to ↑ respiratory drive to augment venous return

Physical exam (*EHJ* 2014;35:2279)
- **Beck's triad** (present in minority of cases): **distant heart sounds** (28%)**,** ↑ **JVP** (76%) w/ blunted *y* descent**, hypotension** (26%); ± pericardial friction rub (30%)
- Reflex tachycardia (77%), cool extremities
- **Pulsus paradoxus** (Se 82%, Sp 70%) = ↓ SBP ≥10 mmHg during inspiration
  ⊕ LR 3.3 (5.9 if pulsus >12), ⊖ LR 0.03
  Ddx = PE, hypovolemia, severe COPD, auto-PEEP, periconstriction (~⅓), RV infarct
  Can be absent if preexisting ↑ LVEDP, arrhythmia, severe AR, ASD, regional tamponade
- Tachypnea and orthopnea but *clear lungs*

Diagnostic studies
- ECG: ↑ HR, ↓ voltage (seen in 42%), electrical alternans (20%), ± signs of pericarditis

- CXR: ↑ cardiac silhouette (89%)
- **Echocardiogram**: ⊕ **effusion**, IVC plethora, **septal shift** with inspiration
  diastolic collapse of RA (Se 85%, Sp 80%) and/or RV (Se <80%, Sp 90%)
  respirophasic Δ's in transvalvular velocities (↑ across TV & ↓ across MV w/ inspir.)
  postsurgical tamponade may be localized and not easily visible
- Cardiac cath (right heart and pericardial): elevation (15–30 mmHg) and equalization of intrapericardial and diastolic pressures (RA, RV, PCWP), blunted *y* descent in RA
  ↑ in stroke volume postpericardiocentesis = ultimate proof of tamponade
  if RA pressure remains high after drainage, Ddx: effusive-constrictive dis. (visceral pericardium constriction), myocardial. dysfxn (eg, concomitant myocarditis)

Treatment (*EHJ* 2014;35:2279)

- Volume (but be careful b/c overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- Avoid vasoconstrictors b/c will ↓ stroke volume & potentially ↓ HR
- Avoid positive pressure ventilation b/c it can further impair cardiac filling (*Circ* 2006;113:1622)
- **Pericardiocentesis** (except if due to aortic/myocardial rupture, for which emergent surgery is treatment of choice; if too unstable, consider small pericardiocentesis to prevent PEA)
- Surgical drainage considered if fluid rapidly reaccumulates, loculated, or hemorrhagic

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Constrictive Pericarditis

Etiology (*Circ* 2011;124:1270)

- Any cause of pericarditis (~1–2% incidence overall after acute pericarditis)
- Highest risk w/ **TB**, **bacterial**, **neoplastic**, **XRT**, connective tissue, postcardiac surgery
- **Viral/idiopathic**, b/c most common cause of pericarditis, also account for signif proportion

Pathophysiology

- Adhesion of visceral and parietal pericardial layers → rigid pericardium that limits diastolic filling of ventricles → ↑ systemic venous pressures
- Venous return is limited only after early rapid filling phase; ∴ rapid ↓ in RA pressure with atrial relaxation and opening of tricuspid valve and *prominent x and y descents*
- Kussmaul sign: JVP does not decrease with inspiration (↑ venous return with inspiration, but negative intrathoracic pressure not transmitted to heart because of rigid pericardium)

Clinical manifestations (*NEJM* 2011;364:1350)

- Right-sided >left-sided heart failure (systemic congestion >pulmonary congestion)

Physical exam

- ↑ **JVP** with **prominent *y* descent**, ⊕ **Kussmaul sign** [Ddx: tricuspid stenosis, acute cor pulmonale, RV dysfxn (CMP, RV MI), SVC syndrome]
- Hepatosplenomegaly, ascites, peripheral edema. Consider in Ddx of idiopathic cirrhosis.

• PMI usually not palpable, **pericardial knock**, usually no pulsus paradoxus

Diagnostic studies

• ECG: nonspecific, AF common (up to 33%) in advanced cases
• CXR: calcification (MTb most common), espec in lateral view (although not specific)
• Echocardiogram: ± thickened pericardium, "**septal bounce**" = abrupt displacement of septum during rapid filling in early diastole
• Cardiac catheterization: atria w/ **Ms** or **Ws** (prominent *x* and *y* descents)
  ventricles: **dip-and-plateau** or **square-root sign** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  discordance between LV & RV pressure peaks during respiratory cycle (*Circ* 1996;93:2007)
• CT or **MRI:** thickened pericardium (>4 mm; Se ~80%) w/ tethering (*Circ* 2011;123:e418)

Constrictive Pericarditis vs. Restrictive Cardiomyopathy (*JACC* 2016;68;2329)

Evaluation	Constrictive Pericarditis	Restrictive Cardiomyopathy
Physical exam	⊕ Kussmaul sign Absent PMI ⊕ Pericardial knock	± Kussmaul sign Powerful PMI, ± S_3 and S_4 ± **Murmurs of MR, TR**
ECG	± Low voltage	Low voltage if infiltrative myopathy ± **Conduction abnormalities**
Echocardiogram	**Respirophasic variation** (25–40%): inspir. → ↑ flow across TV and ↓ flow across MV e′ (tissue velocity) nl/↑ (>12 cm/sec) **Expir.** hepatic vein flow reversal **Septal bounce in early diastole** Normal wall thickness	<10% respirophasic variation Slower peak filling rate Longer time to peak filling rate **e′** ↓ (<8 cm/sec; Se & Sp ~95%) **Inspir.** hepatic vein flow reversal **Biatrial enlargement** ± ↑ wall thickness
CT/MRI	**Usually w/ thickened pericardium**	Normal pericardium
NT-proBNP	Variable	Typically ↑/↑↑ (*JACC* 2005;45:1900)
Cardiac catheterization	Prominent *x* and *y* descents (more so in constriction) Dip-and-plateau sign (more so in constriction)	
	LVEDP = RVEDP RVSP <55 mmHg (Se 90%, Sp 29%) RVEDP >⅓ RVSP (Se 93%, Sp 46%) **Discordance** of LV & RV pressure peaks during respiratory cycle **Systolic area index** (ratio of RV to LV pressure–time area in inspir vs. expir) >1.1 (Se 97%, Sp 100%)	**LVEDP** > **RVEDP** (esp. w/ vol.) RVSP >55 mmHg RVEDP <⅓ RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index ≤1.1 (*JACC* 2008;51:315)
Endomyocardial biopsy	Usually normal	± **Specific etiology of RCMP** (fibrosis, infiltration, hypertrophy)

Treatment

• Diuresis if intravascular volume overload; surgical pericardiectomy if infectious or advanced

HYPERTENSION

ACC/AHA Classification for Office-Based BP (*HTN* 2018;71:e13)		
Category	**Systolic (mmHg)**	**Diastolic (mmHg)**
Normal	<120	<80
Elevated	120–129	<80
Stage 1 hypertension	130–139	80–89
Stage 2 hypertension	≥140	≥90

Average ≥2 measurements >1–2 minutes apart. If disparity in a category between systolic and diastolic, higher value determines stage. Elevated office BP should be confirmed with out-of-office (ABPM or home cuff) to confirm; can treat stage 2 immediately. White coat (≥Stage 1 in office but <at home) at heightened risk of developing HTN. Masked (<Stage 1 in office but ≥at home), if persistent, treat as HTN.

Epidemiology (*Circ* 2021;143:e254; *Lancet* 2021;398:957)

- Prevalence 47% in U.S. adults, higher in African-Americans; M = F
- Of those with HTN, ~40% unaware of dx; of those dx w/ HTN, only ½ achieve target BP

Etiologies (*JACC* 2017;71:127)

- **Essential** (95%): onset 25–55 y; ⊕ FHx. Unclear mechanism but ? additive microvasc renal injury over time w/ contribution of hyperactive sympathetics (*NEJM* 2002;346:913). ↑ Age → ↓ art compliance → HTN. Genetics + environment involved (*Nature* 2011;478:103).
- **Secondary:** Consider if Pt <20 or >50 y or if sudden onset, severe, refractory HTN

Secondary Causes of Hypertension			
Diseases		**Suggestive Findings**	**Initial Workup**
RENAL	**Renal parenchymal** (2–3%)	h/o DM, polycystic kidney disease, glomerulonephritis	CrCl, albuminuria See "Kidney Disease"
	Renovascular (1–2%) Athero (90%) FMD (10%, young women) PAN, scleroderma	ARF induced by ACEI/ARB Recurrent flash pulm edema Renal bruit; hypokalemia (*NEJM* 2009;361:1972)	MRA (>90% Se & Sp, less for FMD), CTA, duplex U/S, angio, plasma renin (low Sp)
ENDO	**Hyperaldo or Cushing's** (1–5%)	Hypokalemia Metabolic alkalosis	See "Adrenal Disorders"
	Pheochromocytoma (<1%)	Paroxysmal HTN, H/A, palp.	
	Myxedema (<1%)	See "Thyroid Disorders"	TFTs
	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	iCa
OTHER	**Obstructive sleep apnea** (qv); alcohol		
	Medications: OCP, steroids, licorice; NSAIDs (espec COX-2); Epo; CsA; TKI		
	Aortic coarctation: ↓ LE pulses, systolic murmur, radial-femoral delay; abnl TTE, CXR		
	Polycythemia vera: ↑ Hct		

Standard workup (*JAMA* 2021;325:1650 & 326:339)

- Goals: (1) identify CV risk factors; (2) consider 2° causes; (3) assess for target-organ damage
- History: CAD, HF, TIA/CVA, PAD, DM, renal insufficiency, sleep apnea, preeclampsia; ⊕ FHx for HTN; diet, Na intake, smoking, alcohol, prescription and OTC meds, OCP
- Physical exam: ✓ **BP in both arms;** funduscopic exam, BMI, cardiac (LVH, murmurs), vascular (bruits, radial-femoral delay), abdominal (masses or bruits), neuro exam
- Testing: K, BUN, Cr, Ca, glc, Hct, U/A, lipids, TSH, urinary albumin:creatinine (if ↑ Cr, DM, peripheral edema), ? renin, ECG (for LVH), CXR, TTE (eval for valve abnl, LVH)
- Ambulatory BP monitoring (ABPM): consider for episodic, masked, resistant, or white coat HTN; stronger predictor of mortality than clinic BP (*NEJM* 2018;378:1509); 24 h target <130/80

Complications of HTN

- Neurologic: **TIA/CVA**, ruptured aneurysms, vascular dementia
- Retinopathy: stage I = arteriolar narrowing; II = copper-wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: **CAD**, **LVH**, **HF, AF**
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, **renal failure**

Treatment (*J Clin HTN* 2014;16:14; *Circ* 2018;138:e426; *NEJM* 2018;378:636)

- Every ↓ 5 mmHg → ~10% ↓ ischemic heart disease, stroke, and HF (*Lancet* 2021;397:1625)
- **Lifestyle modifications** (each may ↓ SBP ~5 mmHg)
  weight loss: goal BMI 18.5–24.9; aerobic exercise: 90–150 min exercise/wk
  diet: rich in fruits & vegetables, low in saturated & total fat (DASH, *NEJM* 2001;344:3)
  limit Na: ideally ≤1.5 g/d or ↓ 1 g/d; ↑ K intake / use salt substitute (*NEJM* 2021;385:1067)
  limit alcohol: ≤2 drinks/d in men; ≤1 drink/d in women & lighter-wt Pts; avoid NSAIDs
- ACC/AHA: initiate BP med if BP ≥130/80 & *either* clinical ASCVD, HF, CKD, T2DM, ≥65 yrs old *or* 10-y ASCVD risk ≥10%; otherwise if BP ≥140/90
- In high CV risk w/o DM, SBP target <120 (via unattended automated cuff) ↓ MACE & mortality vs. <140 mmHg, but w/ ↑ HoTN, AKI, syncope, electrolyte abnl (*NEJM* 2021;384:1921 & 385:1268)
- **Pharmacologic options**
  Pre-HTN: ARB prevents onset of HTN, no ↓ in clinical events (*NEJM* 2006;354:1685)
  HTN: choice of therapy controversial, concomitant disease and stage may help guide Rx; ? improved control with nighttime administration (*EHJ* 2020;41:4564)
  Uncomplicated: CCB, ARB/ACEI, or thiazide (chlorthalidone preferred) are 1st line; βB not.
  For black Pts, reasonable to start with CCB or thiazide.
  + **CAD** (*Circ* 2015;131:e435): ACEI or ARB; ACEI+CCB superior to ACEI+thiazide (*NEJM* 2008;359:2417) or βB+diuretic (*Lancet* 2005;366:895); may require βB and/or nitrates for anginal relief; if h/o MI, βB ± ACEI/ARB ± aldo antag (see "ACS")
  + **HF:** ARNI/ACEI/ARB, βB, diuretics, aldosterone antagonist (see "Heart Failure")
  + **prior stroke:** ACEI ± thiazide (*Lancet* 2001;358:1033)
  + **diabetes mellitus:** ACEI or ARB; can also consider thiazide or CCB
  + **chronic kidney disease:** ACEI or ARB (*NEJM* 2001;345:851 & 861)

- Tailoring therapy: if stage 1, start w/ monoRx; if stage 2, consider starting w/ combo (eg, ACEI + CCB; *NEJM* 2008;359:2417); start at ½ max dose; after ~1 mo, uptitrate or add drug
- **Pregnancy:** methyldopa, labetalol, & nifed pref. Hydral OK; avoid diuretics; Ø ACEI/ARB. Targeting DBP 85 vs. 105 safe and ↓ severe HTN (*NEJM* 2015;372:407).

Resistant HTN (BP >goal on ≥3 drugs incl diuretic; *HTN* 2018;72:e53)

- Exclude: 2° causes (see table) and *pseudoresistance:* inaccurate measure (cuff size), diet noncomp (↑ Na), poor Rx compliance/dosing, white coat HTN (✓ ABPM)
- Ensure effective diuresis (chlorthalidone or indapamide >HCTZ; loop >thiazide if eGFR <30)
- Can add aldosterone antagonist (*Lancet* 2015;386:2059), β-blocker (particularly vasodilators such as carvedilol, labetalol, or nebivolol), α-blocker, or direct vasodilator
- Consider renal denervation therapy (*Lancet* 2018;391:2346; 2021;397:2476)

HYPERTENSIVE CRISES

- **Hypertensive emergency:** ↑ BP (usually SBP >180 or DBP >120) → target-organ damage
  Neurologic damage: encephalopathy, hemorrhagic or ischemic stroke, papilledema
  Cardiac damage: ACS, HF/pulmonary edema, aortic dissection
  Renal damage: proteinuria, hematuria, acute renal failure; scleroderma renal crisis
  Microangiopathic hemolytic anemia; preeclampsia-eclampsia
- **Hypertensive urgency:** SBP >180 or DBP >120 (? 110) w/o target-organ damage

Precipitants

- Progression of essential HTN ± medical noncompliance (espec clonidine) or Δ in diet
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine

Treatment – tailor to clinical condition (*Circ* 2018;138:e426)

- AoD, eclampsia/severe preeclampsia, pheo: target SBP <140 (<120 for AoD) in **1 hour**
- Emerg w/o above: ↓ BP by ~25% in 1 h; to 160/100–110 over next 2–6 h, then nl over 1–2 d
- Acute ischemic stroke (w/in 72 hr from sx onset): <185/110 before lysis initiated, o/w target <220/120 (same SBP goal for ICH)
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

IV Drugs for Hypertensive Crises (*Circ* 2018;138:e426; *Stroke* 2018;49:46)

Drug	Dose	Preferred for
Labetalol	20–80 mg IVB q10min or 0.4–2 mg/min	AoD, ACS, Stroke, Eclampsia
Esmolol	0.5–1 mg/kg load → 50–200 μg/kg/min	AoD, ACS
Nitroprusside*	0.25–10 μg/kg/min	Pulm edema
Nitroglycerin	5–500 μg/min	Pulm edema, ACS

IV Drugs for Hypertensive Crises (*Circ* 2018;138:e426; *Stroke* 2018;49:46)		
Nicardipine	5–15 mg/h (can ↑ 2.5 mg/h q 5 min)	Stroke, AKI, Eclampsia, Pheo
Clevidipine	1–32 mg/h (can titrate q 5–10 min)	Stroke, Pulm edema, AKI, Pheo
Fenoldopam	0.1–1.6 μg/kg/min	AKI
Hydralazine	10–20 mg q20–30min prn	Eclampsia
Phentolamine	5–15 mg bolus q5–15min	Pheo

*Metabolized to cyanide → Δ MS, lactic acidosis, death. Limit use of very high doses (8–10 μg/kg/min) to <10 min.

- HTN urgency: goal to return to normal BP over hrs to days. Reinstitute/intensify anti-HTN Rx. Additional PO options: labetalol 200–800 mg q8h, captopril 12.5–100 mg q8h, hydralazine 10–75 mg q6h, clonidine 0.2 mg load → 0.1 mg q1h.

AORTIC ANEURYSMS

Definitions
- **True** (≥50% dilation of all 3 layers; <50% = ectasia) vs. **false** (rupture w/in adventitia)
- **Location:** root (annuloaortic ectasia), thoracic aortic aneurysm (TAA), thoracoabdominal aortic aneurysm (TAAA), abdominal aortic aneurysm (AAA)
- **Type:** fusiform (circumferential dilation) vs. saccular (localized dilation of aortic wall)

Epidemiology (*Circ* 2010;121:e266, 2011;124:2020; *Nat Rev Cardiol* 2011;8:92)
- **TAA:** ~10/100,000 Pt-yrs; ♂:♀ 2:1; ~60% root/ascending; 40% descending
- **AAA:** ~4–8% prev in those >60 y; 5× more common in ♂; mostly infrarenal

Pathophysiology & risk factors (*JACC* 2020:76:201 & 2021;78:201)
- Medial degen and/or ↑ wall stress; wall stress ∝ [(ΔP × r) / (wall thickness)] (Laplace's law)
- **TAA:** medial degeneration (muscle apoptosis, elastin fiber weakening); a/w CTD, aortitis
- **AAA:** long-standing HTN + athero/inflammation → medial weakening
- **Clinical risk factors:** HTN, athero, smoking, age, ♂, presence of other aortic dilation
- **CTD** (Marfan, Ehlers-Danlos type IV, Loeys-Dietz); **congenital** (bicuspid AoV, Turner's) **aortitis** (Takayasu's GCA, spondyloarthritis, IgG4); infection (eg, syphilis); FQ; trauma

Screening (*JAMA* 2015;313:1156)
- **TAA:** if bicuspid AoV or 1° relative w/: (a) TAA or bicuspid AoV, (b) CTD as above
- **AAA:** ✓ for pulsatile abd mass; U/S ♂ >60 y w/ FHx of AAA & ♂ 65–75 y w/ prior tobacco

Diagnostic studies (*JACC* 2020;76:201)
- **Contrast CT:** quick, noninvasive, high Se & Sp for all aortic aneurysms
- **TTE/TEE:** TTE most useful for root and proximal Ao; TEE can visualize other sites of TAA
- **MRI:** favored over CT for AoRoot imaging; useful in AAA but time consuming; noncontrast "black blood" MR to assess aortic wall
- **Abdominal U/S:** screening/surveillance test of choice for infrarenal AAA

Treatment (*Circ* 2010;121:e266 & 2016;133:680; *JACC* 2020;76:201; *NEJM* 2021;385:1690)
- Goal is to prevent rupture (50% mortality prior to hospital) by modifying risk factors
- **Risk factor modification:** smoking cessation; statins to achieve LDL-C <70 mg/dL
- **BP control** (goal SBP 100–120): **βB** (↓ dP/dt) ↓ aneurysm growth; **ACEI** a/w ↓ rupture risk (*Lancet* 2006;368:659); **ARB** may ↓ rate of aortic root growth in Marfan (*NEJM* 2008;358:2787)
- Mod CV exercise OK, no burst activity requiring Valsalva maneuvers (eg, heavy lifting)
- **Indications for intervention** (individualized based on FHx, body size, sex, anatomy)

TAA: sxs; ascending Ao ≥5.5 cm (4–5 cm if Marfan, L-D, EDS, bicuspid AoV); descending Ao >6 cm; ≥4.5 cm and planned AoV surgery; ↑ >0.5 cm/y

AAA: sx; infrarenal ≥5.5 cm; consider ≥5.0 cm in ♀; ↑ >0.5 cm/y; inflam/infxn

Surgery (*EHJ* 2014;25:2873)

• Resection & replacement w/ graft. If involves root, need to address AoV & coronaries.

Endovascular repair (EVAR) (*Circ* 2015;131:1291; *NEJM* 2019;380:2126)

• Requires favorable aortic anatomy
• **TEVAR** (thoracic EVAR) for descending TAA ≥5.5 cm may ↓ periop morbidity and possibly mortality (*Circ* 2010;121:2780; *JACC* 2010;55:986; *J Thorac CV Surg* 2010;140:1001 & 2012;144:604)
• **AAA:** guidelines support open repair or EVAR for infrarenal AAA in good surg candidates
  ↓ short-term mort., bleeding, LOS; but long-term graft complic. (3–4%/y; endoleak, need for reintervention, rupture) necessitate periodic surveillance, with no difference in mortality long term, except ? in those <70 y (*Lancet* 2016;388:2366; *NEJM* 2019;380:2126)
  In Pts unfit for surgery or high periop risks: ↓ aneurysm-related mortality but no Δ in overall mortality over med Rx (*NEJM* 2010;362:1872). EVAR noninferior (? superior) to open repair in ruptured AAA w/ favorable anatomy (*Ann Surg* 2009;250:818).

Complications (*Circ* 2010;121:e266; *Nat Rev Cardiol* 2011;8:92)

• **Pain:** gnawing chest, back, or abdominal pain; new or worse pain may signal rupture
• **Rupture:** risk ↑ w/ diameter, ♀, current smoking, HTN
  TAA: ~2.5%/y if <6 cm vs. 7%/y if >6 cm
  AAA: ~1%/y if <5 cm vs. 6.5%/y if 5–5.9 cm; ~80% mortality at 24 h
• Aortic insufficiency (TAA), CHF, acute aortic syndromes (qv)
• **Thromboembolic ischemic events** (eg, to CNS, viscera, extremities)
• **Compression of adjacent structures** (eg, SVC, trachea, esophagus, laryngeal nerve)

Follow-up (*Circ* 2010;121:e266; *Nat Rev Cardiol* 2011;8:92; *JAMA* 2013;309:806)

• Expansion rate ~0.1 cm/y for TAA, ~0.3–0.4 cm/y for AAA
• TAA: 6 mo after dx to ensure stable, and if stable, then annually (*Circ* 2005;111:816)
• AAA: <4 cm q2–3y; 4–5.4 cm q6–12mo; more often if rate of expansion >0.5 cm in 6 mo
• Screen for CAD, PAD, & aneurysms elsewhere, espec popliteal. ~25% of Pts w/ TAA will also have AAA, and 25% of AAA Pts will have a TAA: consider pan-Ao imaging.

ACUTE AORTIC SYNDROMES

Definitions (*Circ* 2010;121:e266; *Eur Heart J* 2012;33:26)

- **Aortic dissection:** intimal tear → blood extravasates into Ao media (creates false lumen)
- **Intramural hematoma** (IMH): vasa vasorum rupture → medial hemorrhage that does not communicate with aortic lumen; 6% of aortic syndromes; clinically managed as AoD
- **Penetrating ulcer:** atherosclerotic plaque penetrates elastic lamina → medial hemorrhage

Classification (proximal more common than distal; *JACC* 2019;74:1494 & 2020;76:1703)

- **Proximal:** involves ascending Ao, regardless of origin (= Stanford A, DeBakey I & II)
- **Distal:** involves descending Ao only, distal to L subclavian art. (= Stanford B, DeBakey III)

Risk factors (*Lancet* 2015;385:800)

- **Classic** (in older Pts): **HTN** (h/o HTN in >70% of dissections); **age** (60s–70s), **sex** (~65% ♂); **smoking;** ↑ lipids. **Acute ↑ BP:** cocaine, Valsalva (eg, weightlifting).
- **Genetic:** *CTD* (Marfan, Loeys-Dietz, Ehlers-Danlos type IV); *congenital anomaly* (bicuspid AoV, coarct [eg, Tuner's syndrome], PCKD); FHx (AoD or aneurysm in 1st degree relative)
- **Acquired:** *aortitis* (Takayasu's, GCA, Behçet's, syphilis); *preg.* (typically 3rd trim.); FQ use
- **Trauma:** blunt, decel. injury (eg, MVA); IABP, cardiac/aortic surgery, Impella, cardiac cath

Clinical Manifestations and Physical Exam* (*JAMA* 2000;283:897)

Feature	Proximal	Distal
"Aortic" pain (abrupt, severe, tearing or ripping quality, *maximal at onset* [vs. crescendo for ACS])	**94%** (chest, back)	**98%** (back, chest, abd)
Syncope (often due to tamponade)	**13%**	4%
HF (usually due to acute AI)	**9%**	3%
CVA	**6%**	2%
HTN	36%	**70%**
HoTN or shock (tamponade, AI, MI, rupture)	**25%**	4%
Pulse deficit (if involves carotid, subclavian, fem)	**19%**	**9%**
AR murmur	**44%**	12%

*S/S correlate w/ affected branch vessels & distal organs; may Δ as dissection progresses

Initial evaluation & diagnostic studies (*Circ* 2010;121:e266; *EHJ* 2018;39:739)

- H&P, incl. bilat BP & radial pulses for symmetry; ECG w/ STE if propagates to cor
- **CXR**: abnl in 60–90% [↑ mediast. (absence ⊖ LR 0.3), L pl effusion] but *cannot* r/o AoD

- **CT:** quick and available, Se ≥93%, Sp 98%; facilitates "triple rule-out" ACS vs. PE vs. AoD
- **MRI:** Se & Sp >98%, but time-consuming test & not readily available
- **TEE:** Se >95% prox, 80% for distal; can assess cors/peric/AI; "blind spot" behind trachea
- ⊖ Initial imaging but high clinical suspicion → further studies (⅔ w/ AoD have ≥2 studies)
- **D-dimer** <500 ng/mL has Se/NPV ~97%, Sp ~50%, *but not if high risk* and not for IMH
- Risk score (0–3 points): high-risk (eg, genetics, recent Ao manip); aortic pain; e/o perfusion deficit, AI or shock. Score >1 → imaging; ≤1 & DD <500 has NPV >99% (*Circ* 2018;137:250)

Treatment (*Circ* 2010;121:1544; *EHJ* 2018;39:739; *JACC* 2019;74:1494 & 2020;76:1703)

- ↓ **dP/dt** targeting HR <60 & central BP <120 (or lowest that preserves perfusion; r/o pseudohypotension, eg, arm BP ↓ due to subclavian dissection; use highest BP reading)
- ***First*** **IV βB** (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy in response to vasodilators; verapamil/diltiazem if βB contraindic; ***then*** **↓** ***SBP w/*** **IV vasodilators** (eg, nitroprusside)
- **If HoTN:** urgent surgical consult, IVF to achieve euvolemia, pressors to keep MAP 60-65 mmHg; r/o complication (eg, tamponade, contained rupture, severe AI)
- **Proximal:** surgery considered in **all acute** and in chronic if c/b progression, AI or aneurysm
- **Distal:** med Rx unless complication (see below) or favorable TEVAR anatomy w/ high-risk imaging features (*JACC* 2019;74:1494); pre-emptive TEVAR may ↓ late complic. & mortality

Complications (*occur in ~*20%; *Circ* 2010;121:e266; *Lancet* 2015;385:800)

- *Freq assess (sx, BP, UOP), pulses, labs (Cr, Hb, lactic acid), imaging (~7 d or sooner if Δs)*
- *Uncontrolled BP or persistent pain may indicate complication/extension*
- **Progression:** propagation of dissection, ↑ aneurysm size, ↑ false lumen size
- **Rupture:** pericardial sac → tamponade (avoid pericardiocentesis unless PEA); blood in pleural space, mediast., retroperitoneum; ↑ in hematoma on imaging portends rupture
- **Malperfusion** (partial or complete obstruction of branch artery; can be *static* or *dynamic*) *coronary* → MI (usually RCA → IMI b/c dissection follows outer Ao curvature); *innominate/carotid* → CVA, Horner; *intercostal/lumbar* → spinal cord ischemia/paraplegia; *innominate/subclavian* → upper ext ischemia; *iliac* → lower ext ischemia; *celiac/mesenteric* → bowel ischemia; *renal* → AKI or slow ↑ Cr, refractory HTN
- **AI:** due to annular dilatation or disruption or displacement of leaflet by false lumen
- Mortality: 20–40% for proximal; 6% for uncomplicated and ~20% for complicated distal
- **Long-term serial imaging** (CT or MRI; ↓ rad w/ MRI) at 1, 3, and 6 mo, and then annually

ARRHYTHMIAS

BRADYCARDIAS, AV BLOCK, AND AV DISSOCIATION

Sinus bradycardia (SB, <50–60 bpm) (*NEJM* 2000;342:703, *Circ* 2019;140:e382)

- Etiologies: **meds** (incl βB, CCB, amio, Li, dig), ↑ **vagal tone** (incl. athletes, sleep, IMI), **metabolic** (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: if no sx, none; atropine, β_1 agonists (short-term) or pacing if symptomatic
- Most common cause of sinus pause is *blocked premature atrial beat*

Tachycardia-bradycardia ("tachy-brady") syndrome

- Features may include: periods of unprovoked SB, SA arrest, paroxysms of SB and atrial tachyarrhythmias, chronotropic incompetence w/ ETT
- Treatment: meds alone usually fail (adeq. control tachy → unacceptable brady); usually need **combination of meds** (βB, CCB, dig) for tachycardia & **PPM** for bradycardia

AV Block (*Circ* 2019;140:e382)

Type	Features
1°	Prolonged PR (>200 ms), all atrial impulses conducted (1:1).
2° Mobitz I (Wenckebach)	Progressive ↑ PR until impulse not conducted (→ "grouped beating"). **AV node** pathology: ischemia (IMI), inflammation (myocarditis, endocarditis, MV surgery), high vagal tone (athletes), drug induced. Classically (~50%), absolute ↑ in PR *decreases* over time (→ ↓ RR intervals, duration of pause <2× preceding RR interval); nl QRS. AVB usually worsens w/ carotid sinus massage, improves w/ atropine. Often paroxysmal/nocturnal/asx, no Rx required.
2° Mobitz II	Blocked impulses w/ consistent PR interval, often prolonged QRS **His-Purkinje** pathology: ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation. AVB may improve w/ carotid sinus massage, may worsen w/ atropine. May progress to 3° AVB. Pacing pads; transven. pacing often required.
3° (complete)	No AV conduction. Escape, if present, narrow (jxnal) or wide (vent.)

Nb, if 2:1 block, cannot distinguish type I vs. II 2° AVB (no chance to observe PR prolongation); usually categorize based on other ECG & clinical data. High-grade AVB usually refers to block of ≥2 successive impulses

AV dissociation

- *Default:* slowing of SA node allows subsidiary pacemaker (eg, AV junction) to take over
- *Usurpation:* acceleration of subsidiary pacemaker (eg, AV junctional tach, VT)
- *3° AV block:* atrial pacemaker unable to capture ventricles, subsidiary pacemaker emerges; distinguish from *isorhythmic dissociation* (A ≈ V rate, some P waves nonconducting)

Temporary pacing wires

- Consider w/ bradycardia with hemodyn instability or unstable escape rhythm when perm pacer not readily available. Risks: infxn, RV perf, VT, PTX, CHB if existing LBBB.
- Consider instead of PPM for sx brady from reversible cause (βB/CCB O/D, Lyme, SBE, myocarditis, s/p cardiac surgery/trauma/TAVR), TdP, acute MI (sx brady/high-grade AVB)

SUPRAVENTRICULAR TACHYCARDIAS (SVTS)

Arise above the ventricles, ∴ ***narrow QRS*** *unless aberrant conduction or pre-excitation.*

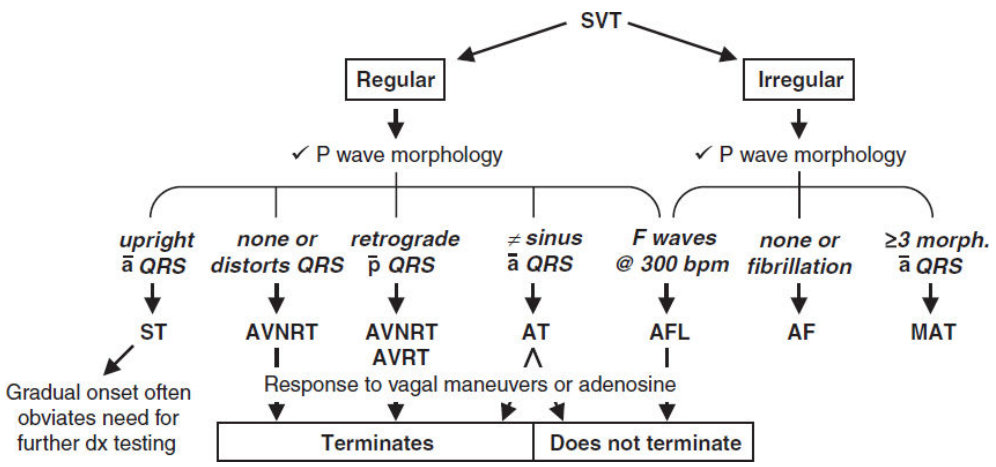
Common Etiologies of SVT (*NEJM* 2012;367:1438)

	Type	Features
Atrial	Sinus tachycardia (ST)	Caused by pain, fever, hypovolemia, hypoxia, PE, anemia, anxiety, withdrawal, β-agonists, etc.
	Atrial tachycardia (AT)	Originate at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig.
	Multifocal atrial tachycardia (MAT)	↑ automaticity at multiple sites in the atria; seen with underlying pulmonary disease
	Atrial flutter (AFL)	Clockwise or counterclockwise macroreentry, usually w/in right atrium
	Atrial fibrillation (AF)	Chaotic atrial activation with rapid, irregular AVN bombardment; often from pulmonary veins
AV Jxn	AV nodal reentrant tach (AVNRT)	Reentrant circuit using dual pathways w/in AVN
	Atrioventricular reciprocating tachycardia (AVRT)	Reentry using AVN & access. path. May show pre-excitation (WPW) or not (concealed access. path.). Can be ortho or antidromic (vide infra).
	Nonparoxysmal junctional tachycardia (NPJT)	↑ jxnal automaticity. May see retro. P, AV dissoc. A/w myo/endocarditis, cardiac surg, IMI, dig.

Diagnosis of SVT Type (*NEJM* 2012;367:1438)

Onset	Abrupt on/off argues against sinus tachycardia
Rate	Not dx b/c most can range from 140–250 bpm, *but:* ST usually <150; AFL often conducts 2:1 → vent. rate 150; AVNRT & AVRT usually >150
Rhythm	Irregular → AF, AFL w/ variable block, or MAT
P wave morphology	Before QRS (ie, long RP) → ST, AT (P ≠ sinus), MAT (≥3 morphologies) None (ie, buried in or deforming terminal QRS, eg, pseudo RSR′ in V_1) → typical AVNRT, NPJT After QRS (ie, short RP) & inverted in inf. leads (ie, *retrograde* atrial) → AVNRT, AVRT (usually slightly after QRS; RP interval >100 ms favors AVRT vs. AVNRT), or NPJT *Fibrillation or no P waves* → AF *Saw-toothed "F" waves* (best seen in inferior leads & V_1) → AFL
Response to vagal stim. or adenosine	Slowing of HR often seen with ST, AF, AFL, AT, whereas reentrant rhythms (AVNRT, AVRT) may abruptly terminate (classically w/ P wave after last QRS) or no response. Occ AT may terminate. In AFL & AF, ↑ AV block may unmask "F" waves or fibrillation

Figure 1-4 Approach to SVT (adapted from *NEJM* 2012;367:1438)



Treatment of SVT (*Circ* 2016;133:e506)		
Rhythm	**Acute Treatment**	**Long-term Treatment**
Unstable	**Cardioversion** per ACLS	n/a
ST	Treat underlying stressor(s)	n/a
AT	βB, CCB or adenosine; ? amiodarone	radiofrequency ablation (RFA); βB or CCB, ± class IC/III AAD
AVNRT or AVRT	**Vagal maneuvers** **Adenosine** (caution in AVRT*) **CCB** or βB, DCCV if other Rx fail	*For AVNRT (see next section for AVRT):* **RFA.** CCB, βB, or dig (chronic or prn) ± Class IC/III AAD (if nl heart)
NPJT	CCB, βB, amiodarone	Rx underlying dis. (eg, dig tox, ischemia)
AF	**βB, CCB, digoxin, AAD**	See "Atrial Fibrillation"
AFL	**βB, CCB, AAD**	RFA; βB or CCB ± class III AAD
MAT	CCB or βB if tolerated	Treat underlying disease. CCB or βB. AVN ablation + PPM if refractory to meds

*Avoid adenosine & nodal agents if accessory pathway + pre-excited tachycardia, see below (*Circ* 2014;130:e199)

- *Catheter ablation:* high overall success rate (AFL/AVNRT ~95%, AVRT ~90%, AF ~70%)
  complications: stroke, MI, bleeding, perforation, conduction block

ACCESSORY PATHWAYS (WOLFF-PARKINSON-WHITE)

Definitions

- **Accessory pathway** (bypass tract) of conducting myocardium connecting atria & ventricles, allowing impulses to bypass normal AVN delay
- **Pre-excitation (WPW) pattern:** ↓ PR interval, ↑ QRS width w/ δ wave (slurred onset, *can be subtle*). ST & Tw abnl (can mimic old IMI).
  Only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde, then ECG will be normal during SR; "concealed" bypass tract).
- PAC can exaggerate pre-excitation if AV node conduction slowed
- **WPW syndrome:** WPW accessory pathway + paroxysmal tachycardia

Classic tachycardias of WPW accessory pathways

- **Orthodromic AVRT:** *narrow-complex* SVT (typically), conducting ↓ AVN & ↑ accessory pathway; requires retrograde conduction and ∴ can occur w/ concealed bypass tracts
- **Antidromic AVRT** (rare): *wide-complex* SVT, conducting ↓ accessory pathway & ↑ AVN; requires antegrade conduction and ∴ should see pre-excitation pattern during SR
- **AF** w/ rapid conduction down accessory pathway; ∴ wide-complex irregular SVT; requires antegrade conduction; ∴ should see pre-excitation in SR. Rarely can degenerate into VF.

Treatment (*Heart Rhythm* 2012;9:1006, *Circ* 2014;130:e199 & 2016;133:e506)

- **AVRT** (orthodromic): vagal, βB, CCB; care w/ adenosine (can precip AF); *have defib ready*
- **AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia *and* ↑ pathway refractoriness. Use **procainamide**, **ibutilide**, or DCCV; ***avoid*** CCB, βB, amio, dig, &
  adenosine, b/c can ↓ refractoriness of pathway → ↑ vent. rate → VF (*Circ* 2016;133:e506).
- **Long term:** RFA if sx; if not candidate for RFA, then AAD (IA, III) or CCB/βB.
  Consider RFA if asx but AVRT or AF inducible on EPS (*NEJM* 2003;349:1803) or if rapid conduction possible (✓ w/ EPS if pre-excitation persists during exercise testing)
  Risk of SCD related to how short RR interval is in AF (eg, <250 ms) and if SVT inducible

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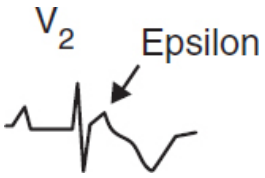
Wide-Complex Tachycardias (WCTs)

Etiologies (*Lancet* 2012;380:1520)

- **Ventricular tachycardia (VT):** accounts for 80% of WCT in unselected population
- **SVT conducted with aberrancy:** either fixed BBB, rate-dependent BBB (usually RBBB), conduction via an accessory pathway or atrially triggered ventricular pacing

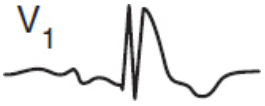
Monomorphic ventricular tachycardia (MMVT)

- All beats look similar; predominantly upward in V_1 = RBBB-type vs. downward = LBBB-type
- In obviously *structurally abnormal* heart: **prior MI** (scar); **CMP**
- In *apparently nl heart that is actually diseased:* **subtle HCM**, **infiltrative CMP**, **myocarditis,**
  arrhythmogenic CMP (ACM): incomplete RBBB,
  ε wave (terminal notch in QRS) & TWI in V_1–V_3 on resting ECG
  LBBB-type VT, dx w/ MRI (*Lancet* 2009;373:1289)
- In structurally *normal* heart w/ normal resting ECG & cardiac MRI:
  RVOT VT: LBBB-type VT or PVCs w/ inferior axis; typically ablate
  LVOT VT: RBBB-type VT or PVCs w/ superior axis; responds to verapamil



Polymorphic ventricular tachycardia (PMVT)

- QRS morphology changes from beat to beat
- Etiologies: **ischemia; CMP;** catecholaminergic
  - **torsades de pointes** (TdP = "twisting of the points," PMVT + ↑ QT): ↑ QT ***acquired*** (meds, lytes, stroke, see "ECG") w/ risk ↑ w/ ↓ HR, freq PVCs (pause dependent) ***or congenital*** (K/Na channelopathies) w/ resting Tw abnl & TdP triggered by sympathetic stimulation (eg, exercise, emotion, sudden loud noises) (*Lancet* 2008;372:750)
  - **Brugada syndrome** (Na channelopathy; *JACC* 2018;72:1046): ♂ > ♀; pseudo-RBBB w/ STE in V_1–V_3 (provoked w/ class IA or IC) on resting ECG



Diagnostic clues that favor VT (assume until proven o/w)

- **Prior MI**, **CHF**, or **LV dysfunction** *best predictors* that WCT is VT (*Am J Med* 1998;84:53)
- Hemodynamics and rate do *not* reliably distinguish VT from SVT
- MMVT is regular, but initially it may be slightly irregular, mimicking AF w/ aberrancy; *grossly* irregularly irregular rhythm suggests AF w/ aberrancy or pre-excitation
- ECG features that favor VT (*Circ* 2016;133:e506)
  - *AV dissociation* (independent P waves, capture or fusion beats) proves VT
  - *Very wide QRS* (>140 ms in RBBB-type or >160 in LBBB-type); *extreme axis deviation*
  - *QRS morphology atypical for BBB* (longest precordial RS >100 ms and R wider than S)
    - RBBB-type: absence of tall R′ (or presence of monophasic R) in V_1, r/S ratio <1 in V_6
    - LBBB-type: onset to nadir >60 ms in V_1, q wave in V_6
  - *Initial R wave in aVR; concordance* (QRS in all precordial leads w/ same pattern/direction)

Long-term management (*EHJ* 2015;36:2793; *Circ* 2018;138:e272; *NEJM* 2019;380:1555)

- Workup: **echo** to ✓ LV fxn, **cath** or **stress test** to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ARVC, ? **EP study** to assess for VT in Pts w/o ICD indication
- **ICD:** 2° prevention for VT/VF arrest (unless due to reversible cause) or cardiac syncope with inducible VT on EP study. 1° prev. if high risk, eg, EF <30–35% (>40 d after MI, >90 d after revasc), ? ARVC, ? Brugada, certain LQTS, severe HCMP. See "Cardiac Rhythm Mgmt Devices." Wearable vest if reversible or waiting for ICD? (*NEJM* 2018;379:1205). Antitachycardia pacing (ATP = burst pacing faster than VT) can terminate VT w/o shock.

- **Meds:** βB, AAD (amio, sotalol, mexiletine); verapamil if LVOT VT
- If med a/w TdP → QT >500 ± PVCs: d/c med, replete K, give Mg, ± pacing (*JACC* 2010;55:934)
- **Ablate:** if isolated VT focus or if recurrent VT triggering ICD firing (↓ VT storm by 34%; *NEJM* 2016;375:111); stereotactic radioablation under investigation (*Circ* 2019;139:313).

ATRIAL FIBRILLATION

Classification (*Circ* 2014;130:e199)

- **Paroxysmal** (terminates spontaneously or within 7 d) vs. **persistent** (>7 d) vs. **long-standing persistent** (>1 y) vs. **permanent** (no plan for SR)
- **Nonvalvular** vs. **valvular** (mechanical heart valve or moderate-severe MS)

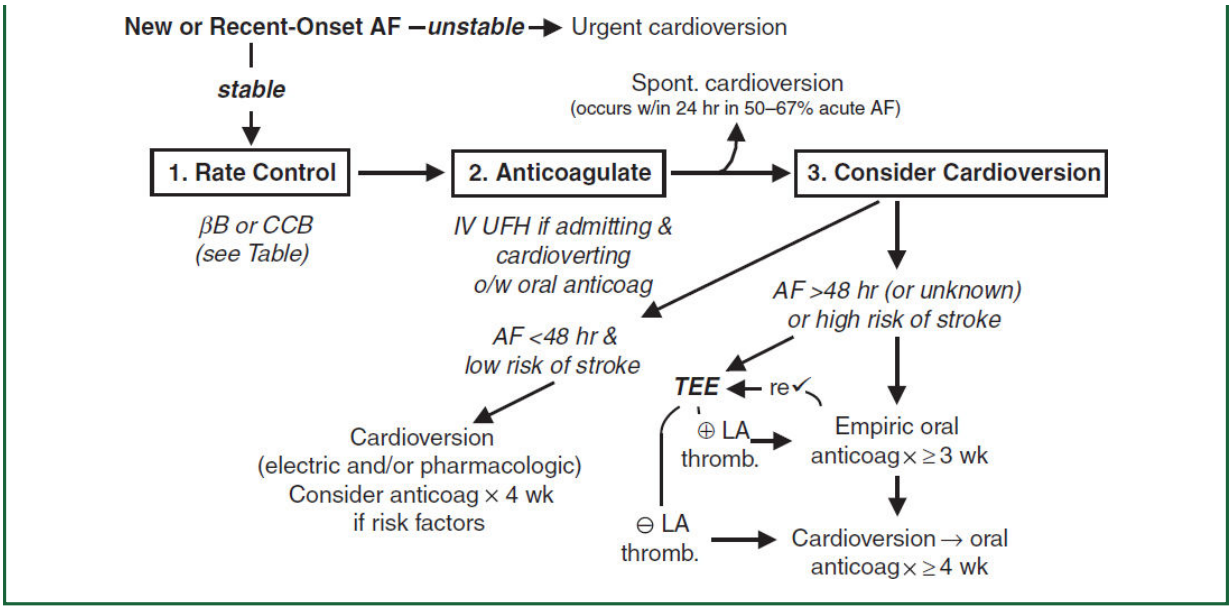
Epidemiology and etiologies (*Circ* A&E 2018;11:e006350)

- 1–2% of pop. has AF (10% of those age ≥80); M >F; lifetime risk ~25%; mean age 75 y
- Acute (up to 50% w/o identifiable cause)
  - **Cardiac:** HF, new CMP, myo/pericarditis, ischemia/MI, HTN crisis, valve dis., cardiac surg
  - **Pulmonary:** acute pulmonary disease or hypoxemia (eg, COPD flare, PNA), PE, OSA
  - **Metabolic:** high catecholamine states (stress, infection, postop, pheo), thyrotoxicosis
  - **Drugs:** alcohol, cocaine, amphetamines, smoking, ibrutinib
  - **Neurogenic:** subarachnoid hemorrhage, ischemic stroke
- Chronic: ↑ age, HTN, ischemia, valve dis. (MV, TV, AoV), CMP, hyperthyroidism, obesity
- Aggressive mgmt of HTN, OSA & EtOH (*NEJM* 2020;382:20) to ↓ risk

Evaluation

- H&P, ECG, CXR, TTE (LA size, thrombus, valves, LV fxn, pericardium), K, Mg, Cr, TFTs
- In acute AF <48º, ~70% spont. convert to SR w/in 48 hrs (*NEJM* 2019;380:1499)

Figure 1-5 Approach to acute AF (Adapted from *Circ* 2014;130:e199)



Rate Control (if sx, goal HR <80; if asx & EF >40%, goal HR <110; *Circ* 2014;130:e199)				
	Agent	**Acute (IV)**	**Maint. (PO)**	**Comments**
CCB	**Verapamil**	5–10 mg over 2′ may repeat in 30′	120–360 mg/d in divided doses	↓ BP (Rx w/ Ca gluc) Can worsen HF Preferred if severe COPD Can ↑ dig levels
CCB	**Diltiazem**	**0.25 mg/kg** over 2′ may repeat after 15′ 5–15 mg/h infusion	120–360 mg/d in divided doses	
βB	**Metoprolol**	2.5–5 mg over 2′ may repeat q5′ × 3	25–100 mg bid or tid	↓ BP (Rx w/ glucagon) Preferred if CAD Risks: HF & bronchospasm.
Digoxin* (onset >30 min)		0.5 then 0.25 mg q6h up to 1.5 mg/24 h	0.125–0.375 mg qd (adj for CrCl)	Consider in HF or low BP Poor exertional HR ctrl
Amiodarone		300 mg over 1 h → then 10–50 mg/h × 24 h		

Lancet 2016;388:818. IV βB, CCB & dig ***contraindic.*** if evidence (ie, pre-excitation or WCT) of WPW (qv).
*Many meds incl. amio, verapamil, quinidine, propafenone, macrolides & azole antifungals ↑ digoxin levels.

Cardioversion

- Consider if: 1st AF, sx, tachycardia-mediated CMP, or difficult to rate control
  If AF >48 h 2–5% risk stroke w/ cardioversion (*pharmacologic or electric*) ∴ either
  TEE to r/o thrombus or ensure therapeutic anticoagulation ≥3 wk prior
  If needs to cardiovert urgently, often anticoagulate acutely (eg, IV UFH)
- For AF <36 hrs, no Δ in % in SR at 4 wks w/ early cardioversion vs. wait & see (βb + a/c), with spont cardioversion in 69% and cardioversion required in 28% (*NEJM* 2019;380:1499)
- Likelihood of success ∝ AF duration & atrial size; control precipitants (eg, vol status, thyroid)
- Before electrical cardiovert, consider pre-Rx w/ AAD (eg, ibutilide), esp. if 1st cardiovert failed
- For pharmacologic cardioversion, class III and IC drugs have best proven efficacy
- If SR returns (spont. or w/ Rx), atria may be *mech. stunned;* also, high risk of recurrent AF over next 3 mo. ∴ **Anticoag postcardioversion ≥4 wk** (? unless AF <48 h and

low risk).

Rhythm control (*Lancet* 2016;388:829)

- Consider if *sx* w/ rate control (eg, HF), difficult to control rate, or tachycardia-mediated CMP
- If minimally sx or asx, previously no clear benefit vs. rate control (*NEJM* 2008;358:2667)
- For recent AF (~1 mo), rhythm-control w/ AAD (flecainide, amio) & cardioversion (if persist. AF) superior to usual care for achieving SR and ↓ adverse CV events (*NEJM* 2020;383:1305)

Antiarrhythmic Drugs (AAD) for AF (*EHJ* 2012;33:2719; *Circ* 2014;130:e199)

Agent		Conversion	Maintenance	Comments
III	Amiodarone	5–7 mg/kg IV over 30–60′→ 1 mg/min, 10-g load	200–400 mg qd (most effective AAD for SR)	↑ QT, TdP rare. Often delay to convert. Poss. pulm, liver, thyroid tox. ↑ INR w/ warfarin.
	Dronedarone	n/a	400 mg bid	↓ side effects & effic. vs. amio
	Ibutilide	1 mg IV over 10′ may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT (3–8% risk of TdP): give w/ IV Mg
	Dofetilide	500 mcg PO bid	500 mcg bid	↑ QT, ↑ risk of TdP; renal adj
	Sotalol	n/a	80–160 mg bid	✓ for ↓ HR, ↑ QT; renal adj
IC	Flecainide	300 mg PO × 1	100–150 mg bid	PreRx w/ AVN blocker. Ø *if structural/ischemic heart dis.*
	Propafenone	600 mg PO × 1	150–300 mg tid	
IA	Procainamide	10–15 mg/kg IV	n/a	↓ BP; ↑ QT; ± AVN blocker

Underlying disease & maintenance AAD of choice:
None or minimal (incl HTN w/o LVH): class IC ("pill in pocket"), sotalol, dronedarone;
HTN w/ LVH: amio; ***CAD:*** sotalol, dofetilide, amio, dronedarone; ***HF***: amio, dofetilide

Ablation (*Heart Rhythm* 2017;14:e445; *JACC* 2020;75:1689)

- Controlling triggers in pulm veins effective when little atrial fibrosis; as AF persists, substrate more complex
- Pulm vein isolation (radiofreq or cryo; *NEJM* 2016;374:2235): ~70% success; superior to AAD (*JAMA* 2014;311:692; *NEJM* 2021;384:305 & 316) & ↑ QoL (*JAMA* 2019;321:1059)
- If NYHA II–IV + EF <35%, ablation ↓ D/HF hosp vs. rate/rhythm meds (*NEJM* 2018;378:417)
- AV node ablation + PPM if other Rx inadequate (*NEJM* 2001;344:1043 & 2002;346:2062)

Oral anticoagulation (*Circ* 2014;130:e199 & 2019;140:125; *EHJ* 2021;42:373)

- *All valvular AF* because stroke risk very high
- Nonvalvular AF (NVAF): stroke risk ~4.5%/y but varies; a/c → 68% ↓ stroke but ↑ bleeding
- **CHA_2DS_2-VASc** to guide Rx: **C**HF (1 point); **H**TN (1); **A**ge ≥75 y (2); **D**M (1), **S**troke/TIA (2); **V**ascular disease (eg, MI, PAD, Ao plaque) (1); **A**ge 65–74 (1); ♀ **S**ex **c**ategory (1)
  Annual risk of stroke (*Lancet* 2012;379:648): at low end, ~1% per point: 0 → ~0%, 1 → 1.3%, 2 → 2.2%, 3 → 3.2%, 4 → 4.0%; at higher scores, risk ↑↑ (5 → 6.7%, ≥6 → ≥10%)
- **Score □2 in ♂ or □3 in ♀ → anticoagulate;** scores 1 in ♂ or 2 in ♀ → **consider anticoag** or ASA or no Rx; **score 0** → reasonable to not Rx

- **Rx options: DOAC** (NVAF only) prefered over warfarin (INR 2–3); if Pt refuses anticoag, ASA + clopi or, even less effective, ASA alone (*NEJM* 2009;360:2066)
- AF + CAD/ PCI: consider DOAC + clopi (not ticag or prasugrel) + ASA (d/c ~1–4 wks) (*Circ* 2021;143:583); consider DOAC only after 12 mos (*JACC* 2021;77:629)
- If concern for procedural bleed, interrupt OAC (1–2 d DOAC, 4–5 d VKA). If CHA_2DS_2-VASc ≥7 (or ≥5 w/ h/o CVA/TIA), consider bridge w/ UFH/LMWH, otherwise do not (*JACC* 2017;69:735).

Direct Oral Anticoagulants (DOACs) for NVAF (*Lancet* 2014;383:955)

Anticoag	Dosing	Efficacy & Safety vs. Warfarin
Apixaban (FXa inhib)	5 mg bid (2.5 mg bid if ≥ 2 of: ≥80 y, ≤60 kg, Cr ≥1.5 mg/dL)	≈ ischemic stroke & ↓ major bleed incl ICH, 11% ↓ death. In Pts felt not cand for warfarin, apixa 55% ↓ stroke w/o ↑ bleed vs ASA alone.
Rivaroxaban (FXa inhib)	20 mg qd (15 mg qd if CrCl 15–50) w/ pm meal	≈ ischemic stroke & major bleeds, but ↓ fatal bleed incl ICH
Edoxaban (Fxa inhib)	60 mg qd if CrCl 51–95 (30 mg if CrCl 15–50)	≈ ischemic stroke & ↓ major bleed incl ICH, 14% ↓ CV death. ↑ ischemic CVA if CrCl >95.
Dabigatran (Thromb inhib)	150 mg bid (75 mg bid if CrCl 15–30)	150 mg: ↓ ischemic stroke & ICH, but ↑ GIB Risks: GI side effects, ↑ MI c/w warfarin
Onset w/in hrs. Reversal: andexanet for FXa inhib; idarucizumab for dabi; 4F-PCC.		

Nonpharmacologic stroke prevent (*JACC* 2015;66:1497)

- If contraindic. to long-term OAC, consider perc. left atrial appendage (LAA) occlusion (*JACC* 2022;79:1). Nb, ideally warfarin + ASA × 45 d → DAPT out to 6 mo → ASA.
- Consider surgical LAA occlusion if undergoing cardiac surgery (*NEJM* 2021;384:2081)

Atrial flutter

- Macroreentrant atrial loop. Typical involves cavotricuspid isthmus (if counterclockwise, flutter waves ⊖ in inf leads, if clockwise, ⊕). Atypical: other pathways related to prior scar.
- Risk of stroke similar to that of AF, ∴ anticoagulate same as would for AF
- Ablation of typical (cavotricuspid isthmus) AFL has 95% success rate

SYNCOPE

Definition

- Symptom of sudden transient loss of consciousness due to global cerebral hypoperfusion
- If CPR or cardioversion required, then SCD and not syncope (different prognosis)
- Presyncope = prodrome of light-headedness without LOC

Etiologies (*JACC* 2017;70:e39; *EHJ* 2018;39:1883)

- **Vasovagal** (a.k.a. neurocardiogenic, ~25%): ↑ sympathetic tone → vigorous contraction of LV → LV mechanoreceptors trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ HR (cardioinhib.) and/or ↓ BP (vasodepressor). Cough, deglutition, defecation, & micturition → ↑ vagal tone and thus can be precipitants. Carotid sinus hypersensitivity (exag vagal resp to carotid massage) is related disorder.
- **Orthostatic hypotension** (~10%)
  - hypovolemia/diuretics, deconditioning; vasodilat. (esp. if combined w/ ⊖ chronotropes)
  - autonomic neuropathy [1° = Parkinson's, MSA/Shy-Drager, Lewy body dementia, POTS (dysautonomia in the young); 2° = DM, EtOH, amyloidosis, CKD] (*JACC* 2018;72:1294)
- **Cardiovascular** (~20%, more likely in men than women)
  - *Arrhythmia* (~15%): challenging to dx because often transient
    - Bradyarrhythmias: SB, SSS, high-grade AV block, ⊖ chronotropes, PPM malfunction
    - Tachyarrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)
  - *Mechanical* (5%)
    - Endocardial/Valvular: critical AS, MS, PS, prosthetic valve thrombosis, myxoma
    - Myocardial: outflow obstruction from HCMP (or VT); pericardial: tamponade
    - Vascular: PE (in ~25% w/o alt dx; *NEJM* 2016;375:1524), PHT, AoD, ruptured AAA
- **Neurologic** (~10%): vertebrobasil insuff, cerebrovasc dissection, SAH, TIA/CVA
- Misc. causes of LOC (but not syncope): seizure, ↓ glc, hypoxia, narcolepsy, psychogenic

Workup (etiology cannot be determined in ~40% of cases) (*JAMA* 2019;321:2448)

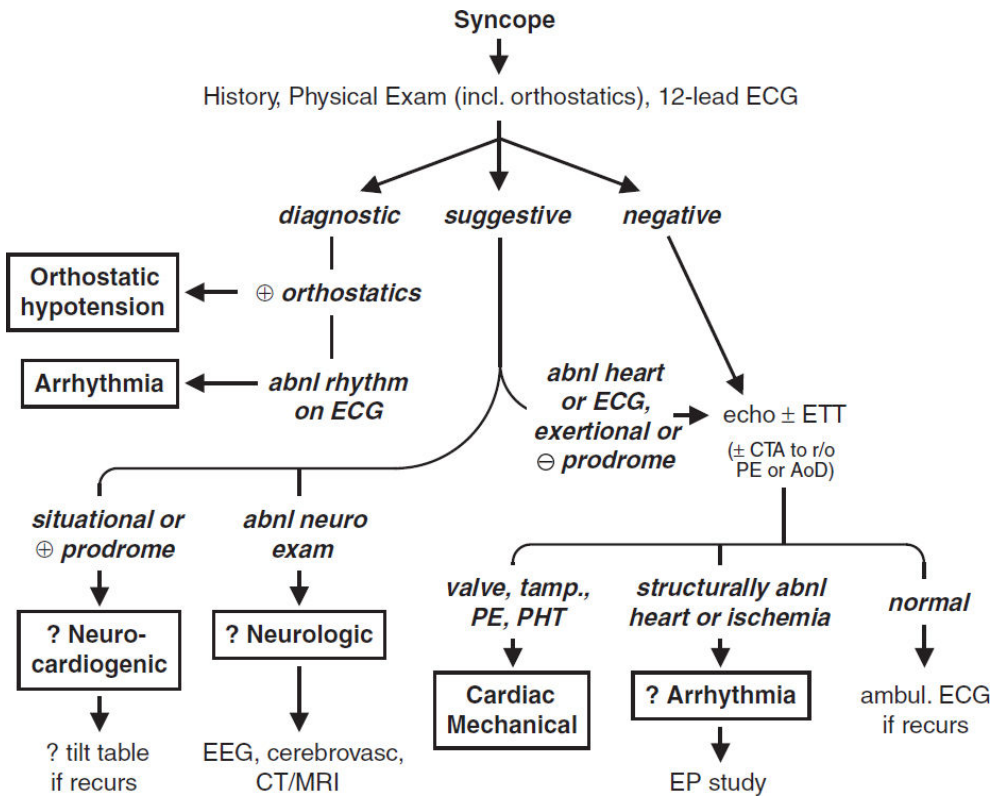
- *H&P incl. orthostatic VS have highest yield and most cost effective*
- *R/o life-threatening dx including: cardiac syncope, severe blood loss, PE, SAH*
- **History** (from Pt and *witnesses* if available)
  - activity and posture before the incident
  - precipitating factors: exertion (AS, HCMP, PHT), positional Δ (orthostatic HoTN), stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/deglutition/micturition/defecation

(neurocardiogenic), head turning or shaving (carotid sinus hypersens.); arm exercise (subclavian steal)
  - sudden onset → cardiac; prodrome (eg, diaphoresis, nausea, blurry vision) → vasovagal
  - associated sx: chest pain, palp., neurologic, postictal, bowel/bladder incontinence, (convulsive activity for <10 sec may occur w/ transient cerebral HoTN & mimic seizure)
- **PMH:** prior syncope, previous cardiac or neuro dis.; cardiac more likely if >35 y, known structural heart dis., h/o AF, CV prodrome, syncope while supine or exertional, cyanosis
- **Medications that may act as precipitants**
  - vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep.
  - diuretics; ⊖ chronotropes (eg, βB and CCB)
  - proarrhythmic or QT prolonging: class IA, IC or III antiarrhythmics (see "ECG")
  - psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH
- **Family history:** CMP, SCD, syncope (vasovagal may have genetic component)
- **Physical exam**
  - **VS incl. *orthostatics*** (⊕ if supine → standing results in ≥20 mmHg ↓ SBP or ≥10 ↓ DBP or SBP <90 mmHg w/in 3 min; POTS if ≥30 bpm ↑ HR w/in 10 min), BP in both arms
  - Cardiac: HF (↑ JVP, displ. PMI, S_3), murmurs, LVH (S_4, LV heave), PHT (RV heave, ↑ P_2)
  - Vascular: ✓ for *asymmetric pulses*, carotid/vert/subclavian *bruits; carotid sinus massage* to ✓ for carotid hypersens (if no bruits): ⊕ if asystole >3 sec or ↓ SBP >50 mmHg
  - Neurologic exam: focal findings, evidence of tongue biting
- **ECG** (abnormal in ~50%, but only definitively identifies cause of syncope in <10%)
  - Conduction: SB <40 bpm, sinus pauses >3 sec or sinus arrhythmia, AVB, BBB/IVCD
  - Arrhythmia: ectopy, ↑ or ↓ QT, preexcitation (WPW), Brugada, ε wave (ACM), SVT/VT
  - Ischemic changes (new or old): atrial or ventricular hypertrophy
- Lab: glc, Hb, HCG (pre-menop ♀), ? D-dimer, ? troponin/NT-proBNP (↓ yield w/o other s/s)

Other diagnostic studies (consider based on results of H&P and ECG)
- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope
  - Holter monitoring (continuous ECG 24–72 h): useful if *frequent* events
  - Event recorder (activated by Pt to record rhythm): limited role if LOC w/o prodrome
  - External loop recorder (continuously saves rhythm, ∴ can be activated *after* an event): useful for episodes (including w/o prodrome) likely to occur w/in 2–6 wks; can be coupled w/ mobile cardiac telemetry than can be auto-triggered for specific rhythms
  - External *patch* recorder (1-lead recording; saves for 1–4 wks): Pt-activated or auto-triggered; more comfortable for Pts
  - *Implantable* loop recorders (SC; can record 2–3 y; can be triggered): useful if episodes <1/mo; dx in 55% of cases; recommended for recurrent syncope w/o

prodrome
- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ARVC], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT/CCTA/Cath: esp. w/ exertional syncope; r/o ischemia or catechol-induced arrhythmia
- Electrophysiologic studies (EPS): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected (eg, prior MI), but cannot be confirmed; avoid if ECG/Echo normal.
  50% abnl (inducible VT, conduction abnormalities) if heart disease, but ? significance
  3–20% abnl if abnl ECG; <1% abnl if normal heart and normal ECG
- Tilt table: debated utility due to poor Se/Sp/reproducibility; consider if suspected neuro- cardiogenic, orthostatic HoTN, POTS, or psychogenic, and initial eval unrevealing
- Cardiac MRI: helpful to dx sarcoid or ARVC if suggestive ECG, echo (RV dysfxn) or ⊕ FHx
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield

Figure 1-6 Approach to syncope



(Adapted from *JACC* 2017;70:e39)

High-risk features (admit w/ tele; *JACC* 2017;70:620; *EHJ* 2018;39:1883)
- Age >60 y, h/o CAD, HF/CMP, valvular or congenital heart dis., arrhythmias, FHx SCD
- Syncope c/w cardiac cause (⊖ prodrome, exertional, supine, trauma) or recurrent

- Complaint of chest pain or dyspnea; abnl VS, cardiac, pulm, or neuro exam; low Hct
- ECG suggesting conduction abnormality, arrhythmia, or ischemia; Pt w/ PPM/ICD
- Canadian Syncope Risk Score (*CMAJ* 2016;188:e289) stratifies from <1% to >20% risk of serious arrhythmias. If low-risk & no arrhythmia in ED × 2 h, 0.2% risk over 30 d.

Treatment (*JACC* 2017;70:620 & 2019;74:2410; *EHJ* 2018;39:1883)

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder, ? ICD if Brugada pattern, sarcoid, ARVC, early repol + syncope
- Vasovagal: avoidance of triggers; physical counterpressure; consider ↑ Na & fluid intake, fludrocortisone or midodrine (*JACC* 2016;68:1; *Ann Intern Med* 2021;174:1349); SSRI; ? βB;
  consider PPM if recurrent + pauses on recorder or tilt test (*EHJ* 2021;42:508)
- Orthostatic: 2–3 L fluid & 10 g Na per day; rise from supine to standing *slowly*, compression stockings; consider: midodrine, fludrocortisone, droxidopa, ? pyridostigmine, ? octreotide

Prognosis (*Ann Emerg Med* 1997;29:459; *NEJM* 2002;347:878)

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope has poor prognosis (20–40% 1-y SCD rate); vasovagal good prognosis
- Unexplained syncope w/ 1.3-fold ↑ in mort., but noncardiac or unexplained syncope w/ nl
  ECG, no h/o VT, no HF, age <45 → low recurrence rate and <5% 1-y SCD rate
- ✓ state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

CARDIAC RHYTHM MANAGEMENT DEVICES

Pacemaker Code				
A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive	1st letter	2nd letter	3rd letter	4th letter
	Chamber paced	Chamber sensed	Response to sensed beat	Program features

Common Pacing Modes	
VVI	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
DDD	A & V sensing/pacing (RA & RV leads). Native A beat inhib A pacing & *triggers V pacing* → tracking of intrinsic atrial activity. Maintains AV synchrony, ↓ AF.
Mode Switch	In atrial tachyarrhythmia (eg, AF), PPM Δs from DDD to nontracking mode (eg, VVI). Prevents PPM from pacing at max V rate in response to rapid atrial rate.
Magnet over generator	PPM: fixed rate pacing (VOO/DOO). ICD: no shock, pacing preserved. Indic: ✓ capture; surgery; inapprop PPM inhib/ICD shock, PM-mediated tachy
Leadless intracardiac PPM for RV or AV synchronous pacing (*JACC Clin EP* 2020;6:94). His or L bundle pacing: more physiologic than RV pacing or even CRT (*JACC* 2018;72:927).	

Indications for Permanent Pacing (*JACC* 2013;61:e6 & 2017;70:e39, *Circ* 2019;140:e382)	
AV block	2° type II, high-grade or 3° AVB; symptomatic 1°, 2° type I AVB or asx with Lamin A/C or neuromuscular disease; bifasc or alter. L & RBBB
Sinus node	SB, pauses (SSS), chronotrop incompet a/w sx or ? if sx w/o clear assoc
Tachy-arrhythmia	AF w/ SSS; sx recurrent SVT term. by pacing after failing drugs/ablation; Sustained pause-dependent VT; ? high-risk congenital long QT
Syncope	Carotid sinus hypersensitivity with asystole >3 sec Syncope with bi- or trifascicular block and HV>70 ms on EP study ? Recurrent vasovagal syncope w/ abnormal tilt test (*JACC* 2017;70:1720)

Pacemaker Complications		
Issue	**Manifestation**	**Description & etiologies**
Perforation	Effusion/tamp/pain	Typically acute, consider if HoTN
Failure to pace	Bradycardia	↓ Battery, lead fx/dislodgment, ↑ pacing threshold due to tissue rxn/injury; oversense → inapprop. inhib
Failure to sense	Inapprop. pacing	Lead dislodgment or sensing threshold too high
PM-mediated tachycardia	WCT at device upper rate	Seen w/ DDD. V → A retrograde conduction; sensed by A lead → triggers V pacing → etc.
PM syndrome	Palpit, HF	Seen w/ VVI, due to loss of AV synchrony

Cardiac resynch therapy (CRT)/Biventricular (BiV) pacing (*JACC* 2013;61:e6)

- 3-lead pacemaker (RA, RV, coronary sinus to LV); R >S in V_1 suggests approp LV capture
- Synch LV fxn (↑ CO/EF, ↓ adv remodeling); ↓ HF sx & hosp, ↑ survival (*NEJM* 2010;363:2385)

- **Indications:** LVEF ≤35% + NYHA II–IV despite med Rx + SR + LBBB ≥150 ms (also reasonable if LBBB ≥120 ms, any non-LBBB ≥150 ms, or >40% V-pacing); mort. benefit w/ CRT-D only if LBBB (& QRS ≥130 ms) (*NEJM* 2014;370:1694)
  ? benefit in NYHA I–III, EF ≤50% w/ PPM indication for AVB (*NEJM* 2013;368:1585)

Implantable cardiac defibrillator (ICD) (*Circ* 2019;140:e382)

- RV lead: defib & pacing (± antitachycardia pacing [ATP] = burst pacing > VT rate to stop VT); ± RA lead for dual-chamber PPM. Subcut-ICD (consider if young), but Ø pace/ATP.
- **2° prev**: survivors of VT/VF arrest w/o revers cause; asx sustained VT + struct. heart dis.
- **$_1$° prev**: IHD (wait ≥40 d after MI): LVEF ≤30% *or* ≤35% & NYHA II–III *or* ≤40%, spont NSVT & inducible. NICM (wait ≥90 d after starting GDMT): LVEF ≤35% & NYHA II–III. High-risk CMP (w/o meeting above criteria): HCM, ACM, sarcoid, laminopathy, Chagas. Channelopathies: LQTS or Brugada if syncope or high-risk. ACHD: if SCD risk factors.
  More recently, for niCMP ICD ↓ SCD but not overall mortality (*NEJM* 2016;375:1221).
  Life expectancy must be >1 y.
- Wearable vest as bridge while waiting for ICD, but no benefit in RCT (*NEJM* 2018;379:1205)
- Subcutaneous ICD non-inferior in patients without PPM indication (*NEJM* 2020;383:526)
- **Risks:** inapprop shock in ~15–20% at 3 y (commonly d/t misclassified SVT); infxn; lead fx
- ICD discharge: ✓ device to see if approp; r/o ischemia; 6-mo driving ban (✓ state law)
- MRI: new devices OK; older may be OK (*NEJM* 2017;377:2555). Consult prescan.

Device infection (*Heart Rhythm* 2017;14:e503, *NEJM* 2019;380:1895)

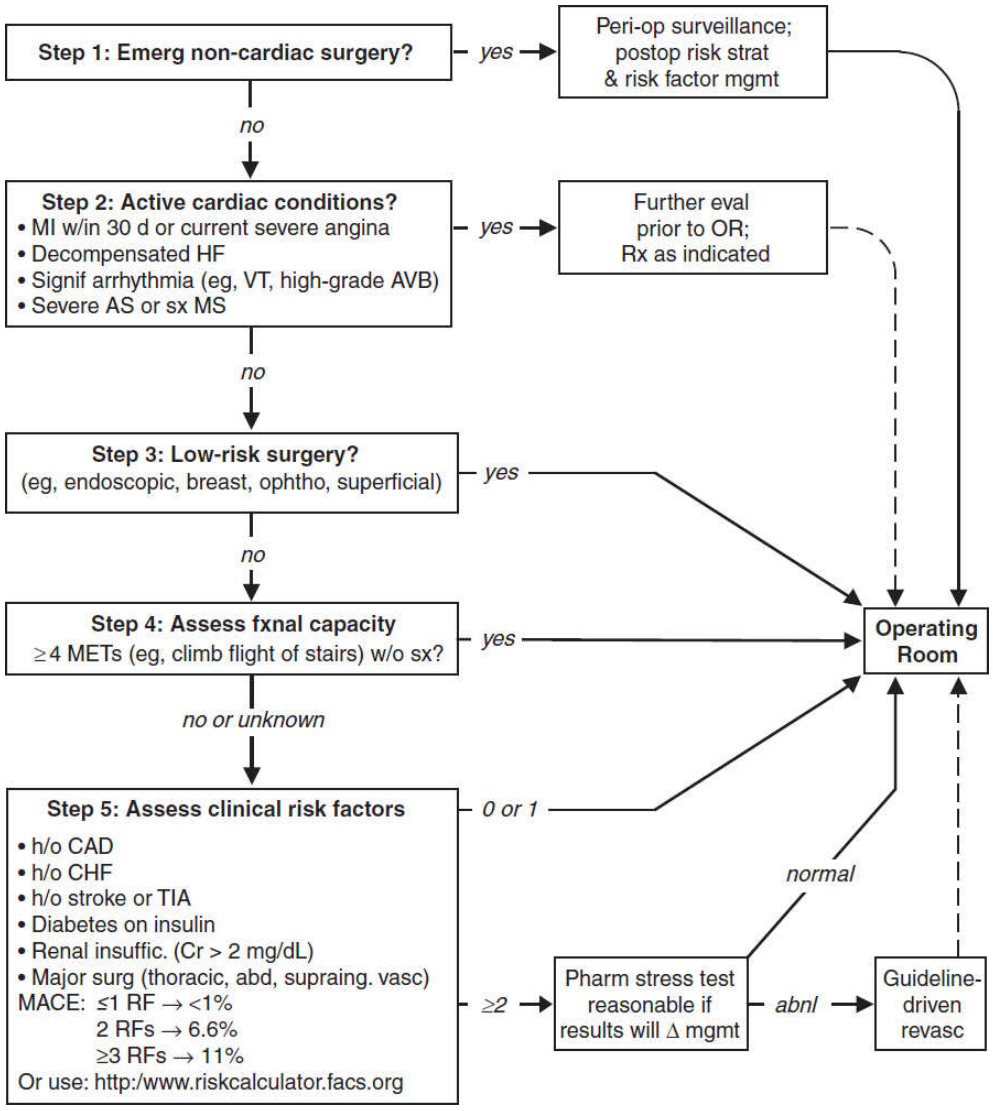
- Presents as *pocket infection* (warmth, erythema, tenderness) and/or *sepsis w/ bacteremia*
- ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%; antibacterial envelope ↓ risk
- TTE/TEE used to help visualize complic. (eg, vegetation), but even ⊖ TEE does not r/o
- Rx: abx; system removal if pocket infxn or GPC bacteremia; Ø routine abx prior to inv. proc.

CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

Goal: characterize risk of Pt & procedure → appropriate testing (ie, results will Δ management) and interventions (ie, reasonable probability of ↓ risk of MACE)

Preoperative evaluation (*Circ* 2014;130:e278, *NEJM* 2015;373:2258, *JAMA* 2020;324:279)

Figure 1-7 Approach to preop CV eval for non-CV surgery



(Modified with permission *Circulation*. 2014;130:2215-2245 © 2014 American Heart Association, Inc.)

Noninvasive Testing Result		
High Risk	**Intermediate Risk**	**Low Risk**
Ischemia at <4 METs *manifested by* ≥1 *of:* • Horiz/down ST ↓ ≥1 mm or STE • ≥5 abnl leads or ischemic ECG Δs • lasting >3 min after exertion • SBP ↓ 10 mmHg or typical angina	***Ischemia at <4–6 METs*** *manifested by* ≥1 *of:* • Horiz/down ST ↓ ≥1 mm • 3–4 abnl leads • 1–3 min after exertion	***No ischemia or at <7 METs w/*** • ST ↓ ≥1 mm or • 1–2 abnl leads

Additional preoperative testing (*Circ* 2014;130:e278)

- ECG if known cardiac disease and possibly reasonable in all, except if low-risk surgery
- TTE if any of following & prior TTE >12 mo ago or prior to Δ in sx: dyspnea of unknown origin; hx of HF w/ ↑ dyspnea; suspect (eg, murmur) or known ≥moderate valvular dis.

Coronary artery disease

- If possible, wait ~60 d after MI in the absence of revascularization before elective surgery
- Coronary revasc guided by standard indications. Has not been shown to Δ risk of death or postop MI when done prior to elective vasc. surgery (*NEJM* 2004;351:2795).

Heart failure (*Circ* 2014;130:e278)

- Decompensated HF should be optimally Rx'd prior to elective surgery
- 30-d CV event rate: symptomatic HF >asx HFrEF >asx HFpEF >no HF

Valvular heart disease

- If meet criteria for valve intervention, do so before elective surgery (postpone if necessary)
- If severe valve disease and surgery urgent, intra- & postoperative hemodynamic monitoring reasonable (espec for AS, because at ↑ risk even if sx not severe; be careful to maintain preload, avoid hypotension, and watch for atrial fibrillation)

Cardiac implantable electronic devices

- Discuss w/ surgical team need for device (eg, complete heart block) & consequences if interference w/ fxn, and likelihood of electromagnetic interference
- Consider reprogramming, magnet use, etc. as needed

Pre- & perioperative pharmacologic management

- **ASA:** continue in Pts w/ existing indication. Initiation prior to surgery does not ↓ 30-d ischemic events and ↑ bleeding (*NEJM* 2014;370:1494), but Pts w/ recent stents excluded.
- **Dual antiplatelet therapy:** delay elective surg 14 d after balloon angioplasty, 30 d after BMS and ideally 6 mo (min 3 mo) after DES (*JACC* 2016; 68:1082) unless risk of bleeding > risk of stent thrombosis or ACS. If must discontinue $P2Y_{12}$ inh, continue ASA and restart $P2Y_{12}$ inh ASAP; can consider IV cangrelor if high-risk (*JAMA* 2012;307:265).
- **β-blockers** (*JAMA* 2020;324:279)
  - Continue βB in Pts on them chronically. Do not stop βB abruptly postop (may cause reflex sympathetic activation). Use IV if Pt unable to take PO.
  - Reasonable to initiate if intermed- or high-risk ⊕ stress test, or RCRI ≥3, espec if vasc surgery. Initiate ≥1 wk prior to surgery (*not day of*), use low-dose, short-

acting βB, and titrate to achieve HR and BP goal (? HR ~55–65). Avoid bradycardia and HoTN.

- **Statins:** ↓ ischemia & CV events in Pts undergoing vascular surg (*NEJM* 2009;361:980). Consider if risk factors & non–low-risk surgery and in all Pts undergoing vascular surgery.
- ACEI/ARB: holding 24 h preop to ↓ intraop HoTN (*Anes* 2017;126:16). Restart ASAP.
- Amiodarone: ↓ incidence of postop AF if started prior to surgery (*NEJM* 1997;337:1785)

Postoperative monitoring

- ECG if known CAD or high-risk surgery. Consider if >1 risk factor for CAD.
- Routine troponin prognostic (*JAMA* 2017;317:1642) but ✓ only if sx/ECG Δs suggestive of ACS

PERIPHERAL ARTERY DISEASE (PAD)

Clinical features (*NEJM* 2016;374:861, *Circ* 2021;144:e171)

- Prev. ↑ w/ age: <1% if <40 y, ~15% if ≥70 y; risk factors incl. **smoking**, **DM**, HTN, chol
- **Claudication** (ache/cramp, often in calves) precip by walking and relieved by stopping (vs. spinal stenosis, qv); Leriche synd = claudic., ↓ or Ø fem pulses, & erectile dysfxn
- **Critical limb ischemia (CLI): rest pain** (↑ w/ elevation b/c ↓ perfusion), **ulcer** (typically at pressure foci, often dry; in contrast, venous ulcers are more often at medial malleolus, wet, and with hemosiderin deposition) or **gangrene**, due to PAD, and >2-wk duration (implies chronicity vs. acute limb ischemia; see below) (*Circ* 2019;140:e657)

Diagnosis (*Circ* 2016;135:e686, *JAMA* 2021;325:2188)

- ↓ peripheral pulses, bruits; signs of chronic PAD: hair loss, skin atrophy, nail hypertrophy
- Ankle: brachial index (ABI): nl 1–1.4; borderline 0.91–0.99; abnl ≤0.90; if >1.4, non-dx possibly due to calcified noncompressible vessel → ✓ PVR, TBI (toe-brachial index). If ABI abnl → segmental ABI w/ PVR to localize disease. If ⊕ sx but nl ABI, ✓ for ↓ lower extrem BP after exercise (≥20% ↓ in ABI w/ exercise or ≥30 mmHg ↓ in ankle pressure).
- Duplex arterial U/S; CTA w/ distal run-off; MRA or angio if dx in ? or possible intervention

Treatment (*JACC* 2013;61:1555, *Circ* 2021;144:e171, *JAMA* 2021;325:2188)

- Risk factor modif. Screen for CAD/AAA. Structured high-intensity walking (*JAMA* 2021;325:1266).
- If sx or if asx with ABI ≤0.90, ASA, clopi, or ticag to ↓ D/MI/stroke (*NEJM* 2017; 376:32). More intensive antiplt Rx ↓ both MACE & limb ischemic events (*JACC* 2016;67:2719). Adding riva 2.5 mg bid to ASA ↓ MACE but ↑ bleeding (*Lancet* 2018;391:219; *NEJM* 2020;382:1994).
- Statins & PCSK9i ↓ MACE & limb ischemic events (*Circ* 2018;137:338). Cilostazol (if no HF).
- Endovascular (angioplasty vs. stent) or surgical revasc if limiting/refractory sx or CLI

Acute limb ischemia (ALI) (*Circ* 2016;135:e686)

- Sudden decrement in limb perfusion (ie, acutely cold & painful) that threatens viability
- Etiologies: embolism > acute thrombosis (eg, athero, APS, HITT), trauma to artery
- Clinical manifestations (**6 Ps**): pain (distal to proximal, ↑ in severity), poikilothermia, pallor, pulselessness, paresthesias, paralysis
- Testing: pulse & neuro exam; arterial & venous Doppler; angiography, CTA or MRA
- Urgent consultation w/ vascular medicine and/or vascular surgery

Categorization & Treatment of ALI						
Audible Doppler		Motor Fxn Loss	Sen. Loss	Cap. Refill	Status	Treatment
Art.	Ven.					
Y	Y	None	None	OK	Viable	A/C + urgent revasc
N	Y	Some	Some	Slow	Threatened	A/C + *emerg* revasc
N	N	Total	Complete	Absent	Irreversible	Amputation

DYSPNEA

Pathophysiology	Etiologies
Airway obstruction (↑ resistance to airflow)	**Asthma**, **COPD**, bronchiectasis, cystic fibrosis, tumor, foreign body, vocal cord dysfunction, anaphylaxis
Alveolar / Parenchymal disease	**Pulmonary edema**: *cardiogenic or noncardiogenic* **ILD; pneumonia**; atelectasis
Vascular (V/Q mismatch)	Large vessel: **PE**, tumor emboli Small vessel: PHT, vasculitis, ILD, emphysema, PNA
Chest wall (↑ resistance to expansion; weakness of respir. muscles)	Pleural disease**: large effusion**, fibrosis, pneumothorax Chest wall/diaphragm: kyphoscoliosis, ↑ abd girth Neuromuscular disorders (ALS, GBS, MG) Hyperinflation (COPD, asthma)
Stimulation of receptors	Chemoreceptors: **hypoxemia**, metabolic acidosis Mechanoreceptors: ILD, pulmonary edema, PHT, PE
↓ **O_2 carrying cap.** (but nl P_aO_2)	**Anemia**, methemoglobinemia, CO poisoning
Psychological	Anxiety, panic attack, depression, somatization

Evaluation

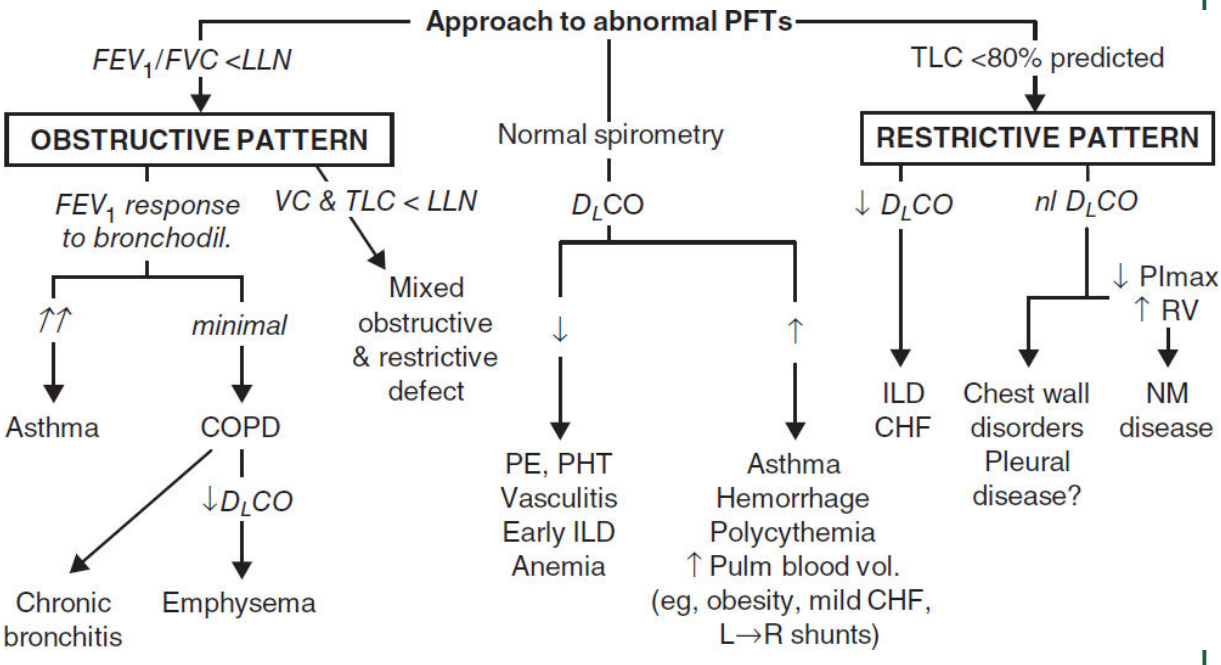
- History: quality of sensation, tempo, positional dependence, exac./allev. factors, exertion
- Cardiopulmonary exam, S_aO_2, CXR (see Appendix & Radiology inserts), ECG, ABG, U/S Predictors of CHF: h/o CHF, PND, S_3, CXR w/ venous congestion, AF (*JAMA* 2005;294:1944) Dyspnea w/ nl CXR: CAD, asthma, PE, PHT, early ILD, anemia, acidosis, NM disease
- Based on results of initial evaluation: PFT, chest CT, TTE, cardiopulmonary testing
- **BNP & NT-proBNP** ↑ in CHF (also ↑ in AF, RV strain from PE, COPD flare, PHT, ARDS) BNP <100 pg/mL to r/o CHF (90% Se), >400 to r/i (*NEJM* 2002;347:161) NT-proBNP <300 pg/mL to r/o CHF (99% Se); age-related cut points to r/i: >450 pg/mL (<50 y), >900 (50–75 y), >1800 (>75 y) (*EHJ* 2006;27:330)

↑ in chronic HF, ∴ need to compare to known “dry BNP.” May be falsely low in obesity.

PULMONARY FUNCTION TESTS (PFTs)

- **Spirometry:** evaluate for obstructive disease
  - Flow-volume loops: diagnose and/or localize obstruction
  - Bronchodilator: indicated if obstruction at baseline or asthma clinically suspected
  - Methacholine challenge: helps dx asthma if spirometry nl, >20% ↓ FEV_1 → asthma
- **Lung volumes:** evaluate for hyperinflation or restrictive disease including NM causes
- **D_LCO:** evaluates functional surface area for gas exchange; helps differentiate causes of obstructive and restrictive diseases and screens for vascular disease & early ILD

Figure 2-1 Approach to abnormal PFTs



ASTHMA

Definition and epidemiology (*Lancet* 2018;391:783)

- Chronic inflam disorder w/ **airway hyperresponsiveness + variable airflow obstruction**
- Affects 5–10% population; ~85% of cases by age 40 y

Clinical manifestations (*NEJM* 2013;369:549)

- Classic triad = **wheezing, cough, dyspnea;** others include chest tightness, sputum; symptoms typically *chronic* with *episodic exacerbation*
- Precipitants **(triggers)**
  - *respiratory irritants* (smoke, perfume, etc.) & *allergens* (pets, dust mites, pollen, etc.)
  - *infections* (URI, bronchitis, sinusitis)
  - *drugs* (eg, ASA & NSAIDs via leukotrienes, βB via bronchospasm, MSO_4 via histamine)
  - emotional stress, cold air, exercise (increase in ventilation dries out airways)

Physical examination

- Wheezing and prolonged expiratory phase
- Presence of nasal polyps, rhinitis, rash → *allergic component*
- Exacerbation → ↑ RR, ↑ HR, accessory muscle use, diaphoresis, pulsus paradoxus

Diagnostic studies (*JAMA* 2017;318:279)

- **Spirometry:** ↓ FEV_1, ↓ FEV_1/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC
  - ⊕ bronchodilator response (↑ FEV_1 ≥12% & ≥200 mL) strongly suggestive of asthma
  - methacholine challenge (↓ FEV_1 ≥20%) if PFTs nl: Se >90%
- Allergy suspected → consider checking serum IgE, eos, skin testing/RAST

Ddx ("all that wheezes is not asthma…")
- Hyperventilation & panic attacks
- Upper airway obstruction or inh foreign body; laryngeal/vocal cord dysfxn (eg, 2° to GERD)
- CHF ("cardiac asthma"); COPD; bronchiectasis; ILD (including sarcoidosis); vasculitis; PE

"Asthma plus" syndromes
- Atopy = asthma + allergic rhinitis + atopic dermatitis
- Aspirin-exacerbated respiratory disease (Samter's syndrome) = asthma + ASA sensitivity + nasal polyps (*J Allergy Clin Immunol* 2015;135:676)
- ABPA = asthma + pulmonary infiltrates + hypersensitivity to *Aspergillus* (*Chest* 2009;135:805)
  Dx: ↑ IgE to *Asperg.* & total (>1000), ↑ *Asperg.* IgG levels, ↑ eos, central bronchiectasis
  Rx: steroids ± itra-/voriconazole for refractory cases (*NEJM* 2000;342:756)
- Eosinophilic granulomatosis w/ polyangiitis (EGPA, previously Churg-Strauss) = asthma + eosinophilia + granulomatous vasculitis

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CHRONIC MANAGEMENT

"Reliever" medications (used prn to quickly relieve sx)
- Low-dose inhaled **corticosteroids** (ICS) + *long-acting* inh **β_2-agonists** (LABA): budesonide-formoterol (*NEJM* 2019;380:2020)
- *Short-acting* inh **β_2-agonists** (SABA): albuterol Rx of choice
- *Short-acting* inh **anticholinergics** (ipratropium) ↑ β_2-agonist delivery → ↑ bronchodilation

"Controller" meds (taken daily to keep control) (*JAMA* 2020;324:2301)
- **ICS** Rx of choice. Superior to LAMA if sputum w/ ≥2% eos (*NEJM* 2019;380:2009). PO steroids may be needed for severely uncontrolled asthma; avoid if possible b/c of systemic side effects.
- LABA (eg, salmeterol, formoterol) safe & ↓ exacerb. when added to ICS (*NEJM* 2018;378:2497)
- *Long-acting* inh **antimuscarinics** (LAMA; eg, tiotropium, umeclidinium): may consider if sx despite ICS+LABA (*JAMA* 2018;319:1473)

- **Leukotriene receptor antagonists** (LTRA): some Pts very responsive, esp. ASA-sens and exercise-induced. Warning for serious neuropsychiatric effects, including suicide.
- **Nedocromil/cromolyn:** limited use in adults. Useful in young Pts, exercise-induced bronchospasm; ineffective unless used before trigger or exercise exposure.

Immunotherapies (*NEJM* 2017;377:965)

- Allergen ImmunoRx ("allergy shots") may help if sig. allerg. component (*JAMA* 2016;315:1715)
- Anti-IgE (omalizumab) for uncontrolled mod-to-severe allergic asthma (w/ IgE >30) on ICS ± LABA (*JAMA* 2017; 318:279); ↓ exacerbations in severe asthma (*Cochrane* 2014;CD003559)
- Anti-IL5 (mepolizumab, reslizumab) ↓ exacerb in severe asthma (*NEJM* 2014;371:1189 & 1198)
- Anti-IL5Rα (benralizumab) ↓ steroid use, ↓ exac. in sev asthma w/ eos (*NEJM* 2017;376:2448)
- Anti-IL4Rα (dupilumab) blocks IL-4 & IL-13; ↓ exacerb in severe asthma, ↓ steroid use, ↑ FEV_1 (*NEJM* 2018;378:2475 & 2486)
- Anti-TSLP (tezepelumab-ekko) ↓ exacerbations in severe asthma; can use in non-allergic/non-eosinophilic asthma (*NEJM* 2021;384:1800)

Principles of treatment

- Education and avoidance of environmental triggers (*Lancet* 2015;386:1075); yearly flu shot
- Use quick-relief rescue medication as needed for all Pts
- Goal to achieve **complete control** = daily sx ≤2/wk, Ø nocturnal sx or limitation of activity, reliever med ≤2/wk, nl peak expiratory flow rate or FEV_1; partly controlled = 1–2 of the above present in a wk; uncontrolled = ≥3 of the above present in a wk
- Step up treatment as needed to gain control, step down as tolerated
- Can abort exacerb by quadrupling ICS if deteriorating control (*NEJM* 2018;378:902)

Asthma Stepwise Therapy (Adapted from GINA 2021 and NHLBI 2020 Guidelines)					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Day sx	≤2 d/wk	3–6 d/wk	Daily	Sx all day Nightly awakenings SABA several times/day Extreme limitation in activity	
Noct. awaken	≤2/mo	3–4/mo	>1/wk		
Controllers	**Low-dose ICS + formoterol prn** *or* SABA & low-dose ICS prn	**Low-dose ICS daily,** *or* **Low-dose ICS + formoterol prn,** *or* SABA & low-dose ICS prn *or* LTRA daily	**Low-dose ICS + LABA daily** *or* Med-dose ICS *or* Low-dose ICS + LTRA	**Med-dose ICS + LABA,** *or* High-dose ICS ± Tiotropium ± LTRA	**High-dose ICS + LABA + LAMA daily,** *or* **High-dose ICS + LABA** **± Refer for biologics** ± Oral steroids (lowest dose)
Relievers:	**prn low-dose ICS + formoterol**				

Category for sx determined by most severe day or nocturnal element

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EXACERBATION

Evaluation

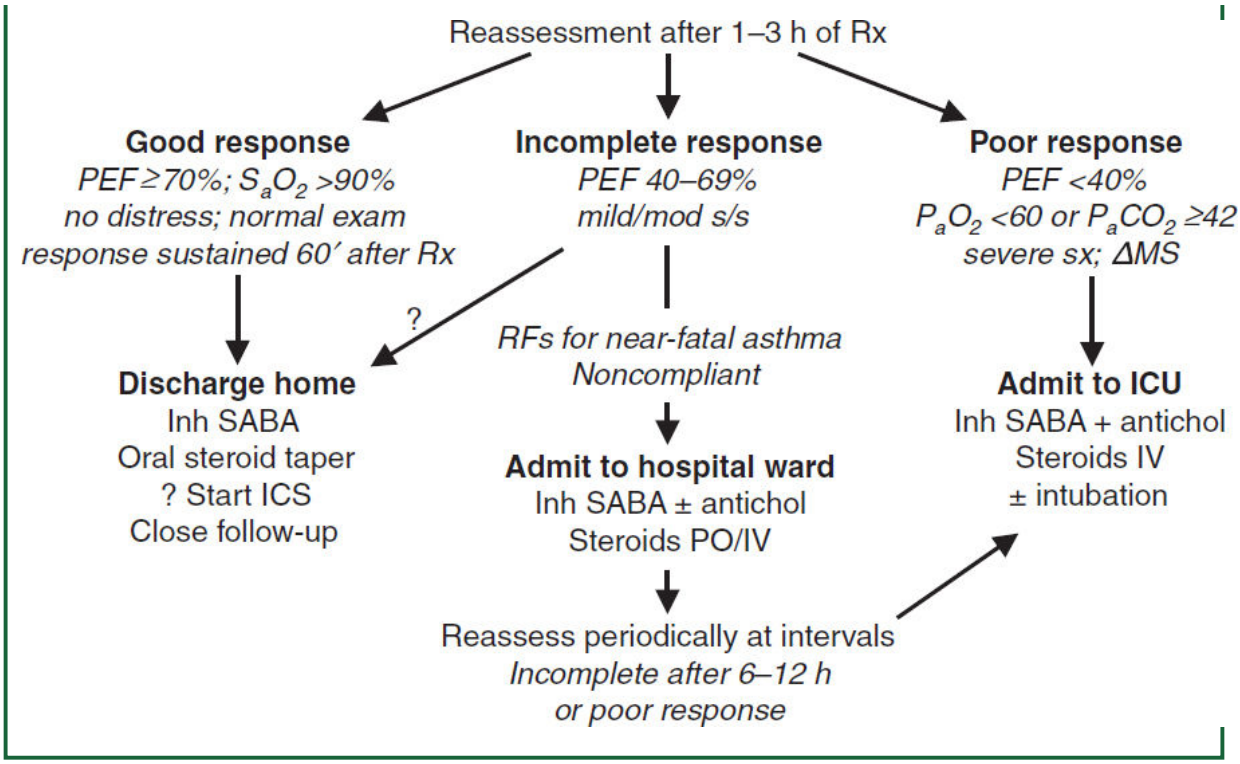
- History: baseline PEF, steroid requirement, ED visits, hospital admissions, prior intubation
  Current exacerbation: duration, severity, potential precipitants, meds used
  Risk factors for life-threatening: prior intubation, h/o near-fatal asthma, ED visit/hosp for asthma w/in 1 y, current/recent PO steroids, not using ICS, overdependent on SABA, Ψ, h/o noncompliance
- Physical exam: VS, pulm, accessory muscle use, pulsus paradoxus, abdominal paradox
  Assess for barotrauma: asymmetric breath sounds, tracheal deviation, subcutaneous air → pneumothorax, precordial (Hamman's) crunch → pneumomediastinum
- Diagnostic studies: **peak expiratory flow** (know personal best; <80% personal best c/w poor control, <50% c/w severe exacerbation); **S_aO_2; CXR** to r/o PNA or PTX; ABG if severe (low P_aCO_2 initially; nl or high P_aCO_2 *may* signify tiring)

Severity of Asthma Exacerbation			
	Mild-Moderate	**Severe**	**Life-Threatening**
Symptoms	Talks in phrases	Talks in words, tripod positioning	Drowsy Confused
Vitals/ Exam	RR >20, HR 100–120, Room air S_aO_2 90–95%	RR >30, HR >120 Room air S_aO_2 <90%	Silent chest Bradycardia
PEF	>50% predicted or best	≤50% predicted or best	Not indicated
Initial Treatment	O_2, SABA 4–10 puffs q20min, prednisone	Tx to acute facility, SABA, ipratropium, methylpred, IV Mg	Tx to acute facility, prepare for intubation SABA, ipratropium, methylpred, IV Mg

Initial treatment details (GINA 2021 Guidelines)

- **Oxygen** to keep S_aO_2 ≥93–95%
- **Inhaled SABA** (eg, albuterol) by MDI (4–8 puffs) or nebulizer (2.5–5 mg) q20min
- **Corticosteroids:** prednisone 40–60 mg PO if outPt; methylpred IV if ED or inPt
- **Ipratropium** MDI (4–6 puffs) or nebulizer (0.5 mg) q20min if severe (*Chest* 2002;121:1977)
- *Reassess after 60–90 min of Rx*
  Mild–mod exacerbation: cont SABA q1h
  Sev exacerbation: SABA & ipratropium q1h or cont.; if refractory, consider Mg ± heliox
- *Decide disposition within 4 h of presentation and after 1–3 h of Rx*
- **High-dose steroids:** methylpred 125 mg IV q6h (*NEJM* 1999;340:1941)

Figure 2-2 Disposition of patients after initial treatment of asthma exacerbation



ICU-level care

- **Invasive ventilation:**
  - Large ET tube, P_{plat} <30 cm H_2O (predicts barotrauma better than PIP), max exp time
  - PEEP individualized to patient physiology
  - Paralysis, inhalational anesthetics, bronchoalveolar lavage w/ mucolytic, heliox (60–80% helium) and ECMO have been used with success
  - IV ketamine: bronchodilating effects and can be used for refractory status asthmaticus
- NPPV likely improves obstruction (*Chest* 2003;123:1018), but controversial and rarely used

ANAPHYLAXIS

Definition and pathophysiology (*Ann Emerg Med 2006;47:373*)

- Severe, rapid onset (mins to hrs), potentially life-threatening systemic allergic response
- IgE-mediated mast cell degranulation with release of histamine, tryptase, and TNF
- Precipitates systemic reactions (bronchospasm, tissue swelling, fluid shifts, vasodilation)
- Common triggers: penicillins, cephalosporins, shellfish, nuts, insect stings, IV contrast (not truly an IgE-mediated mechanism, but clinically similar)

Diagnosis: any of the three following criteria

1) Acute illness with skin ± mucosal involvement (rash, flushing, hives), AND at least one of:
   Respiratory compromise (wheeze, stridor, dyspnea, hypoxemia)
   Hypotension or hypoperfusion (syncope, incontinence)
2) Two or more of the following after exposure to a **likely** allergen: skin/mucosal involvement, respiratory compromise, ↓ BP or hypoperfusion, GI symptoms
3) Hypotension after exposure to **known** allergen for that Pt

Treatment

- **Epi:** 0.5 mg IM (0.5 mL of 1 mg/mL solution) q5–15min as needed. For those who do not respond, IV infusion starting at 0.1 mcg/kg/min.
- **Airway:** suppl O_2 ± intubation or cricothyroidotomy (if laryngeal edema); β_2-agonists
- Fluid resuscitation w/ ≥1–2 L crystalloid (may extravasate up to 35% of intravasc volume)
- Antihistamines relieve hives & itching, *no effect on airway or hemodynamics;* H1RA (diphenhydramine 50 mg IV/IM)

- Methylprednisolone 1–2 mg/kg/d × 1–2 d for those who do not respond to epi
- Avoid unopposed α-adrenergic vasopressors

Disposition

- Mild rxn limited to urticaria or mild bronchospasm can be observed for ≥6 h; admit all others
- Watch for **biphasic reaction;** occurs in 23%, typically w/in 8–10 h but up to 72 h

Angioedema (*J Allergy Clin Immunol* 2013;131:1491)

- Localized swelling of skin/mucosa; involves face, lips, tongue, uvula, larynx, and bowels
- Etiologies: mast cell-mediated (eg, NSAIDs); bradykinin-mediated (eg, **ACEI,** ARNi, hereditary angioedema, acquired C1 inhibitor deficiency); idiopathic
- Diagnosis: C4 and C1 inhibitor level, tryptase (if suspect anaphylaxis), ESR/CRP
- Rx: intubation if risk of airway compromise. Allergic angioedema: H1/H2 antihist., steroids.
  If 2° ACEI: d/c ACEI, antihist., icatibant (bradykinin-receptor antag; *NEJM* 2015;372:418).
  Hereditary angioedema: plasma-derived C1 inhibitor, ecallantide (kallikrein inhibitor)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and epidemiology (*Lancet* 2017;389:1931)

- Progressive airflow limitation caused by airway and parenchymal inflammation

Emphysema vs. Chronic Bronchitis		
	Emphysema	**Chronic Bronchitis**
Definition	Dilation/destruction of parenchyma (path definition)	Productive cough >3 mo/y × ≥2 y (clinical definition)
Pathophysiology	Tissue destruction V/Q: ↑ dead space fraction → hypercarbia, but only mild hypoxemia	Small airways affected V/Q: ↑ shunt fraction → severe hypoxemia, hypercapnia PHT, cor pulmonale
Clinical manifestations	Severe, constant dyspnea Mild cough	Intermittent dyspnea Copious sputum production
Physical exam	"Pink puffer" Tachypneic, noncyanotic, thin Diminished breath sounds	"Blue bloater" Cyanotic, obese, edematous Rhonchi & wheezes

Pathogenesis (*Lancet* 2017;389:1931)

- **Cigarette smoke** (centrilobular emphysema, affects 15–20% of smokers)
- Recurrent airway infections
- α_1-antitrypsin deficiency: early-onset panacinar emphysema or signif basilar disease, 1–3% of COPD cases. Suspect if age <45, lower lungs affected, extrathoracic manifestations (liver disease [not if heterozygote MZ], FMD, pancreatitis). ✓ serum A1AT level (nb, acute phase reactant).
- Low FEV_1 in early adulthood associated w/ COPD (*NEJM* 2015;373:111)

Clinical manifestations

- Chronic cough, sputum production, dyspnea; later stages → freq exacerb, AM HA, wt loss

- Exacerbation triggers: infection, other cardiopulmonary disease, including PE
  Infxn: overt tracheobronchitis/pneumonia from viruses, *S. pneumoniae, H. influenzae, M. catarrhalis* or triggered by changes in strain of colonizers (*NEJM* 2008;359:2355)
- Physical exam: ↑ AP diameter of chest ("barrel chest"), hyperresonance, ↓ diaphragmatic excursion, ↓ breath sounds, ↑ expiratory phase, rhonchi, wheezes during exacerbation: tachypnea, accessory muscle use, pulsus paradoxus, cyanosis
- *Asthma-COPD overlap syndrome* (ACOS; *NEJM* 2015;373:1241): features of both present. For example: reversibility of airway obstruction w/ bronchodilator in COPD; neutrophilic inflammation in asthma (more classic in COPD); eos in COPD.

Diagnostic studies (*JAMA* 2019;321:786)

- CXR (see Radiology inserts): hyperinflation, flat diaphragms, ± interstitial markings & bullae
- PFTs: **obstruction:** ↓↓ FEV_1, ↓ **FVC, FEV_1/FVC <0.7 (no sig Δ post bronchodilator),** expiratory coving of flow-volume loop; **hyperinflation:** ↑↑ RV, ↑ TLC, ↑ RV/TLC; **abnormal gas exchange:** ↓ D_LCO (in emphysema)
- ABG: ↓ P_aO_2, ± ↑ P_aCO_2 (in chronic bronchitis, usually only if FEV_1 <1.5 L) and ↓ pH
- Screen *symptomatic* Pts w/ spirometry; don't screen if asx; screen for α1-AT deficiency

Chronic treatment (Adapted from GOLD 2021 Report)

COPD Staging and Recommended Therapies by GOLD Criteria		
Exacerbations/Yr	**Mild Symptoms**	**Mod/Severe Symptoms**
<2	**A** Short-acting inh dilator prn	**B** LAMA
≥2	**C** LAMA	**D** LAMA + LABA ± ICS
	Consider adding PDE-4 inhib to bronchodilator	

Smoking cessation & vaccinations in all. Pulm rehab in groups B–D. O_2 as indicated per S_aO_2.

- **Bronchodilators** (*1st-line*)**: long-acting muscarinic antag (LAMA),** β_2-agonists (LABA)

  - LAMA (eg, tiotropium): ↓ exacerb, slows ↓ FEV_1, ↓ admit, ↓ resp failure; better than ipratropium or LABA (*NEJM* 2008;359:1543; 2011;364:1093; 2017;377:923)
  - LABA: ~11% ↓ in exacerbations, no ↑ in CV events (*Lancet* 2016;387:1817)
  - LAMA + LABA: ↑ FEV_1, ↓ sx vs. either alone (*Chest* 2014;145:981) and superior to LABA + inh steroid (*NEJM* 2016;374:2222)
- **Corticosteroids** (inhaled, ICS): ~11% ↓ in exacerbations & slows ↓ FEV_1; no Δ in mortality (*Lancet* 2016;387:1817). Greatest benefit if eos >300 (*Lancet Repir Med* 2018;6:117).
- "Triple Therapy" (LAMA+LABA+ICS) ↓ exac, ↓ hosp, ↑ PNA (*NEJM* 2020;383:35)
- Roflumilast (PDE-4 inhib) + bronchodil: ↑ FEV_1, ↓ exacerb in Pts with severe COPD, chronic bronchitis, and a hx of exacerbations (*Lancet* 2015;385:857)
- Anti-IL5 (eg, mepolizumab, benralizumab): mixed data on ↓ exacerb in Pts w/ eos (*NEJM* 2017;377:1613 & 2019;381:1023)
- Antibiotics: daily azithro ↓ exacerbations, but not routine (*JAMA* 2014;311:2225)
- **Oxygen:** if P_aO_2 ≤55 mmHg or S_aO_2 ≤89% (during rest, exercise, or sleep) to prevent cor pulmonale; only Rx proven to ↓ mortality (*Annals* 1980;93:391; *Lancet* 1981;i:681); no benefit in Pts w/ moderate hypoxemia (S_aO_2 89–93%) (*NEJM* 2016;375:1617) or nocturnal O_2 alone (*NEJM* 2020;383:1129); unknown benefit of isolated exertional O_2 (*AJRCCM* 2020;202:121).
- Night NPPV if recent exacerb & P_aCO_2 >53 ↓ risk of readmit or death (*JAMA* 2017;317:2177)
- **Prevention:** Flu/Pneumovax; smoking cessation → 50% ↓ in lung function decline (*AJRCCM* 2002;166:675) and ↓ long-term mortality (*Annals* 2005;142:223)
- Rehabilitation: ↓ dyspnea and fatigue, ↑ exercise tolerance, ↑ QoL (*NEJM* 2009;360:1329)
- Surgery & bronchoscopic interventions
  - Lung volume reduction surgery: ↑ exercise capacity, ↓ mortality *if* FEV_1 >20%, upper lobe, low exercise capacity (*NEJM* 2003;348:2059)
  - Bronchoscopic lung reduction w/ endobronchial valves or coils: ↑ lung fxn but significant complications (PTX, PNA) (*NEJM*

2015;373:2325; *Lancet* 2015;386:1066; *JAMA* 2016;315:175)

- Lung transplant: ↑ QoL and ↓ sx (*Lancet* 1998;351:24), ? survival benefit (*Am J Transplant* 2009;9:1640)

Staging and prognosis

- Assess breathlessness, cough, sputum, exercise capacity & energy (tools such as CAT and mMRC may be used as part of assessment)
- Ratio of diam PA/aorta >1 associated with ~3× ↑ risk of exacerbations (*NEJM* 2012;367:913)
- FEV_1 stages: I = ≥80%; II = 50–79% (~11% 3-y mort.); III = 30–49% (~15% 3-y mort.); IV = <30% (~24% 3-y mort.)

EXACERBATION

COPD Exacerbation Treatment		
Agent	**Dose**	**Comments**
Ipratropium	MDI 4–8 puffs q1–2h *or* Nebulizer 0.5 mg q1–2h	First-line therapy (*NEJM* 2011;364:1093)
Albuterol	MDI 4–8 puffs q1–2h *or* Nebulizer 2.5–5 mg q1–2h	Benefit if component of reversible bronchoconstriction
Corticosteroids	Prednisone 40 mg/d × 5d (*JAMA* 2013;309:2223); some Pts will benefit from higher dose/longer course if severe Methylprednisolone 125 mg IV q6h × 72 h for more severe exacerbations	↓ treatment failure, ↓ hosp. stay ↑ FEV_1 but no mortality benefit, ↑ complications (*Cochrane* 2009:CD001288) OutPt Rx after ED visit ↓ relapse (*NEJM* 2003;348:2618)
Antibiotics	Amox, TMP-SMX, doxy, azithro, antipneumococcal FQ all reasonable (no single abx proven superior). Consider local flora and avoid repeat courses of same abx. ≤5d course likely enough for mild–mod exacerbation (*JAMA* 2010;303:2035).	*H. flu, M. catarrhalis, S. pneumo* ↑ PEF, ↓ Rx failure, ? ↓ short-term mort, ↓ subseq exacerb (*Chest* 2008;133:756 & 2013;143:82) Consider if CRP >20 + ↑ sputum purulence or CRP >40 (*NEJM* 2019;381:111)

COPD Exacerbation Treatment		
Oxygenation	↑ F_iO_2 to achieve P_aO_2 ≥55–60 *or* S_aO_2 88–92%	**Watch for CO_2 retention** (due to ↑ V/Q mismatch, loss of hypoxemic resp drive, Haldane effect)*, but must maintain acceptable S_aO_2!*
Noninvasive positive-pressure ventilation	Initiate *early* if moderate/severe dyspnea, ↓ pH / ↑ P_aCO_2, RR >25 Results in 58% ↓ intubation, ↓ LOS by 3.2 d, 59% ↓ mortality Contraindications: Δ MS, inability to cooperate or clear secretions, hemodynamic instability, UGIB (*NEJM* 1995;333:817; *Annals* 2003;138:861; *Cochrane* 2004;CD004104; *ERJ* 2005;25:348)	
Endotracheal intubation	Consider if P_aO_2 <55–60, ↑'ing P_aCO_2, ↓'ing pH, ↑ RR, respiratory fatigue, Δ MS or hemodynamic instability	
Other measures	Mucolytics overall not supported by data (*Chest* 2001;119:1190) Monitor for cardiac arrhythmias	
Post-exacerb care	Follow up w/in 1 mo; smoking cessation if current smoker; vaccinations (influenza, pneumococcal), referral to pulm rehab (*AJRCCM* 2007;176:532)	

SOLITARY PULMONARY NODULE

Principles

- Definition: single, well-defined, <3 cm, surrounded by nl lung, no LAN or pleural effusion
- Often "incidentalomas," esp with ↑ CT use, but may still be early, curable malignancy

Etiologies	
Benign (70%)	**Malignant (30%)**
Granuloma (80%): TB, histo, coccidio **Hamartoma** (10%) Bronchogenic cyst, AVM, pulm infarct Echinococcosis, ascariasis, aspergilloma GPA, rheumatoid nodule, sarcoidosis Lipoma, fibroma, amyloidoma	**Bronchogenic carcinoma** (75%) periph: adeno (most common) & large cell central: squamous & small cell **Metastatic** (20%): sarcoma, melanoma, breast, head & neck, colon, testicular, renal Carcinoid, primary sarcoma

Initial evaluation

- **History:** h/o cancer, smoking, age (<30 y = 2% malignant, +15% each decade >30)
- **CT:** size/shape, Ca^{2+}, LAN, effusions, bony destruction, **compare w/ old studies**
  Ø Ca → ↑ likelihood malignant; laminated → granuloma; "popcorn" → hamartoma
- High-risk features for malig: size (eg, ≥2.3 cm diameter), spiculated, upper lobe, ♀, >60 yo, >1 ppd current smoker, no prior smoking cessation (*NEJM* 2003;348:2535 & 2013;369:910)

Diagnostic studies

- **PET:** detects metab. activity of tumors, 97% Se & 78% Sp for malig (esp if >8 mm). Useful for deciding which lesions to bx vs. serial CT & for surgical staging b/c may detect mets.
- **Transthoracic needle biopsy** (TTNB): if tech feasible, 97% will obtain definitive tissue dx
- **Video-assisted thoracoscopic surgery** (VATS): for percutaneously inaccessible lesions; highly sensitive and allows resection

- **Transbronchial bx** (TBB): most lesions too small to sample w/o endobronchial U/S; bronch w/ brushings low-yield unless invading bronchus; navigational bronch 70% yield
- PPD, fungal serologies, ANCA

Management (*JAMA* 2022;327:264)

- **Low risk** (<5%): serial CT (freq depending on risk); shared decision w/ Pt re: bx
- **High risk** (and surgical candidate): TBB, TTNB, or VATS → lobectomy if malignant
- **Subsolid nodules:** longer f/u (b/c if malignant can be slow-growing) & PET

Follow-up Imaging for Solid Nodules (*Radiographics* 2018;38:1337)

#	Pt Risk	Nodule <6 mm	Nodule 6–8 mm	Nodule >8 mm
Single	Low	No routine f/u	CT at 6–12 mo, consider at 18–24 mo	CT at 3 mo, consider PET/CT or bx
	High	CT at 12 mo?	CT at 6-12 & 18-24 mo	
Multi	Low	No routine f/u	CT at 3–6 mo, consider at 18–24 mo	CT at 3–6 mo, consider at 18–24 mo
	High	CT at 12 mo?	CT at 3–6 & 18–24 mo	CT at 3–6 & 18–24 mo

HEMOPTYSIS

Definition and pathophysiology

- Expectoration of blood or blood-streaked sputum
- **Massive hemoptysis:** >100 mL/h or >500 mL in 24 h; massive hemoptysis usually from tortuous or invaded bronchial arteries

Etiologies (*Crit Care Med* 2000;28:1642)	
Infection/Inflammation	**Bronchitis** (most common cause of trivial hemoptysis) **Bronchiectasis** incl **CF** (common cause of massive hemoptysis) TB or aspergilloma (can be massive); pneumonia or lung abscess
Neoplasm	Usually primary **lung cancer**, sometimes metastasis (can be massive)
Cardiovasc	**PE** (can be massive), pulmonary artery rupture (2° to instrumentation), CHF, mitral stenosis, trauma/foreign body, bronchovascular fistula
Other	**Vasculitis** (GPA, anti-GBM, Behçet's, SLE), AVM, anticoag (w/underlying lung disease), coagulopathy, cocaine, pulm hemosiderosis

Diagnostic workup

- Localize bleeding site (r/o *GI or ENT source* by H&P ± endo); determine whether **unilateral or bilateral, localized or diffuse, parenchymal or airway** by CXR/chest CT ± bronch
- PT, PTT, CBC to rule out **coagulopathy**
- Sputum culture/stain for bacteria, fungi and AFB; cytology to **r/o malignancy**
- ANCA, anti-GBM, ANA, urinalysis to ✓ for **vasculitis** or **pulmonary-renal syndrome**

Treatment

- **Death is from asphyxiation not exsanguination**; maintain gas exchange, reverse coagulopathy and Rx underlying condition; cough suppressant may ↑ risk of asphyxiation
- Inhaled tranexamic acid promising (*Chest* 2018;154:1379)

- Massive hemoptysis: **put bleeding side dependent;** selectively intubate nl lung if needed
  Angiography: Dx & Rx (vascular occlusion balloons or **selective embol of bronchial art**)
  Rigid bronch: allows more options (electrocautery, laser) than flexible bronch
  Surgical resection

BRONCHIECTASIS

Definition and epidemiology (*NEJM* 2002;346:1383)

- Obstructive airways disease of bronchi and bronchioles, chronic transmural inflammation w/ airway dilatation and thickening, collapsibility, mucus plugging w/ impaired clearance

Initial workup

- H&P: cough, dyspnea, copious sputum production, ±hemoptysis, inspiratory "squeaks"
- CXR: scattered or focal; rings of bronchial cuffing; "tram track" of dilated, thick airways
- PFTs: obstructive; chest CT: airway dilation & thickening ± cystic Δs, infiltrates, adenopathy

Etiology	Other Features	Evaluation
Chronic infxns (eg, MTb, ABPA)	Chronic cough, freq/persist infiltrate, refract asthma (ABPA)	Sputum cx (incl mycobact, fungal), ± bronch/BAL, IgE & eos (ABPA)
1° ciliary dyskin	Sinusitis, infertility, otitis	Dynein mutations
Immunodefic	Recurrent infxns often as child	IgA, IgG, IgM, IgG subclasses
RA, Sjogren, ANCA	Resp sx may precede joint sx	RF, CCP, SS-A, SS-B, ANCA
IBD	Not relieved by bowel resection	Colonoscopy, biopsy
α_1-AT deficiency	Lower lobe emphysema	α_1-AT level and genotype
Anatomic	R middle lobe synd. from sharp takeoff, foreign body aspiration	Bronchoscopy

Treatment

- Acute exacerbations: antibiotics directed against prior pathogens; if no prior Cx data → FQ
- Chronic mgmt: treat underlying condition, chest PT, inhaled hypertonic saline, bronchodil.; prophylactic azithro shown to ↓ exacerb in non-CF bronchiectasis (*JAMA* 2013:1251)

- Airway clearance: guaifenesin, instrumental devices (eg, Aerobika, Acapella), chest PT

Non-tuberculous mycobacterium (NTM; eg, MAC, ***Mycobacterium kansaii***)

- Chronic cough, ↓ wt; Lady Windermere syndrome: R middle lobe and lingula bronchiectasis in elderly ♀ who suppress expectoration
- Dx: CT scan (tree-in-bud, nodules, cavities, bronchiect.), sputum ×3 or BAL, AFB stain + Cx
- Treatment: susceptibility-based Rx pref over empiric Rx w/ [azithro or clarithro] + rifamycin & ethambutol for ≥12 mo (*CID* 2020;71:e1)

CYSTIC FIBROSIS

Definition and pathophysiology (*NEJM* 2015;372:351)

- Autosomal recessive genetic disorder due to mutations in chloride channel (CFTR gene)
- ↑ mucus thickness, ↓ mucociliary clearance, ↑ infections → bronchiectasis

Clinical features

- Recurrent PNA, sinus infections
- Distal intestinal obstruction syndrome (DIOS), pancreatic insufficiency (steatorrhea, malabsorption, failure to thrive, weight loss), CF-related diabetes, infertility

Treatment (*Lancet* 2021;397:2195)

- Acute exacerbations: may be assoc w/ persistent drop in FEV_1 (*AJRCCM* 2010;182:627); continue aggressive airway clearance, target abx based on sputum cx (incl double coverage for PsA); common pathogens include PsA, *S. aureus*, non-typeable *H. flu*, *Stenotrophomonas*, *Burkholderia*, NTM
- Chronic mgmt: airway clearance with chest PT, inhaled hypertonic saline, inhaled DNAse (dornase alfa), SABA; oral azithromycin if chronic respiratory symptoms, inhaled tobramycin or aztreonam if persistent PsA infection
- CFTR potentiator (ivacaftor) or corrector (lumacaftor, tezacaftor) depending on mutation; combo (elexacaftor+tezacaftor+ivacaftor) if homozygous for ΔF508 (*Lancet* 2019;394:1940)
- Lung transplantation; refer to lung transplant center when FEV_1 <30% predicted, rapidly declining FEV_1, 6MWT <400 m, evidence of PHT, significant clinical decline

INTERSTITIAL LUNG DISEASE

WORKUP OF ILD (*Thorax* 2008;63:v1)

May present as incidental finding, subacute dyspnea, or rapidly progressive hypox. resp fail.

Broad categories

- (1) **Sarcoid;** (2) **Exposures** (eg, drugs, XRT, organic & inorganic dusts, vaping);
- (3) **Collagen vasc dis** (eg, scleroderma, ANCA, myositis, RA); (4) **Idiopathic PNAs** (qv)

Rule out mimickers of ILD

- **Congestive heart failure** (✓ BNP, trial of diuresis); **infection:** viral, atypical bacterial; **malignancy:** lymphangitic carcinomatosis, bronchoalveolar, leukemia, lymphoma

History and physical exam

- Occupational, exposures (eg, birds), tobacco, meds, XRT, FHx, precipitating event
- Tempo (acute → infxn, CHF, hypersens pneumonitis, eos PNA, AIP, COP, drug-induced)
- Extrapulm signs/sx (skin Δs, arthralgias, arthritis, myalgias, sicca sx, alopecia, Raynaud's)

Diagnostic studies (see Appendix & Radiology inserts)

- CXR and **high-resolution chest CT**
  - Upper lobe predom: hypersensitivty, coal, silica, smoking-related, sarcoidosis, Langerhan's
  - Lower lobe predom: NSIP, UIP, asbestosis
  - Adenopathy: malignancy, sarcoidosis, berylliosis, silicosis
  - Pleural disease: collagen-vascular diseases, asbestosis, infections, XRT

- PFTs: ↓ D_LCO (*early sign*), restrictive pattern (↓ volumes), ↓ P_aO_2 (esp. w/ exercise);
  If restrictive + obstructive, consider sarcoid
  If combined pulmonary fibrosis and emphysema (CFPE) → near-nl lung vol on PFTs
- Serologies: ✓ ACE, ANA, RF, RNP, ANCA, CCP, SSA/SSB, Scl 70, CK, aldolase, myositis panel
- Bronchoalveolar lavage: in select cases if suspect superimposed infection, hemorrhage, eosinophilic syndromes
- Bx (transbronch w/ or w/o cryo vs. VATS depending on location) if unclear etiology

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SPECIFIC ETIOLOGIES OF ILD

Sarcoidosis (*AJRCCM* 2020;201:e26; *JAMA* 2022;327:856)

- Prevalence: African Americans, northern Europeans, and females; onset in 3rd-5th decade
- Pathophysiology: depression of cellular immune system peripherally, activation centrally

Clinical Manifestations of Sarcoidosis	
Organ System	**Manifestations**
Pulmonary	Hilar LAN; fibrosis; pulm hypertension. Stages: I = bilat hilar LAN; II = LAN + ILD; III = ILD only; IV = diffuse fibrosis.
Cutaneous (~15%)	Waxy skin plaques; lupus pernio (violaceous facial lesions) Erythema nodosum (red tender nodules due to panniculitis, typically on shins). Ddx: idiopathic (34%), infxn (33%, strep, TB), sarcoid (22%), drugs (OCP, PCNs), vasculitis (Behçet's), IBD, lymphoma.
Ocular (10–30%)	Anterior >posterior uveitis; ↑ lacrimal gland
Endo & renal (10%)	Nephrolithiasis, hypercalcemia (10%), hypercalciuria (40%) Due to vitamin D hydroxylation by macrophages
Neuro (10% clin, 25% path)	CN VII palsy, periph neuropathies, CNS lesions, seizures
Cardiac (5% clin, 25% path)	Conduction block, VT, CMP
Liver, spleen, BM	Granulomatous hepatitis (25%), splenic & BM gran. (50%)
Constitutional	Fever, night sweats, anorexia & wt loss (a/w hepatic path)
Musculoskeletal	Arthralgias, periarticular swelling, bone cysts

- *Löfgren's syndrome:* erythema nodosum + hilar adenopathy + arthritis (good prognosis)
- Diagnostic studies: **LN bx → noncaseating granulomas** + multinucleated giant cells Endobronchial ultrasonography superior to conventional bronch (*JAMA* 2013;309:2457) ^{18}FDG PET can be used to identify extent and potentially targets for dx bx ↑ **ACE** (Se 60%, 90% w/ active dis., Sp 80%, false ⊕ in granulomatous diseases)
- To assess extent: CXR, PFTs, full ophtho exam, ECG, CBC (lymphopenia, ↑ eos), Ca, LFTs; ± Holter, echo, cardiac MRI, brain MRI, etc., based on s/s
- Rx: **steroids** if sx or extrathoracic organ dysfxn (eg, prednisone 20–40 mg/d), improves sx, but doesn't Δ long-term course; hydroxychloroquine for extensive skin disease; MTX, AZA, mycophenolate, or anti-TNF for chronic/refractory disease
- Prognosis: ~$^{2}/_{3}$ spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon; ~$^{1}/_{3}$ have progressive disease

Exposure

- **Drugs/latrogenic**

  Amiodarone: interstitial pneumonitis ↔ org. PNA ↔ ARDS; Rx: d/c amio; steroids

  Other drugs: nitrofurantoin, sulfonamides, inh, hydralazine

  Chemo: bleomycin, busulfan, cyclophosphamide, MTX, immunotherapy, XRT
- **Pneumoconioses** (inorganic dusts) (*NEJM* 2000;342:406; *Clin Chest Med* 2004;25:467)

  Coal worker's: upper lobe coal macules; may progress to massive fibrosis

  Silicosis: upper lobe opacities ± eggshell calcification of lymph nodes; ↑ risk of TB

  Asbestosis: lower lobe fibrosis, calcified pleural plaques, DOE, dry cough, rales on exam. Asbestos exposure → pleural plaques, benign pleural effusion, diffuse pleural thickening, rounded atelectasis, mesothelioma, lung Ca (esp. in smokers)

  Berylliosis: multisystemic granulomatous disease that mimics sarcoidosis

- **Hypersensitivity pneumonitides** (organic dusts): loose, noncaseating *granulomas*
  Antigens: farmer's lung (spores of thermophilic actinomyces); bird fancier's lung (proteins from feathers and excreta of birds or down); humidifier lung (thermophilic bacteria)

Collagen vascular diseases (*Chest* 2013;143:814)

- **Rheumatologic disease**
  Scleroderma: ILD in ~50%; PHT seen in ~10% of Pts with limited disease
  PM-DM: ILD & skin/muscle findings; MCTD: PHT & fibrosis; Sjogren's: ILD & sicca sx
  SLE & RA: pleuritis and pleural effusions more often than ILD; SLE can cause DAH
- **Vasculitis** (can p/w *DAH*)
  Granulomatosis w/ polyangiitis (GPA): ⊕ c-ANCA w/ necrotizing granulomas
  Eosinophilic GPA (EGPA): ⊕ c- or p-ANCA w/ eosinophilia & necrotizing granulomas
  Microscopic polyangiitis: ⊕ p-ANCA w/o granulomas
- **Goodpasture's syndrome** = DAH + RPGN; typically in smokers; ⊕ anti-GBM in 90%
- **Lymphangioleiomyomatosis** (LAM): cystic, ↑ in ♀, Rx w/ sirolimus (*NEJM* 2011;364:1595)

Idiopathic interstitial pneumonias (IIPs) (*AJRCCM* 2013;188:733)

- Definition: **ILD of unknown cause;** dx by radiographic, histologic, and clinical features

IIPs		
Type	**Imaging/Histology**	**Clinical**
IPF	UIP imaging pattern: reticular opacities, honeycombing, traction bronchiectasis; peripheral, subpleural, & basal	Sx >12 mo 5-y mort ~80%
NSIP	Homogenous ground-glass opacities or consolid., reticular irreg lines; subpleural sparing; symmetric, peripheral, basal. Cellular & fibrotic subtypes.	Sx mos–y 5-y mort 10%
COP	Patchy, migratory consolidations; subpleural & peribronchial. Excessive proliferation of granulation tissue in small airways and alveolar ducts.	Post-infxn, XRT, rxn to drug. 5-y mort <5%

IIPs		
AIP	Diffuse ground-glass opacities, consolidations w/ lobular sparing. Path/imaging similar to DAD (diffuse, bilateral, central>periph ground glass or consolidative opacities).	Sx <3 wk 6-mo mort 60%
DIP	Diffuse ground-glass opacities, reticular lines; lower zones. Peripheral macrophage in alveoli.	30–50 yo *smokers* Sx wks–mos Death rare
RB-ILD	Bronchial thickening, centrilobular nodules, patchy ground-glass opacities; upper lobe predom. Mϕ in alveoli.	

UIP, usual interstitial PNA (IP); IPF, idiopathic pulm fibrosis; NSIP, nonspecific IP; COP, cryptogenic organizing PNA; AIP, acute IP (Hamman-Rich syndrome); DIP, desquamative IP; RB-ILD, resp bronchiolitis-assoc ILD.

- Rx for IPF: suppl O_2, pulm rehab, Rx for GERD, PHT screening, lung tx referral;
  pirfenidone (antifibrotic) or **nintedanib** (tyrosine kinase inhib mediating fibrogenic growth factors) ↓ rate of FVC decline (*Lancet* 2021;398:1450)
  high-dose steroids may be used for acute exacerbations, but no RCT data
- Steroids for other IIPs: NSIP (esp. cellular type) and COP (*AJRCCM* 2000;162:571); ? benefit for AIP and DIP/RB-ILD (for which Pts should stop smoking)

Pulmonary infiltrates w/ eosinophilia (PIE) = eos on BAL é peripheral blood

- **Allergic bronchopulmonary aspergillosis (ABPA)**
- EGPA
- Löffler's syndrome: parasites/drugs → transient pulm infilt + cough, fever, dyspnea, eos
- Acute eosinophilic PNA (AEP): acute hypox febrile illness; Rx: steroids, tobacco cessation
- Chronic eosinophilic pneumonia (CEP): "photonegative" of CHF, typically in women

Miscellaneous

- Pulm alveolar proteinosis (PAP): accumulation of surfactant-like phospholipids; white & gummy sputum; BAL milky fluid (*NEJM* 2003;349:2527); Rx w/ lung lavage & GMCSF

- Langerhans cell granulomatosis (LCG): young ♂ smokers; apical cysts; PTX (25%)

PLEURAL EFFUSION

Pathophysiology

- **Systemic factors** (eg, ↑ PCWP, ↓ oncotic pressure) → *transudative* effusion
- **Local factors** (ie, Δ pleural surface permeability) → *exudative* effusion

Transudates

- **Congestive heart failure** (**40%**): 80% bilateral, ± cardiomegaly on CXR occasionally exudative (especially after aggressive diuresis or if chronic)
- **Constrictive pericarditis** (knock on exam, calcification or thickening on imaging)
- **Cirrhosis** ("hepatic hydrothorax"): diaphragmatic pores allow passage of ascitic fluid often right-sided (²/₃) & massive (even w/o marked ascites)
- Nephrotic syndrome: usually small, bilateral, asymptomatic (r/o PE b/c hypercoag)
- Other: PE (usually exudate), malignancy (lymphatic obstruction), myxedema, CAPD

Exudates

- **Lung parenchymal infection (25%)**
  - Bacterial (parapneumonic): can evolve along spectrum of *exudative* (but sterile) → *fibropurulent* (infected fluid) → *organization* (fibrosis & formation of rigid pleural peel). Common causes: *Strep pneumo, Staph aureus, Strep milleri, Klebsiella, Pseudomonas, Haemophilus, Bacteroides, Peptostreptococcus*, mixed flora in aspiration pneumonia.
  - Mycobacterial: >50% lymphs 80% of the time, ADA >40, pleural bx ~70% Se
  - Fungal, viral (usually small), parasitic (eg, amebiasis, echinococcosis, paragonimiasis)

- **Malignancy** (**15%**): primary lung cancer most common, metastases (esp. breast, lymphoma, etc.), mesothelioma (✓ serum osteopontin levels; *NEJM* 2005;353:15)
- **Pulmonary embolism** (**10%**): effusions in ~40% of PEs; exudate (75%) >transudate (25%); hemorrhagic—*must have high suspicion b/c presentation highly variable*
- **Collagen vascular disease:** RA (large), SLE (small), GPA, EGPA
- **Abdominal diseases:** pancreatitis, cholecystitis, esophageal rupture, abdominal abscess
- Hemothorax (Hct_{eff}/Hct_{blood} >50%): trauma, PE, malignancy, coagulopathy, leaking aortic aneurysm, aortic dissection, pulmonary vascular malformation
- Chylothorax (triglycerides >110): thoracic duct damage due to trauma, malignancy, LAM
- Other:
  - Post-CABG: left-sided; initially bloody, clears after several wks
  - Dressler's syndrome (pericarditis & pleuritis post-MI), uremia, post-radiation therapy
  - Asbestos exposure: benign; ⊕ eosinophils
  - Drug-induced (eg, nitrofurantoin, methysergide, bromocriptine, amiodarone): ⊕ eos
  - Uremia; post-XRT; sarcoidosis
  - Meigs' syndrome: benign ovarian tumor → ascites & pleural effusion
  - Yellow-nail syndrome: yellow nails, lymphedema, pleural effusion, bronchiectasis

Diagnostic studies (*NEJM* 2018;378:740)

- **Thoracentesis** (ideally U/S guided) (*NEJM* 2006;355:e16)
  - *Indications:* **all effusions >1 cm in decubitus view**
    - if suspect due to CHF, can diurese and see if effusions resolve (75% do so in 48 h); *asymmetry, fever*, *chest pain or failure to resolve* → thoracentesis
    - **parapneumonic effusions should be tapped ASAP** (*cannot* exclude infxn clinically)
  - *Diagnostic studies:* ✓ total protein, LDH, glucose, cell count w/ differential, Gram stain & culture, pH; remaining fluid for additional studies as dictated by clinical scenario

Complications: PTX (5–10%), hemothorax (~1%), re-expansion pulm edema (if >1.5 L removed), spleen/liver lac.; post-tap CXR not routinely needed (*Annals* 1996;124:816)

↓ PTX w/ U/S and experienced supervisor; even with INR ~1.9, on DOAC, or on clopi, risk of bleed low w/ U/S & experienced operator (*Mayo* 2019;94:1535)

- **Transudate vs. exudate** (*JAMA* 2014;311:2422)

  Light's criteria: exudate = TP_{eff}/TP_{serum} >0.5 *or* LDH_{eff}/LDH_{serum} >0.6 *or* LDH_{eff} >⅔ ULN of LDH_{serum}; 97% Se, 85% Sp; best Se of all methods; however, will misidentify 25% of transudates as exudates; ∴ if clinically suspect transudate but meets criterion for exudate, confirm w/ test w/ higher Sp

  Exudative criteria w/ better Sp: $chol_{eff}$ >55 mg/dL (95–99% Sp); $chol_{eff}$ >45 mg/dL *and* LDH_{eff} >200 (98% Sp); $chol_{eff}/chol_{serum}$ >0.3 (94% Sp); serum-effusion alb gradient ≤1.2 (92% Sp); serum-effusion TP gradient ≤3.1 (91% Sp)

  CHF effusions: *TP may* ↑ *with diuresis or chronicity* → "pseudoexudate"; alb gradient ≤1.2, $chol_{eff}$ >60 mg/dL (Se 54%, Sp 92%) or clin judgment to distinguish (*Chest* 2002;122:1524)

- **Complicated vs. uncomplicated parapneumonic** (*Chest* 1995;108:299)

  complicated = ⊕ Gram stain or culture *or* pH <7.2 *or* glucose <60

  complicated parapneumonic effusions usually require tube thoracostomy for resolution

  empyema = frank pus, also needs tube thoracostomy (*J Thorac CV Surg* 2017;153:e129)

- Additional pleural fluid studies (*NEJM* 2002;346:1971)

  NT-proBNP ≥1500 pg/mL has 91% Se & 93% Sp for CHF (*Am J Med* 2004;116:417)

  WBC & diff.: exudates tend to have ↑ WBC vs. transudates but nonspecific neutrophils → parapneumonic, PE, pancreatitis lymphocytes (>50%) → cancer, TB, rheumatologic eos (>10%) → blood, air, drug rxn, asbestos, paragonimiasis, Churg-Strauss, PE

  RBC: Hct_{eff} 1–20% → cancer, PE, trauma; Hct_{eff}/Hct_{blood} >50% → hemothorax

  AFB: yield in TB 0–10% w/ stain, 11–50% w/ culture, ~70% w/ pleural bx

adenosine deaminase (ADA): seen w/ granulomas, >70 suggests TB, <40 excludes TB

cytology: ideally ≥150 mL and at least 60 mL should be obtained (*Chest* 2010;137:68)

glucose: <60 mg/dL → malignancy, infection, RA

amylase: seen in pancreatic disease and esophageal rupture (salivary amylase)

rheumatoid factor, C_H50, ANA: *limited utility* in dx collagen vascular disease

triglycerides: >110 → chylothorax, 50–110 → ✓ lipoprotein analysis for chylomicrons

cholesterol: >60; seen in chronic effusions (eg, CHF, RA, old TB)

creatinine: effusion/serum ratio >1 → urinothorax

fibulin-3: ↑ plasma and/or effusion levels → mesothelioma (*NEJM* 2012;367:1417)

- Chest CT; pleural biopsy; VATS
- Undiagnosed persistent pleural effusions (*Clin Chest Med* 2006;27:309)

Transudative: most commonly CHF or hepatic hydrothorax. ✓ s/s CHF or cirrhosis, NT-proBNP$_{eff}$; consider intraperitoneal injection of technetium-99m sulfur colloid

Exudative (ensure using Sp test listed above): most commonly malig, empyema, TB, PE. ✓ s/s malig, chest CT (I^+), ADA or IFN-γ release assay; consider thoracoscopy.

Characteristics of Pleural Fluid (not diagnostic criteria)						
Etiology	**Appear**	**WBC diff**	**RBC**	**pH**	**Glc**	**Comments**
CHF	clear, straw	<1000 *lymphs*	<5000	normal	≈ serum	bilateral, cardiomegaly
Cirrhosis	clear, straw	<1000	<5000	normal	≈ serum	right-sided
Uncomplicated parapneumonic	turbid	5–40,000 *polys*	<5000	normal to ↓	≈ serum (>40)	
Complicated parapneumonic	turbid to purulent	5–40,000 *polys*	<5000	↓↓	↓↓ (<40)	need drainage
Empyema	purulent	25–100,000 *polys*	<5000	↓↓↓	↓↓	need drainage
Tuberculosis	serosang.	5–10,000 *lymphs*	<10,000	normal to ↓	normal to ↓	⊕ AFB ⊕ ADA
Malignancy	turbid to bloody	1–100,000 *lymphs*	<100,000	normal to ↓	normal to ↓	⊕ cytology
Pulmonary embolism	*sometimes* bloody	1–50,000 *polys*	<100,000	normal	≈ serum	no infarct → transudate
Rheumatoid arthritis/SLE	turbid	1–20,000 *variable*	<1000	↓	RA ↓↓↓ SLE nl	↑ RF, ↓ C_H50 ↑ imm. complex
Pancreatitis	serosang. to turbid	1–50,000 *polys*	<10,000	normal	≈ serum	left-sided, ↑ amylase
Esophageal rupture	turbid to purulent	<5000 >50,000	<10,000	↓↓↓	↓↓	left-sided, ↑ amylase

Treatment

- Symptomatic effusion: therapeutic thoracentesis, treat underlying disease process
- Parapneumonic effusion (*Chest 2000;*118*:*1158)
  - uncomplicated → antibiotics for pneumonia
  - >½ **hemithorax *or* complicated *or* empyema → tube thoracostomy** (otherwise risk of organization and subsequent need for surgical decortication)
  - loculated → tube thoracostomy or VATS; intrapleural t-PA + DNase ↓ need for surgery
- Malignant effusion: serial thoracenteses vs. tube thoracostomy + pleurodesis (success rate ~80–90%) vs. indwelling pleural catheter, which ↓ hosp days but ↑ adverse events (*JAMA* 2017;318:1903); systemic steroids & pH <7.2 a/w ↑ pleurodesis failure rate

- TB effusions: effusion will often resolve spontaneously; however, treat Pt for active TB
- Hepatic hydrothorax
  - Rx: Δ pressure gradient (ie, ↓ ascitic fluid volume, NIPPV)
  - avoid chest tubes; prn thoracenteses, pleurodesis, TIPS or VATS closure of diaphragmatic defects if medical Rx fails; NIPPV for acute short-term management
  - spontaneous bacterial empyema (SBEM) can occur (even w/o SBP being present), ∴ thoracentesis if suspect infection
  - transplant is definitive treatment and workup should begin immediately

VENOUS THROMBOEMBOLISM (VTE)

Definitions

- Superficial thrombophlebitis: pain, tenderness, erythema along superficial vein
- Deep venous thrombosis (DVT): ***Proximal*** = thrombosis of iliac, femoral, or popliteal veins (nb, "superficial" femoral vein part of deep venous system). ***Distal*** = calf veins below knee; lower risk of PE/death than proximal (*Thromb Haem* 2009;102:493).
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1000 person y; 250,000/y (*Archives* 2003;163:1711)

Risk factors

- Virchow's triad for thrombogenesis. **Stasis:** bed rest, inactivity, CHF, CVA w/in 3 mo, air travel >6 h. **Injury to endothelium:** trauma, surgery, prior DVT, inflam, central catheter.
  Thrombophilia: genetic disorders (qv), HIT, OCP, HRT, tamoxifen, raloxifene.
- Malignancy (12% of "idiopathic" DVT/PE; *Circ* 2013;128:2614)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Obesity, smoking, acute infection, postpartum (*JAMA* 1997;277:642; *Circ* 2012;125:2092)

Thromboprophylaxis (*Blood Adv* 2018;2:3198)	
Patient & Situation	**Prophylaxis**
Low-risk med; same-day surg & <40 y	Early, aggressive ambulation ± mechanical
Moderate-risk (hosp., ≥1 risk factor) or high-risk medical (hosp., ICU, cancer, stroke)	**LMWH** or **UFH** (if renal failure) or fonda (if HIT ⊕). Pharmacologic favored vs. mechanical, but may personalize based on bleeding & thrombotic risk.
Low-risk surgery (minor surgery)	Mechanical Ppx

Thromboprophylaxis (*Blood Adv* 2018;2:3198)	
Moderate-risk surgery (eg, major surgery, trauma, immobilization)	If low bleeding risk: **LMWH** or **UFH** SC If high bleeding risk: **mech Ppx**
High-risk nonorthopedic surgery (multiple risk factors), stroke or ICH	**[LMWH** or **UFH** SC**] + mech**. Stroke s/p lytic or ICH: mech 24 h or until bleed stable, then + pharm.
Ortho surgery (cont pharmacoRx up to 35 d [hip] or 10–14 d [knee])	**LMWH** or **DOAC** (or fonda, UFH, or warfarin [INR 2–3]) **+ mech Ppx.**

UFH: 5000 U SC bid or tid. Enox: 30 mg bid for highest risk or 40 mg qd for moderate risk or spinal/epidural anesthesia. For riva 10 mg/d, apixa 2.5 mg/d, edox 30 mg/d, dabi 110 mg post-op and then 220 mg/d.

Clinical manifestations—DVT

- Calf pain, swelling (>3 cm c/w unaffected side), venous distention, erythema, warmth, tenderness, palpable cord, ⊕ Homan's sign (calf pain on dorsiflexion, seen in <5%)
- 50% of Pts with sx DVT have asx PE
- Popliteal (Baker's) cyst: may lead to DVT due to compression of popliteal vein

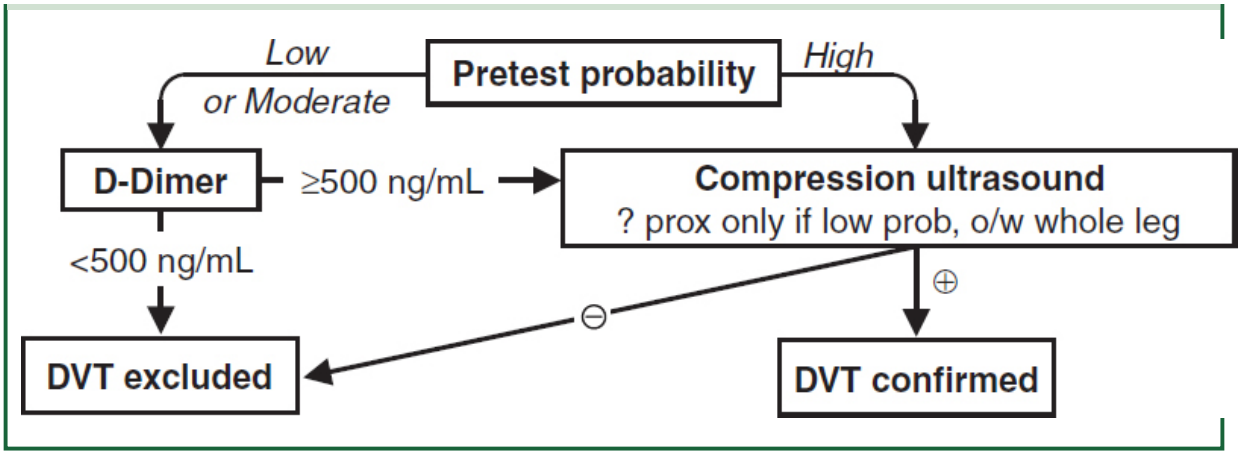
"Simplified Wells" Pretest Probability Scoring of DVT (*JAMA* 2006;295:199)		
+1 point each for: active cancer (Rx ongoing or w/in 6 mo or palliative); paralysis, paresis, or recent immobilization of lower extremities; recently bedridden for ≥3 d or major surgery w/in 12 wk; localized tenderness along distribution of deep venous system; entire leg swelling; calf ≥3 cm larger than asx calf (at 10 cm below tibial tuberosity); pitting edema confined to sx leg; collateral superficial veins (nonvaricose); previous DVT –2 points if alternative dx at least as likely as DVT		
Pretest Probability Assessment (useful if outPt, less so if inPt; *JAMA IM* 2015;175:1112)		
Score ≤0	Score 1 or 2	Score ≥3
Low probability (5%)	Moderate probability (17%)	High probability (53%)

- For UE DVT, +1 point each for venous cath, local pain, & unilateral edema, –1 if alternative dx. ≤1 = unlikely; ≥2 = likely. U/S if likely or if unlikely but abnl D-dimer (*Annals* 2014;160:451)

Diagnostic studies—DVT

- D-dimer: <500 helps r/o; ? use 1000 as threshold if low risk (*Annals* 2013;158:93)
- Compression U/S >95% Se & Sp for sx DVT (lower if asx); survey whole leg if ≥ mod prob

Figure 2-3 Approach to suspected DVT



Clinical manifestations—PE

- Dyspnea (~50%), pleuritic chest pain (~40%), cough (~23%), hemoptysis (~8%)
- ↑ RR (>70%), crackles (51%), ↑ HR (30%), fever, cyanosis, pleural friction rub, loud P_2
- *Massive:* syncope, HoTN, PEA; ↑ JVP, R-sided S_3, Graham Steell (PR) murmur

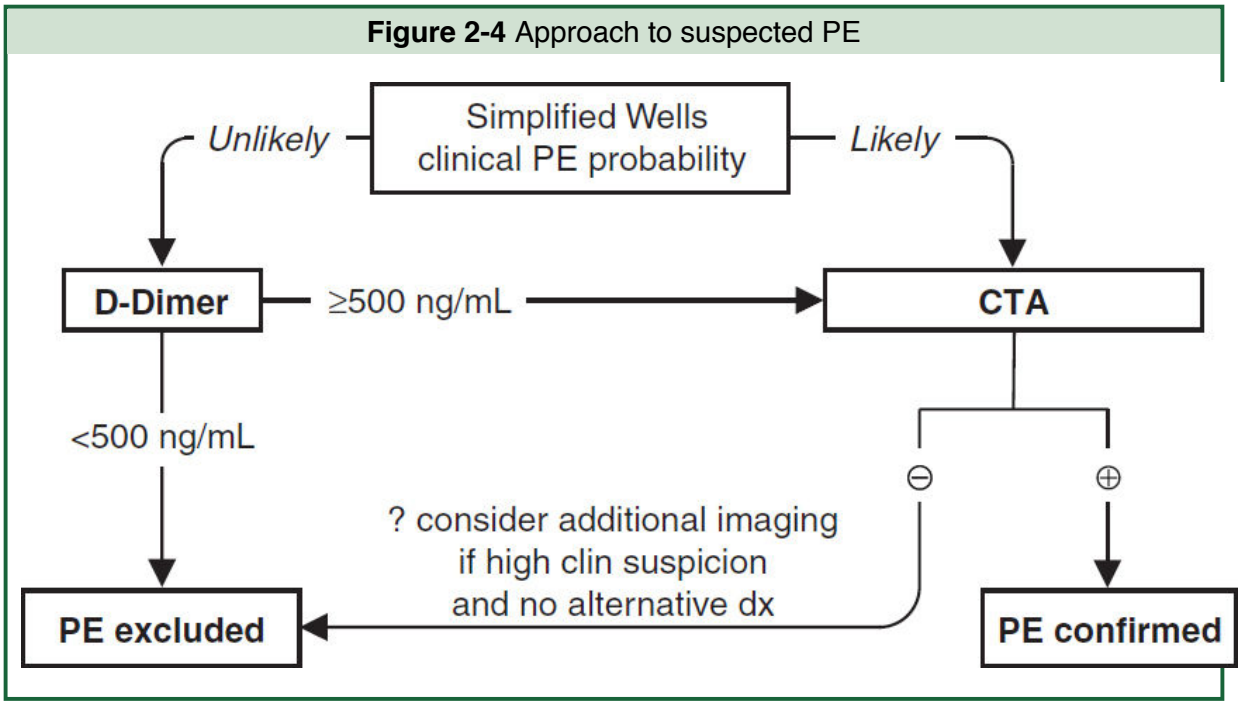
Modified Wells Pretest Probability Scoring for PE (*Annals* 2011;154:709)	
• Prior PE or DVT=1.5 points • Active cancer =1.0 • Immobilization (bed rest ≥3 d) or surgery w/in 4 wk=1.5 • Alternative dx less likely than PE=3	• Clinical signs of DVT=3 • HR >100 bpm=1.5 • Hemoptysis=1.0
Simplified Wells Probability Assessment	
≤4 = "Unlikely" (13% probability)	>4 "Likely" (39% probability)

Diagnostic studies—PE (*EHJ* 2014;35:3033)

- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, $S_IQ_{III}T_{III}$ & TWI V_1–V_4 (McGinn-White pattern; *Chest* 1997;111:537)
- ABG: hypoxemia, hypocapnia, respiratory alkalosis, ↑ A-a gradient (*Chest* 1996;109:78) 18% w/ room air P_aO_2 85–105 mmHg, 6% w/ nl A-a gradient (*Chest* 1991;100:598)

- D-dimer: high Se, poor Sp (~25%); ELISA has >99% NPV ∴ use to r/o PE if "unlikely" pretest prob (*JAMA* 2006;295:172); cut-off 500 if <50 y, 10× age if ≥ 50 y (*JAMA* 2014;311:1117)
- Echocardiography: useful for risk stratification (RV dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (~98%), low Sp (~10%). Sp improves to 97% for high-prob VQ. Use if pretest prob of PE high and CT not available or contraindicated. Can also exclude PE if low pretest prob, low-prob VQ, but 4% false (*JAMA* 1990;263:2753).
- **CT angiography** (CTA; see Radiology inserts; *JAMA* 2015;314:74): Se ~90% & Sp ~95%; PPV & NPV >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant (∴ need to consider both); ~1/4 of single & subseg may be false ⊕; CT may also provide other dx
- Lower extremity compression U/S shows DVT in ~9%, sparing CTA

Figure 2-4 Approach to suspected PE



Workup for idiopathic VTE (*NEJM* 2015;373:697)

- **Thrombophilia workup:** ✓ if ⊕ FH; may be helpful but consider timing as thrombus, heparin and warfarin Δ results. Useful for relatives, if dx APLAS (given requires warfarin), or if not planning lifelong anticoagulation for Pt.

- **Malignancy workup:** 12% Pts w/ "idiopathic" DVT/PE will have malignancy; age-appropriate screening adequate; avoid extensive w/u

Risk stratification for Pts with PE

- **Clinical**: Simplified PE Severity Index (sPESI) risk factors include age >80 y; h/o cancer; h/o cardiopulm. disease; HR ≥110; SBP <100; S_aO_2 <90%
- **Imaging**: TTE for RV dysfxn; CTA for RV/LV dimension ratio >0.9. **Biomarker**: Tn & BNP.
- **Classification** (*EHJ* 2020;41:543)
  - **High risk ("massive")**: hemodyn unstable w/ arrest, obstructive shock, or persistent HoTN
  - **Intermediate risk ("submassive")**: sPESI ≥1
    "Intermediate-high" if *both* RV dysfunction & elevated Tn
    "Intermediate-low" if *either* or *neither* RV dysfunction or elevated Tn
  - **Low risk**: clinically stable, sPESI = 0, normal RV function, normal Tn

Whom to treat (*JAMA* 2020;324:1765; *Chest* 2021;160:e545)

- **Superficial venous thrombosis:** elevate extremity, warm compresses, compression stockings, NSAIDs for sx. *Anticoag* if high risk for DVT (eg, ≥5 cm, proximity to deep vein ≤5 cm, other risk factors) for 4 wk as ~10% have VTE w/in 3 mo (*Annals* 2010;152:218).
- **LE DVT:** proximal → anticoag; distal → anticoag if severe sx, o/w consider serial imaging over 2 wk and anticoag if extends (although if bleeding risk low, many would anticoag).
- **UE DVT:** anticoagulate (same guidelines as LE; *NEJM* 2011;364:861). If catheter-associated, need not remove if catheter functional and ongoing need for catheter.
- **PE:** anticoagulate (unless isolated subsegmental and risk for recurrent VTE low)

Initial anticoagulation options (*EHJ* 2020;41:543; *Chest* 2021;160:e545)

- *Initiate immediately if high or intermed suspicion but dx test results will take ≥4 h*
- Either (a) initial parenteral → long-term oral or (b) solely DOAC if no interven. planned

- **LMWH** (eg, enoxaparin 1 mg/kg SC bid *or* dalteparin 200 IU/kg SC qd)
  Preferred over UFH (especially in *cancer*) except: renal failure (CrCl <25), ? extreme obesity, hemodynamic instability or bleed risk (*Cochrane* 2004;CD001100)
- **IV UFH:** 80 U/kg bolus → 18 U/kg/h → titrate to PTT 1.5–2.3 × cntl (eg, 60–85 sec); preferred option when contemplating thrombolysis or catheter-based Rx (qv)
- IV direct thrombin inhibitors (eg, argatroban, bivalirudin) used in HIT ⊕ Pts
- **Fondaparinux:** 5–10 mg SC qd (*NEJM* 2003;349:1695); use if HIT ⊕; avoid if renal failure
- **Direct oral anticoag** (DOAC; *NEJM* 2010;363:2499; 2012;366:1287; 2013;369:799 & 1406)
  Preferred b/c as good/better than warfarin in preventing recurrent VTE w/ less bleeding
  Apixaban (10 mg bid × 7 d → 5 bid) or rivaroxaban (15 mg bid for 1st 3 wk → 20 mg/d) can be given as sole anticoagulant w/ initial loading dose
  Edoxaban or dabigatran can be initiated after ≥*5 d of parenteral anticoag*
- DVT & low-risk PE w/o comorbidities and able to comply with Rx can be treated as outPt
- Generally safe to anticoagulate if platelets >50,000 but contraindicated if <20,000

Systemic thrombolysis (*EHJ* 2020;41:543; *Chest* 2021;160:e545)

- Typically TPA 100 mg over 2 h or wt-adjusted TNK bolus; risk of ICH ~2-5%, ↑ w/ age
- Consider if low bleed risk w/ acute PE + HoTN or cardiopulm deterioration after anticoag
- **High-risk PE:** ↓ death & recurrent PE each by ~50% (*JAMA* 2014;311:2414; *EHJ* 2015;36:605)
- **Intermediate-risk PE:** ↓ hemodyn decompensation, ↑ ICH & major bleeding, ↓ mortality in short- but not long-term; ? consider if <75 y and/or low bleed risk (*JAMA* 2014;311:2414)
- *Half-dose lytic* (50 mg or 0.5 mg/kg if <50 kg; 10-mg bolus → remainder over 2 h) in ~intermed. PE: ↓ pulm HTN & ? PE or death

w/ ≈ bleeding vs. heparin alone (*AJC* 2013;111:273)

- **DVT:** consider if (a) acute (<14 d) & extensive (eg, iliofemoral), (b) severe sx swelling or ischemia, and (c) low bleed risk

Mechanical intervention (*JACC* 2020;76:2117)

- **Catheter-directed** pharmacomech: low-dose lytic infused (eg, tPA 1 mg/h for 12–24 hr per catheter) + U/S or mech fragmentation of clot. Consider if hemodyn. compromise or high risk & not candidate for systemic lysis or surgical thrombectomy. Preferred to systemic lytic by some centers. Also consider if intermediate-high risk and evidence of early hemodynamic deterioration (*Circ* 2014;129:479). Lack of data on hard outcomes.
- **Catheter-based clot extraction** (eg, AngioVac or FlowTriever): ↓ PA pressure
- **Surgical embolectomy:** if large, proximal PE + hemodynamic compromise + contraindic. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn
- **IVC filter:** use if anticoag contraindic.; no benefit to adding to anticoag (*JAMA* 2015;313:1627)
  Complications: migration, acute DVT, ↑ risk of recurrent DVT & IVC obstruction (5–18%)

Duration of full-intensity anticoagulation

- Superficial venous thrombosis: 4 wk
- 1st prox DVT *or* PE 2° reversible/time-limited risk factor *or* distal DVT: 3–6 mo
- 1st *unprovoked* prox DVT/PE: ≥3 mo, then reassess; benefit to prolonged Rx. Consider clot, bleed risk, Pt preference, and intensity of Rx when crafting strategy.
- 2nd VTE event or cancer: indefinite (or until cancer cured) (*NEJM* 2003;348:1425)

Long-term anticoagulation options

- For nonpregnant Pt without severe renal dysfunction or active cancer → DOAC
- For severe renal insufficiency or APLAS → warfarin. Start w/ parenteral anticoag unless ? need for lytic, catheter-based Rx or surg; bridge to INR ≥2 × ≥24 h.
- Pregnancy or unable to take oral therapy → LMWH or fondaparinux

- Cancer → DOAC (but in Pts w/ UGI cancers, more GI bleeding w/ riva) or LMWH

Extended DOAC strategies

- After ≥6 mo of anticoag, following regimens compared w/ no extended Rx (or ASA):
- Full-dose DOAC: 80–90% ↓ recurrent VTE, 2–5× bleeding, but no signif excess in major bleeding (*NEJM* 2010;363:2499; 2013;368:699 & 709)
- ½ dose apixa or riva: ≥75% ↓ recur. VTE, w/o ↑ bleeding (*NEJM* 2013;368:699 & 2017;376:1211)

Complications & prognosis

- Postthrombotic syndrome (23–60%): pain, edema, venous ulcers
- Recurrent VTE: 1%/y (after 1st VTE) to 5%/y (after recurrent VTE)
- Chronic thromboembolic PHT after acute PE ~2–3%, consider thromboendarterectomy
- Mortality: ~10% for DVT and ~10–15% for PE at 3–6 mo (*Circ* 2008;117:1711)

PULMONARY HYPERTENSION (PHT)

PHT defined as PA mean pressure ≥20 mmHg at rest (*ERJ* 2019;53:1801913)

PA mean = CO × PVR + PA wedge pressure. Trans pulm gradient = PA mean – PA wedge.

Etiologies (Revised WHO Classification) (*JACC* 2013;62:D34)	
Primary pulmonary arterial HTN (PAH) (group 1) Precapillary PHT PCWP ≤15 mmHg ↑ transpulm grad ↑ PVR	• Idiopathic (IPAH): yearly incidence 1–2 per million; mean age of onset 36 y (♂ older than ♀); ♂ : ♀ = ~2:1, usually mild ↑ in PAP • Familial (FPAH) • Associated conditions (APAH) • Connective tissue dis.: CREST, SLE, MCTD, RA, PM, Sjögren • Congenital L→R shunts: ASD, VSD, PDA • Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome) • HIV; drugs & toxins: anorexic agents, SSRIs, l-tryptophan • Pulmonary veno-occlusive disease: ? 2° chemo, BMT; orthopnea, pl eff, CHF, nl PCWP; art vasodil. *worsen* CHF (*AJRCCM* 2000;162:1964) • Pulmonary capillary hemangiomatosis
Left heart disease (group 2). ↑ PCWP	• Left atrial or ventricular (diastolic or systolic) dysfunction • Left-sided valvular heart disease (eg, MS/MR)
Lung diseases and/or chronic hypoxemia (group 3)	• COPD • Alveolar hypoventilation (eg, NM disease) • ILD • Chronic hypoxemia (eg, high altitude) • Sleep apnea • Developmental abnormalities
Chronic thrombo-embolic dis (group 4)	• Prox or distal PEs; ~½ w/o clinical h/o PE (*NEJM* 2011;364:351) • Nonthrombotic emboli (tumor, foreign body, parasites)
Miscellaneous/ Multifactorial (group 5)	• Sarcoidosis, histiocytosis X, LAM, schistosomiasis, ESRD • Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis, histoplasmosis, XRT) • Other: thyroid dis., glycogen storage dis., Gaucher dis, HHT, sickle cell, etc., chronic myeloprolif d/o, splenectomy

Clinical manifestations

- Dyspnea, exertional syncope (hypoxia, ↓ CO), exertional chest pain (RV ischemia)
- Symptoms of R-sided CHF (eg, peripheral edema, RUQ fullness, abdominal distention)
- WHO class: I = asx w/ ordinary activity; II= sx w/ ord. activ; III = sx w/ min activ.; IV = sx at rest

Physical exam

- PHT: prominent P_2, R-sided S_4, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ± RV failure: ↑ JVP, hepatomegaly, peripheral edema

Diagnostic studies & workup (*JAMA* 2022;327:1379)

- High-res chest CT: dilat. & pruning of pulm arteries, ↑ RA & RV; r/o parenchymal lung dis.
- ECG: RAD, RBBB, RAE ("P pulmonale"), RVH (Se 55%, Sp 70%)
- PFTs: disproportionate ↓ D_LCO, mild restrictive pattern; r/o obstructive & restrictive lung dis.
- ABG & polysomnography: ↓ P_aO_2 and S_aO_2 (espec w/ exertion), ↓ P_aCO_2, ↑ A-a gradient; r/o hypoventilation and OSA
- TTE: ↑ RVSP (but estimate over/under by ≥10 mmHg in ½ of PHT Pts; *Chest 2011;139:988*) ↑ RA, RV, & PA; ↑ pressure → interventricular septum systolic flattening ("D" shape) ↓ RV systolic fxn (TAPSE <1.6 cm); TR, PR; r/o LV dysfxn, MV, AoV, congenital disease
- RHC: ↑ RA, RV, & PA pressures; ✓ L-sided pressures and for shunt
  - if PAH: nl PCWP, ↑ transpulmonary gradient (mean PAP-PCWP >12–15), ↑ diastolic pulmonary gradient (PA diastolic – PCWP >7), ↑ PVR, ± ↓ CO
  - if 2° to L-heart disease: PCWP (or LVEDP) >15; if PVR nl → "passive PHT"; PVR >240 suggests mixed picture: if ↓ PCWP → ↓ PVR, then "reactive" PHT; if no Δ, then "fixed"
- CTA (large/med vessel), V/Q scan (small vessel to r/o CTEPH), ± pulm angio if ↑ concern
- Labs: ANA (~40% ⊕ in PAH), anti-Scl-70, anti-RNP; LFTs; HIV
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Treatment (*JAMA* 2022;327:1379)

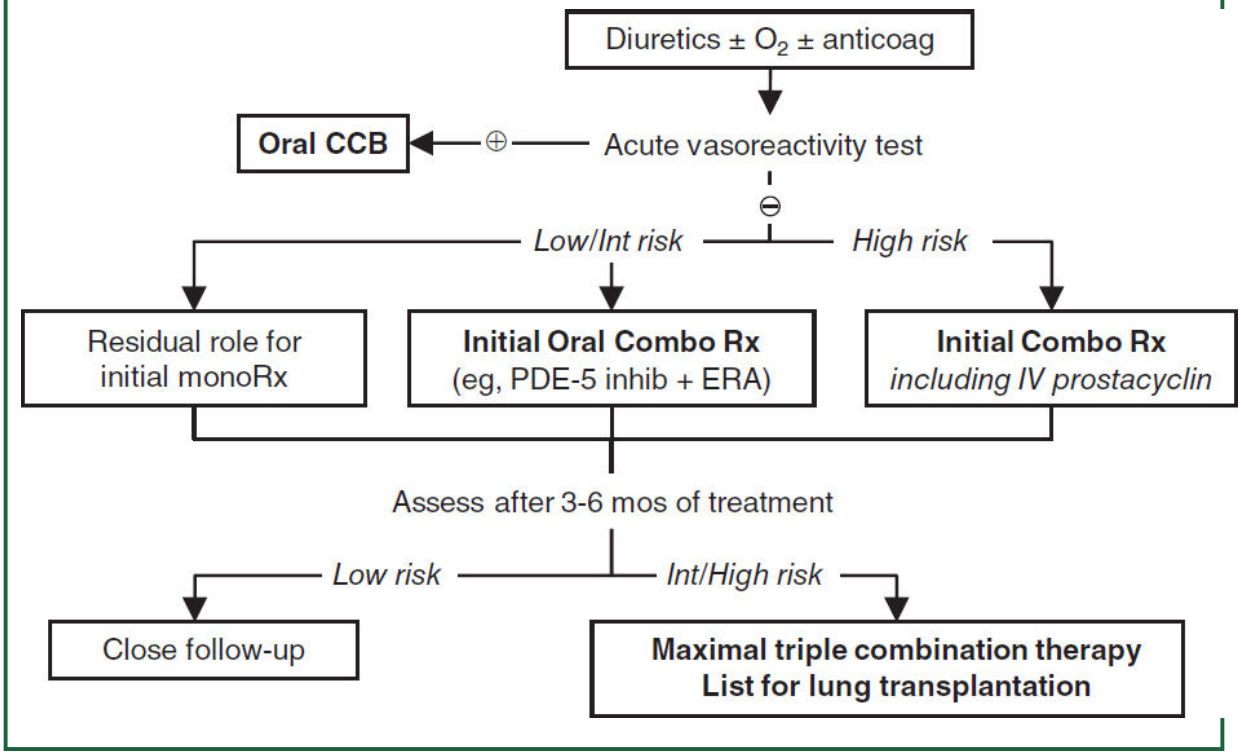
- Principles: 1) prevent & reverse vasoactive substance imbalance and vascular remodeling 2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq systemic DBP
- **Supportive**
  Oxygen: maintain S_aO_2 >90–92% (reduces vasoconstriction)
  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent
  Anticoag: not routinely used; ↓ VTE risk of RHF; ? prevention of *in situ* microthrombi; ? mortality benefit even if in NSR, no RCTs (*Chest* 2006;130:545)
  Supervised exercise training; aggressive apnea/hypoventilatory Rx w/ CPAP/BiPAP
- **Vasodilators** (ideally right heart catheterization prior to initiation; *NEJM* 2004;351:1425) *acute vasoreactivity test:* use inh NO, adenosine or prostacyclin to identify Pts likely to have long-term response to CCB (⊕ response = ↓ PAP ≥10 mmHg to <40 mmHg w/ ↑ or stable CO); ~10% Pts acute responders; no response → still candidate for other vasodilators

Vasoactive Agents	**Comments** (data primarily in Group 1)
PDE-5 inhibitor sildenafil, tadalafil, vardenafil	↑ cGMP → vasodilatation, ↓ smooth muscle proliferation, ↓ sx, ↑ 6MWT, no data on clinical outcomes. Often 1st line b/c minimal side-effect profile: HA, vision Δ's, sinus congestion.
Endothelin receptor antagonists (ERAs) bosentan, ambrisentan, macitentan	↓ Smooth muscle remodeling, vasodilatation, ↓ fibrosis, ↓ sx, ↑ 6MWT, ↓ worsening PAH or need for prostanoids w/ trend for ↓ PAH mortality (w/ macitentan). Side effects: ↑ LFTs, HA, anemia, edema, teratogen (*NEJM* 2013;369:809).
IV prostacyclin epoprostenol (Flolan)	Vasodilatation, ↓ plt agg, ↓ smooth muscle prolif; benefits ↑ w/ time (? vasc remodeling). ↑ 6MWT, ↑ QoL, ↓ **mortality**. Side effects: HA, flushing, jaw pain, abd cramps, N/V, diarrhea, catheter infxn.
Prostacyclin analogs [iloprost (inh), treprostinil (IV, inh, SC)]	Same mech as prostacyclin IV, but easier admin, ↓ side effects, w/o risk of catheter infxn. ↓ sx, ↑ 6MWT. Inh Rx w/ improved V/Q matching. Inh trepostinil ↑ 6MWT in ILD-PH (*NEJM* 2021;384:325).
Prostacyclin receptor agonist (selexipag, PO)	Indicated for WHO Group I to delay disease progression and risk of hospitalization. Add in WHO FC II & III (*NEJM* 2015;373:2522).
Soluble guanylate cyclase stimulator riociguat	NO-independent ↑ cGMP → vasodilatation, ↓ smooth muscle - proliferation, ↓ sx, ↑ 6MWT in PAH; ↓ sx, ↓ PVR, ↑ 6MWT in CTEPH (*NEJM* 2013;369:319 & 330)

Oral CCB nifedipine, diltiazem	Consider if ⊕ acute vasoreactive response. Not 1st line b/c side effects: HoTN, lower limb edema.

- Upfront combination Rx (PDE-5 inhibitor + ERA vs. monotherapy): ↓ sx, ↓ NT-proBNP, ↑ 6MWT, ↓ hospitalizations (*NEJM* 2015;373:834)
- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence
- CTEPH: riociguat. Pulm endarterectomy potentially curative (*AJRCCM* 2011;183:1605) vs. balloon pulmonary angioplasty in non-operative Pts (*Circ Outcomes* 2017;10:e004029).
- Refractory PHT: balloon atrial septostomy: R→L shunt causes ↑ CO, ↓ S_aO_2, net ↑ tissue O_2 delivery; lung txp (single or bilateral; heart-lung needed if Eisenmenger physiology)
- PHT risk stratification based on CHF symptoms, syncope, WHO functional class, 6MWT, CPET, NTproBNP, imaging, hemodynamics (*Eur Heart J* 2016;37:67)

Figure 2-5 Treatment of PAH (modified from *ERJ* 2019;53:1801889)



Management of ICU patient

- Avoid tachyarrhythmias & overly aggressive volume resuscitation

- Caution w/ vasodilators if any L-sided dysfunction
- *Intubation can cause hemodynamic collapse*
- Dobutamine and inhaled NO or prostacyclin
- Consider R-sided mechanical support (*Circ* 2015;132:536)
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 100 mg over 2 h)

Prognosis

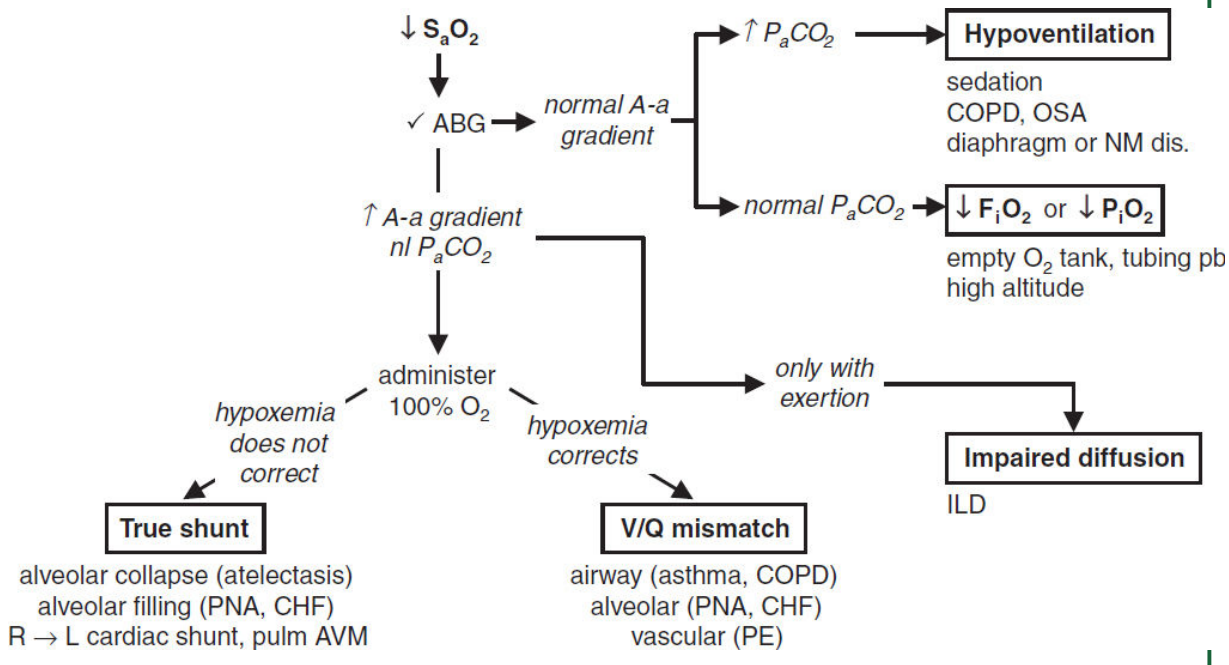
- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78–S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT <300 m, peak VO_2 <10.4 mL/kg/min, ↑ RA or RV or RV dysfxn, RA >20 or CI <2.0, ↑ BNP (*Chest* 2006;129:1313)

RESPIRATORY FAILURE

$$\text{Hypoxemia} \rightarrow P_AO_2 = [F_iO_2 \times (760 - 47)] - \frac{P_aCO_2}{R}$$

- **A-a gradient = $P_AO_2 - P_aO_2$:** normal (*on room air*) = "4 + age/4" or "2.5 + (0.2 × age)"
- Hypoxemia + nl A-a gradient: problem is ↓ P_iO_2/F_iO_2 or ↑ P_aCO_2 (ie, hypoventilation)
- Hypoxemia + ↑ A-a gradient: problem is either
  - **R → L shunt**, anatomic (congenital heart dis) or severe pathophys (alveoli filled w/ fluid; eg, PNA, pulm edema); cannot overcome w/ 100% O_2 b/c of sigmoidal Hb-O_2 curve
  - **V/Q mismatch** where "shunt-like" areas (↓ V & nl Q) cause unoxygenated blood to mix with oxygenated blood; can be overcome w/ ↑ O_2 delivery
  - Diffusion limitation: generally seen with exercise/↑CO

Figure 2-6 Workup of acute hypoxemia



- **Cyanosis:** when >5 g/dL of deoxygenated Hb in vessels of skin/mucous membranes. Central: ↓ S_aO_2 (pulm disease, shunt); abnl Hb [metHb, sulfHb, COHb (not true cyanosis)] Peripheral: ↓ blood flow → ↑ O_2 extraction (eg, ↓ CO, cold, arterial or venous obstruction)

Chemical Causes of Cellular Hypoxia						
Condition	**Causes**	**Classic features**	**P_aO_2**	**Pulse Ox**	**CO-Ox sat**	**Treatment (+ 100% O_2)**
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O_2
Methemo-globinemia	Nitrates, sulfonamide, benzocaine, dapsone	Chocolate brown blood	nl	mild ↓ ~85%	↓	Methylene blue
Cyanide	Nitroprusside, fires, industrial	Bitter almond odor; pink skin	nl	nl (↑ S_vO_2)	nl	Hydroxy-cobalamin

CO binds to Hb more avidly than does O_2. Pulse oximeter (Ox) misreads COHb as HbO_2 → falsely nl sat.
Oxidizing drugs Δ Hb (ferrous) to MetHb (ferric), which cannot carry O_2. Pulse ox misreads MetHb as HbO_2.

$$\text{Hypercapnia} \rightarrow P_aCO_2 = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

Etiologies of High ↑ P_aCO_2			
"Won't Breathe"	**"Can't Breathe"**		
↓ RR	**↓ V_T**		**↑ V_D and/or ↓ V_T**
Respiratory Drive	**NM System**	**CW/Pleura**	**Lung/Airways**
Voluntary hypervent. Nl PI_{max} & A-a grad	↓ PI_{max} ↓ PE_{max}	Abnl PEx Abnl CT	Abnl PFTs ↓ End tidal CO_2
Metabolic alkalosis **1° neurologic:** brain-stem stroke, tumor, 1° alveolar hypovent **2° neurologic:** sedatives, CNS infxn, hypothyroidism	**Neuropathies:** cervical spine, phrenic nerve, GBS, ALS, polio **NMJ:** MG, LE **Myopathies:** diaphragm PM/DM, ↓ PO_4, musc dystrophies	**Chest wall:** obesity, kyphosis, scoliosis **Pleura:** fibrosis effusion	**Lung parenchyma:** emphysema, ILD/fibrosis, CHF, PNA **Airways:** asthma, COPD, OSA, CF bronchiectasis

↑ VCO_2 typically transient cause of ↑ $PaCO_2$; Ddx: exercise, fever, hyperthyroidism, ↑ work of breathing, ↑ carbs.

MECHANICAL VENTILATION

Indications

- Improve gas exchange: ↑ oxygenation, ↑ alveolar vent and/or reverse acute resp acidosis
- Relieve respiratory distress: ↓ work of breathing (can account for up to 50% of total O_2 consumption), ↓ respiratory muscle fatigue
- Apnea, airway protection, pulmonary toilet

SUPPORTIVE STRATEGIES PRIOR TO INTUB. OR AFTER EXTUB.

Oxygen Delivery Systems (*Lancet* 2016;387:1867)		
System or Device	**O_2 Flow[a]**	**F_iO_2 Range & Comments**
Low-flow nasal cannula	1–6	24–40%, 1L adds ~3% F_iO_2
Standard face mask	5–10	35–50%, minimum 5 L/min
Partial rebreather mask	>10	40–70%
Nonrebreather mask	>10	60–80% (not 100% b/c air leaks)
Air-entrainment mask (Venturi or Venti mask)	10–15[b]	24–50%, F_iO_2 stays constant
High-flow nasal cannula (HFNC) (*NEJM* 2015;372:2185; *JAMA* 2015;313:2331 & 2016;315:1354)	≤40	21–100%. In nonhypercapnic acute hypoxemic resp failure, ± ↓ intub. (espec if P_aO_2/F_iO_2 ≤200) & ↓ 90-d mort vs. stnd O_2 or NPPV. Routine use after extub. ↓ need for reintub

[a]L/min. [b]Total airflow >60L/min. (Adapted from Marino P. *The ICU Book*, 4th ed, Philadelphia: LWW, 2014:431)

Noninvasive Positive Pressure Ventilation (NPPV) (*NEJM* 2015;372:e30)	
Indications (*Lancet* 2009;374:250)	*Clinical:* mod–severe dyspnea, RR >24–30, signs of ↑ work of breathing, accessory muscle use, abd paradox *Gas exchange:* P_aCO_2 >45 mmHg (& significantly worse than baseline), hypoxemia, P_aO_2/F_iO_2 <200
Contraindications (*Crit Care Med* 2007;35:2402)	Claustrophobia, poor mask fit, Δ**MS**, vomiting, **cannot protect airway**, extrapulm organ failure, HD instab, sev UGIB, ↑ secretions

Noninvasive Positive Pressure Ventilation (NPPV) (*NEJM* 2015;372:e30)	
Continuous positive airway pressure (CPAP)	≈ PEEP. Pt breathes spont. at own rate while vent maintains constant positive airway pressure throughout respiratory cycle. No limit on O_2 delivered (ie, can give hi-flow → F_iO_2 ≈1.0) Used if primary problem ***hypoxemia*** (eg, CHF)
Bilevel positive airway pressure (BiPAP)	≈ PSV + PEEP. Able to set both inspiratory (usually 8–10 cm H_2O) and expiratory pressures (usually <5 cm H_2O). Used if primary problem *hypoventilation*; F_iO_2 delivery limited
Mask ventilation (? helmet better; *JAMA* 2016;315:2435)	Tight-fitting mask connecting patient to a standard ventilator Can receive PS ~20–30 cm H_2O, PEEP ~10 cm H_2O, F_iO_2 ~1.0 Used for short-term support (<24 h) for a reversible process
Conditions w/ strong evidence	**Cardiogenic pulmonary edema:** may ↓ intub. ± mortality (*JAMA* 2005;294:3124; *Lancet* 2006;367:1155; *NEJM* 2008;359:142) **COPD exac.** w/ ↑ P_aCO_2: ↓ intub. & mort., but if pH <7.3 → intubate Acute hypoxemic resp failure: ↓ intub. & mortality (*JAMA* 2020;324:57) High-risk extub. (age >65, CHF, APACHE II >12): NPPV × 24 h directly after extub. → ↓ reintub. and, if P_aCO_2 >45 mmHg during SBT, ↓ mortality. Does not Δ total # vent days (*JAMA* 2018;320:1881). Hypoxemic resp failure after abdominal surgery: ↓ reintubation **Immunosupp.** w/ infiltrates: ↓ complications & mortality

VENTILATOR MANAGEMENT

Ventilator Modes and Principles (*NEJM* 2001;344:1986; *Chest* 2015;148:340)	
Cont mandatory ventilation (CMV), aka Assist control (AC)	Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger *fully assisted* vent breaths ∴ Vent-triggered breaths identical to Pt-triggered breaths Tachypnea → ? resp. alkalosis, breath-stacking, & auto-PEEP May be pressure targeted or volume targeted (qv)
Pressure support vent (PSV)	Support Pt-initiated breaths w/ a set inspiratory pressure & PEEP A mode of *partial* vent support because no set rate
Other	Synch intermittent mand. vent: deliver min # supported breaths; V_T of additional Pt-initiated breaths determined by Pt's effort Proportional assist ventilation (PAV): delivers variable pressure to achieve targeted % of work of breathing

Volume or Pressure Targeted

Volume or Pressure Targeted	
Volume targeted	Vent delivers a set V_T; pressures depend on airway resist. & lung/CW compl. **Benefit:** ↑ control over ventilation (ideal initial ventilator setting); benefit in ALI/ARDS; easy to measure mechanics (PIP, P_{plat}, airway resist., compl.) Volume control (VC) ⊕: vent delivers variable pressure (depending on real- time lung compliance) to achieve set V_T
Pressure targeted	Vent delivers a fixed inspiratory pressure regardless of V_T V_T depends on airway resistance and lung/chest wall compliance **Benefit:** may ↑ Pt comfort (PSV) requiring less sedation
General principles	**Institutional/practitioner preference** and **Pt comfort** usually dictate ventilator strategy; no strategy has proven superior **Alarms** can be set for ↓ or ↑ volumes and ↑ airway pressures in pressure- targeted and volume-targeted strategies, respectively **Risks:** volutrauma (ie, overdistention, if set volume too high; *NEJM* 2013;369:2126), barotrauma [can happen w/ relatively high set volumes (espec if stiff lungs) or if pressure target set too high; key is to monitor transpulmonary pressure (difference between P_{plat} and esophageal ≈ intrapleural), not just airway pressure]; can result in PTX, pneumomediastinum **Hypo-/hyperventilation:** need to ✓ minute vent & pH/P_aCO_2

Variables on the Ventilator	
F_iO_2	Fraction of inspired air that is oxygen
V_T (tidal vol)	Volume of breath delivered; lung-protective ventilation: goal ≤6 mL/kg IBW If no ARDS, similar # of vent days at higher V_T (*JAMA* 2018;320:1872)
f (resp. rate)	Rate set by ventilator, f may be lower than RR if Pt triggering breaths. Adjust to achieve desired P_aCO_2.

Variables on the Ventilator	
Positive end-expiratory pressure (PEEP)	Positive pressure applied during exhalation via resistor in exhalation port Benefits: prevents alveolar collapse, ↓ shunt, ↑ O_2 via alveolar recruitment and improved compliance, allows severely obstructed Pt to initiate breath Cardiac effects: ↓ preload by ↑ intrathoracic pressure → ↓ venous return; ↓ afterload by ↓ cardiac transmural pressure; may ↑ or ↓ CO and may ↑ or ↓ oxygen delivery based on the above Auto-PEEP or intrinsic PEEP (iPEEP): inadeq. exhalation time → lungs unable to completely empty before next breath (ie, "breath stacking"); if flow at end-expiration, there must be pressure = auto-PEEP. Will ↓ preload and may ↓ CO, espec if hypovolemic Will ↑ work of breathing as must be overcome by Pt to trigger breaths; can prevent Pt from triggering ventilator, extrinsic PEEP helps Can be detected if end-expiratory flow ≠ 0 before next breath Can measure by occluding expiratory port of vent at end-expiration Can ↓ by: ↑ exp time, ↓ RR, ↓ V_T, Rx bronchospasm and secretions If iPEEP >set PEEP, minimize iPEEP, then set PEEP to ~80% of iPEEP to ↓ ineffective triggering
Inspiratory time	Normally I:E ratio is ~1:2; however, can alter I time (and consequently flow rate, see later); use in pressure-control mode
Inspiratory flow rates	↑ flow rate → ↓ I time → ↑ E time → ∴ may improve ventilation in obstructive disease, but may affect resp rate and bronchodilation/constriction
Peak inspiratory pressure (PIP)	Dynamic measurement during inspiration; set in pressure-targeted mode Determined by airway resistance and lung/chest wall compliance ↑ PIP w/o ↑ P_{plat} → ↑ airway resist (eg, bronchospasm, plugging) ↓ PIP → ↓ airway resistance or air leak in the system
Plateau pressure (P_{plat})	Static measurement at the end of inspiration when there is no flow Determined by resp system compliance (resist. not a factor since no flow) ↑ P_{plat} → ↓ lung or chest wall compliance (eg, PTX, pulmonary edema, pneumonia, atelectasis), ↑ PEEP or auto-PEEP P_{plat} <30 cm H_2O ↓ barotrauma (↓ V_T, ↓ PEEP or ↑ compl [eg, by diuresis])

Tailoring the ventilator settings

- To improve oxygenation: options include ↑ F_iO_2, ↑ PEEP

  S_aO_2 88–92% acceptable (*AJRCCM* 2016;193:43), do not exceed 96% (*BMJ* 2018;363:k4169)

First, ↑ F_iO_2. If >0.6 and oxygenation remains suboptimal, then try ↑ PEEP:

If ↑ P_aO_2/F_iO_2 *and* P_{plat} stable, suggests recruitable lung (ie, atelectasis). If PEEP 20 & F_iO_2 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see "ARDS").

If ↑ PEEP yields no Δ *or* ↓ P_aO_2/F_iO_2 *or* ↑ P_aCO_2, suggests additional lung *not* recruitable and instead overdistending lung → ↑ shunt & dead space; ∴ ↓ PEEP

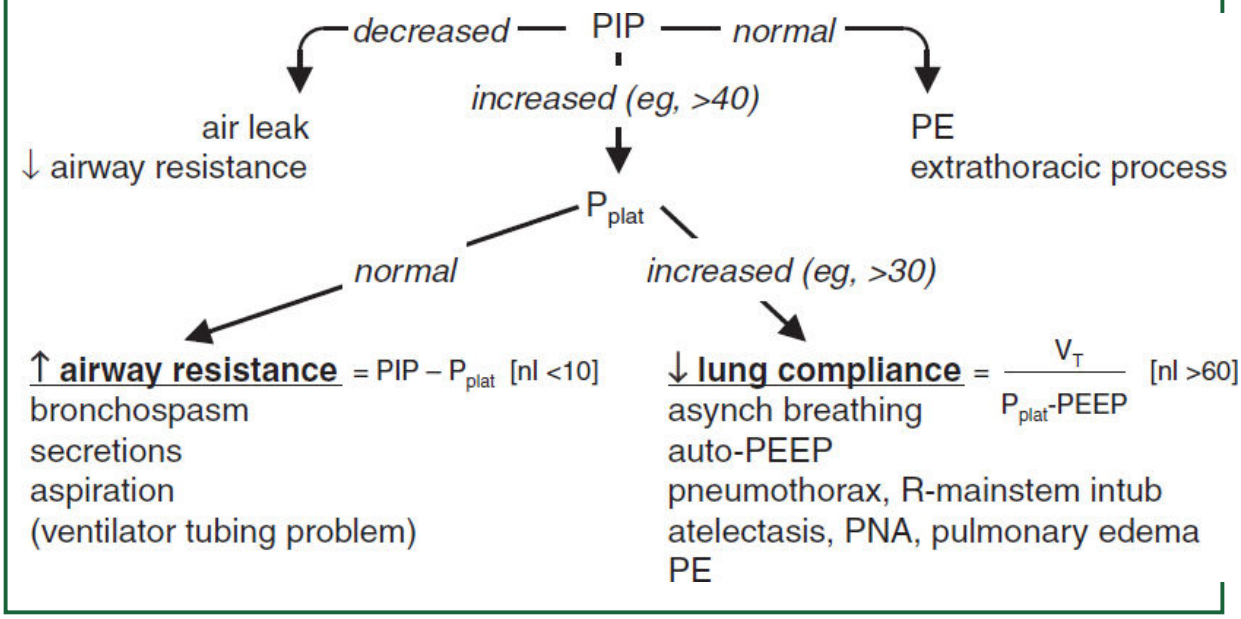
If no ARDS, PEEP ≤5 (& S_aO_2 >92%) noninferior to PEEP 8 (*JAMA* 2020;324:2509)

• To improve ventilation: ↑ V_T or inspiratory pressure, ↑ RR (may need to ↓ I time). Nb, tolerate ↑ P_aCO_2 (permissive hypercapnia) in ALI/ARDS (qv) as long as pH >7.2.

Acute ventilatory deterioration (usually ↑ PIP)

• Response to ↑ PIP: disconnect Pt from vent, bag, auscultate, suction, ✓ CXR & ABG

Figure 2-7 Approach to acute ventilatory deterioration



(Adapted from Marino PL. *The ICU Book*, 4th ed., Philadelphia: LWW, 2014)

Liberating from the ventilator (*NEJM* 2012;367:2233; *Lancet* 2016;387:1856)

• Perform daily assessment of readiness for spontaneous breathing trial (SBT)

- Clinical screening criteria: VS stable, minimal secretions, adequate cough, cause of respiratory failure or previously failed SBT reversed
- Vent parameters: P_aO_2/F_iO_2 >200, PEEP ≤5, f/V_T <105, V_E <12 L/min, VC >10 mL/kg; rapid shallow breathing index (f/V_T) >105 predicts failure, NPV 0.95 (*NEJM* 1991;324:1445)
- Daily awakening trial (d/c all sedation; *Lancet* 2008;371:126): open eyes & w/o: agitation, RR >35, S_aO_2 <88%, resp distress or arrhythmias (if fail, restart sedation at ½ prior dose)
- SBT = CPAP × 30 min superior to T-piece × 120 min (*JAMA* 2019;321:2175) failure if: deteriorating ABGs, ↑ RR, ↑ or ↓ HR, ↑ or ↓ BP, diaphoresis, anxiety
- Tolerate SBT → extubation. Fail SBT → ? cause → work to correct → retry SBT qd
- If high-risk, extubate to either NPPV or NPPV alternating w/ HFNC (*JAMA* 2019;322:1465)
- ? acetazolamide in Pts w/ COPD & metabolic alkalosis (*JAMA* 2016;315:480)

Complications

- Oxygen toxicity (theoretical); proportional to duration + degree of ↑ oxygen (F_iO_2 >0.6)
- Ventilator-induced lung injury (see "ARDS")
- Ventilator-associated pneumonia (~1%/d, mortality rate ~30%)
  - typical pathogens: MRSA, *Pseudomonas*, *Acinetobacter* and *Enterobacter* species
  - preventive strategies (*AJRCCM* 2005;171:388): wash hands, HOB elevated, non-nasal intub., enteral nutrition rather than TPN?, routine suction of subglottic secretions, avoid unnecessary abx & transfusions; routine oral antiseptic controversial
- Stress ulcers/GIB: prophylaxis w/ PPI ↓ GIB, but no Δ in overall course (*NEJM* 2018;379:2199)
- Laryngeal
  - edema: for Pts vent >36 h; ? predicted by ⊕ cuff leak test. Methylprednisolone 20 mg IV q4h starting 12 h pre-extub. → ↓↓ edema and 50% ↓ in reintubation (*Lancet* 2007;369:1003).
  - ulceration: consider *tracheostomy* for Pts in whom expect >14 d of mech vent → ↓ duration mech vent, ↓ # ICU days (*BMJ*

2005;330:1243); no benefit to performing at ~1 wk vs. waiting until ~2 wk (*JAMA* 2010;303:1483)

- Malnutrition (for all critically ill Pts): *enteral nutrition* initiated early is safe but not necessary (*JAMA* 2012;307:795), but bolus may ↑ risk of VAP & *C diff.* (*JPEN* 2002;26:174); no clear benefit to ✓ing gastric residuals (*JAMA* 2013;309:249); permissive enteral underfeeding (~½ of calculated caloric req) & standard enteral feeding w/ similar outcomes (*NEJM* 2015;372:2398); *parenteral nutrition* should be delayed until after day 8 to ↓ risk of infections, cholestasis, RRT, ventilator days (*NEJM* 2011;365:506)
- Oversedation/delirium: BDZs and polypharmacy are risk factors
  propofol: HoTN in ~25%; *propofol infusion syndrome* (PRIS) ? espec w/ high (>5 mg/kg/h) & prolonged (>48 h) infusions & concom vasopressors → ↑ AG, cardiac dysfxn, rhabdomyolysis, ↑ triglycerides, & renal failure (*Crit Care* 2009;13:R169)
  dexmedetomidine: no benefit on vent-free days (*JAMA* 2016;315:1460 & 2017;317:1321); similar outcomes to propofol when utilized as sole agent (*NEJM* 2021;384:1424)

ACUTE RESPIRATORY DISTRESS SYNDROME

Berlin definition (*JAMA* 2012;307:2526)

- Acute onset within 1 week of clinical insult or worsening respiratory status
- Bilateral infiltrates without alternative explanation (eg, effusion, atelectasis, nodules)
- Edema not fully explained by fluid overload or congestive heart failure
- Hypoxemia: P_aO_2/F_iO_2 determined with 5 cm H_2O of PEEP
  P_aO_2/F_iO_2 200–300 = mild ARDS (may be on NPPV), 100–200 = mod, <100 = severe

Pathophysiology (*Lancet* 2016;388:2416)

- ↑ intrapulmonary shunt → hypoxemia (∴ Rx w/ PEEP to prevent derecruitment)
- ↑ increased dead space fraction (see Appendix), predicts ↑ mort (*NEJM* 2002;346:1281)
- ↓ compliance: $V_T/(P_{plat} - PEEP)$ <50 mL/cm H_2O

Pathology

- Diffuse alveolar damage (DAD) seen in 40% of autopsies (*AJRCCM* 2013;187:761)
- If no clear inciting event and ILD considered as alt dx, consider bx (*Chest* 2015;148:1073)

Etiologies	
Direct Injury	**Indirect Injury**
• Pneumonia (~40%) • Aspiration (~15%) • Near drowning • Inhalation injury • Lung contusion	• Sepsis (~25%) • Shock • DIC • Pancreatitis • Trauma/multiple fractures • Transfusion (TRALI)

Treatment (*Lancet* 2021;398:622)

- Goal is to maintain gas exchange, sustain life, & avoid ventilator-induced lung injury (VILI)
- In Pts on O_2 for COVID-19 PNA, dexamethasone ↓ 28-day mortality (*NEJM* 2021;384:693)

Mechanisms of VILI	Ventilator Strategies (see ARDSnet.org)
Barotrauma/volutrauma: alveolar dist → mech damage	**V_T ≤6 mL/kg, P_{plat} ≤30 cm H_2O**, tolerate ↑ P_aCO_2 (but keep pH >7.2), ↓ mortality (*NEJM* 2000;342:1301)
Biotrauma → SIRS	Low V_T, open lung strategy w/ high PEEP
Atelectrauma: repetitive alveoli recruit & decruit	**Titrate PEEP to prevent tidal alveolar collapse** See below for options
Hyperoxia: ? injury; worsened V/Q matching	↑ **PEEP** rather than F_iO_2 (keep <0.60) O_2-induced injury only theoretical in humans

The 6 Ps

- **PEEP** (see below)
- **Proning:** if P_aO_2/F_iO_2 <150, prone positioning ≥16 h ↓ mort ~50% (*NEJM* 2013;368:2159)
- **Paralysis:** no benefit routinely (*NEJM* 2019;380:1997); consider if Pt-vent dyssynchrony
- **Peeing (fluid balance):** target CVP 4–6 cm H_2O (if nonoliguric & normotensive) → ↑ vent/ICU-free days, but no Δ mortality (*NEJM* 2006;354:2564); PA catheter unproven (*NEJM* 2006;354:2213); consider BNP >200 to trigger diuresis (UOP goal 4.5–9 mL/kg/h × 3 h)
- **Pulm vasodilators:** inhaled NO or prostacyclins ↑ P_aO_2/F_iO_2; no ↓ mort or vent-free days (*BMJ* 2007;334:779)
- **Perfusion (V-V ECMO):** may be useful if refractory (*NEJM* 2018;378:1965)

PEEP titration methods (best method unclear)

- No benefit at given V_T if titrated to P_aO_2 alone (*NEJM* 2004;351:327; *JAMA* 2008;299:637)
- Best PEEP trial: incremental PEEP titration using compliance, O_2, hemodynamics
  If able to ↑ PEEP w/o ↑ P_{plat}, suggests "recruitability"
  ∴↑ PEEP if → ↑ S_aO_2 (target ≥88–90%) & P_{plat} ≤30 cm H_2O → ↓ time on vent, better lung mechanics (*JAMA* 2008;299:646), ? ↓ mortality (*JAMA* 2010;303:865)

- ARDSnet “high” PEEP table for optimal F_iO_2/PEEP combo for goal S_aO_2 (ARDSnet.org)
- Recruitment maneuvers: stepwise preferred over sustained inflation, evidence insufficient to recommend routine use (*Resp Care* 2015;60:1688); recruitment maneuvers at high pressures ? ↑ mortality (*JAMA* 2017;318:1335)
- Esophageal balloon: used to estimate pleural pressure and thereby estimate trans-pulmonary pressure (ie, true airway distending pressure). Adjusting PEEP according to esoph pressure to maintain optimal transpulm. pressure does not Δ ventilator-free days or mortality, although does ↓ need for advanced rescue Rx (see above) (*JAMA* 2019;321:846).
- Driving pressure ($\Delta P = P_{plateau} – PEEP$): ↓ ΔP a/w ↑ survival; target <15 (*NEJM* 2015;372:747)

Prognosis (*JAMA* 2016;315:788)

- Mortality ~40% overall in clinical trials; 9–15% resp. causes, 85–91% extrapulm (MODS)
- Survivors: PFTs ~normal, ↓ D_LCO, muscle wasting, weakness persists (*NEJM* 2003;348:683), ↓ exercise tolerance, ↓ QoL, ↑ psych morbidity (*NEJM* 2011;364:1293); 44% of previously employed Pts jobless at 12 mos (*AJRCCM* 2017;196:1012)

SEPSIS AND SHOCK

Definitions (*JAMA* 2016;315:801; 2017;317:290 & 301)	
Sepsis	Life-threatening organ dysfxn (SOFA ≥2) due to infection Quick SOFA (qSOFA): ≥2 of the following: RR ≥22, ΔMS, SBP ≤100 mmHg
Septic shock	Sepsis-induced circulatory and cellular/metabolic abnormalities severe enough to ↑ mortality; hypotension requiring pressors for MAP ≥65 and lactate >2 despite adequate fluid resuscitation
Sequential Organ Failure Assessment (SOFA): ↑ points for worsening organ dysfxn: respiration (↓ P:F ratio); coag (↓ plt); liver (↑ bili); CV (↓ MAP or ↑ pressors); CNS (↓ GCS); renal (↑ Cr or ↓ UOP)	

Shock (see "PA Catheter & Tailored Therapy" for subtypes; *NEJM* 2013;369:1726)

- Tissue hypoxia due to ↓ tissue perfusion and hence ↓ tissue O_2 delivery and/or ↑ O_2 consumption or inadequate O_2 utilization
- Typical signs include HoTN (SBP <90 mmHg or drop in SBP >40 mmHg), tachycardia, oliguria (UOP <0.5 cc/kg/h), Δ mentation, metabolic acidosis ± ↑ lactate
- Hard to dx as ↑ SVR can maintain SBP, but tissue perfusion poor; shock index (HR/SBP) >0.9 and pulse pressure [(SBP – DBP)/SBP] <25% clues to significant shock

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MANAGEMENT (*Crit Care Med* 2021;49:e1063)

Fluids

- Aggressive IV fluid resuscitation (30 mL/kg) admin in boluses w/in 3 h of presentation
- Crystalloid as good as colloid for resuscitation (*JAMA* 2013;310:1809; *NEJM* 2014;370:1412)
- No consistently seen benefit of balanced crystalloid (LR, Plasma-Lyte) vs. NS in terms of mortality, organ failure or need for RRT (*NEJM* 2018;378:829 & 2022:386:815)
- $NaHCO_3$ may ↓ mortality & need for RRT if AKI & pH <7.2 (*Lancet* 2018;392:31)

- Predictors of fluid responsiveness: pulse pressure variation >13% w/ respiration (*Chest* 2008;133:252); resp. variation in IVC diam, or >10% ↑ in pulse pressure w/ passive leg raise. Static CVP poor surrogate.
- After early resuscitation, if ALI/ARDS, target CVP 4–6 mmHg because additional fluids may be harmful → ↑ ventilator/ICU days (*NEJM* 2006;354:2564; *Chest* 2008;133:252)

Pressors & inotropes (also see "ICU Medications")

- MAP target 65 mmHg as good as 80–85 and ↓ AF (*NEJM* 2014;370:1583; *JAMA* 2020;323:938)
- Norepinephrine: ↓ arrhythmia & mortality c/w dopamine (*NEJM* 2010;362:779; *Crit Care Med* 2012;40:725) and ∴ is pressor of choice in septic shock
- Vasopressin: adding to norepi (vs. using high-dose norepi) ↓ risk of AF & RRT by ~¼ (*JAMA* 2018;319:1889)
- If refractory vasoplegia: angiotensin II (Giaprezza), methylene blue, steroids (vide infra)
- If targets (see below) not reached after adequate fluids and pressors, consider inotropes

Targets

- Lactate clearance (≥20%/2 h) as effective as $S_{cv}O_2$ to guide resusc. (*JAMA* 2010;303:739)
- Targeting capillary refill time ≤3 sec (check q30min) as good if not better than lactate clearance (*JAMA* 2019;321:654)

Antibiotics

- Start empiric IV abx as soon as possible after recognition of severe sepsis or septic shock; every hr delay in abx admin a/w 7.6% ↑ in mortality (*Crit Care Med* 2006;34:1589), abx admin w/in 3 h of presentation in the ED a/w ↓ in-hospital mortality (*NEJM* 2017;376:2235)
- If possible, obtain 2 sets of BCx before urgently starting abx (but do not delay abx)
- Broad gram-positive (incl MRSA) & gram-neg (incl highly resistant) coverage, ± anaerobes
- Procalcitonin-guided *cessation* (not initiation) ↓ mortality (*Crit Care Med* 2018;46:684)
- Empiric micafungin in critically ill Pts w/ Candida colonization & sepsis of unknown etiology ↓ invasive fungal infxns & tended ↑

invasive fungal infxn-free survival, espec. in Pts w/ 1,3-b-D-glucan >80 (*JAMA* 2016;316:1555)

Steroids (*Crit Care Med* 2018;46:1411)

- Hydrocortisone 50 mg IV q6 + fludrocortisone 50 μg via NGT daily in septic shock ↓ duration of shock and may ↓ mortality (*NEJM* 2018; 378:797 & 809)
- Consider in Pts w/ refractory shock on escalating doses of pressors

Early Goal-Directed Therapy (EGDT)

- Historically: IVF & pressors for MAP ≥65 mmHg, CVP 8–12 mmHg, UOP ≥0.5 mL/kg/h; inotropes & PRBCs for $S_{cv}O_2$ ≥70% in 6 h (*NEJM* 2001;345:1368)
- However, now in era of early abx and adequate fluid resuscitation, no ↓ in mortality w/ EGDT vs. current usual care, and ↑ hospital costs (*NEJM* 2017; 376:2223)

TOXICOLOGY

Drug/Toxin	Signs/Sx and Diagnostics	Management Options
Acetaminophen	Vomiting, ↑ AG & nl OG metabolic acidosis, hepatitis & hepatic failure, renal failure	N-acetylcysteine (NAC) infusion Hemodialysis if massive O/D See "Acute liver failure"
Salicylates	Tinnitus, hyperventilation, abd. pain, vomiting, ΔMS, mixed ↑ AG & nl OG metabolic acidosis + respiratory alkalosis	IVF resuscitation Alkalinization w/ $NaHCO_3$ Maintain respiratory alkalemia Consider hemodialysis
Opioids	↓ mentation, ↓ RR, miosis	IV naloxone
Benzodiazepines	↓ mentation, ataxia, ↓ RR	Flumazenil *not* rec (can precipitate withdrawal/seizures)
Calcium channel blockers	Bradycardia, AV block, hypotension, HF, hyperglycemia	IVF, vasopressors, Ca infusion, hyperinsulinemic euglycemia, ? intralipid emulsion, pacing
Beta blockers	Bradycardia, AV block, hypotension, HF, hypoglycemia	Glucagon, vasopressors, pacing
Digoxin	N/V, bradycardia, AV block, delirium, xanthopsia ✓ serum dig level (but may be inaccurate if <6 h since last dose), renal function	Correct hypokalemia Digibind if hyperkalemia, life-threatening dysrhythmia Consider hemodialysis Lidocaine for arrhythmias
Tricyclic antidepressants	Hypotension, seizures, arrhythmia, ↑ QRS, ↑ QT	IVF resuscitation, IV sodium bicarbonate, vasopressors
Lithium	N/V/D, tremor, hyperreflexia, clonus, drowsiness, seizure, ↑ QT, AV block, bradycardia	IVF (NS), maintain UOP Consider hemodialysis
Ethylene glycol	CNS depression, ↑ AG & OG metabolic acidosis	Ethanol or fomepizole, $NaHCO_3$ Consider hemodialysis
Methanol (*NEJM* 2018;378:270)	CNS depression, blindness ↑ AG & OG met. acidosis	Ethanol or fomepizole, $NaHCO_3$ Consider hemodialysis

Isopropanol	CNS depression, gastritis	Supportive care
Carbon monoxide	HA, dizziness, nausea, ΔMS carboxyHb level, CO-oximetry	100% normobaric oxygen, hyperbaric O_2 in severe cases
Organopho- sphate	Salivation, lacrimation, diaphoresis, miosis, emesis, bronchospasm, ΔMS	Endotracheal intubation for respiratory failure, atropine, pralidoxime, benzodiazepines
Cyanide	Coma, seizure, metabolic acidosis, hypotension	IV Na nitrite and Na thiosulfate IV hydroxocobalamin

Call local Poison Control for assistance with management. (*Chest* 2011;140:1072)

LUNG TRANSPLANT

Overview

- Indications: end stage, progressive decline despite max medical Rx, <2-y life expectancy; COPD, ILD (IPF), pulmonary HTN, cystic fibrosis, alpha 1-antitrypsin
- Contraindic: age >70, uncontrolled/unRx'd infxn, malig in prior 5 yrs, severe non-pulm dis., BMI ≥35 or <16, active smoking, EtOH/drug depend., med nonadherence, psychosocial

Posttransplant care

- Immunosuppression: no single best regimen. Calcineurin inhibitor (tacro >cyclosporine, ↓ incidence of graft failure (*JHLT* 2021;40:S165) + steroids + MMF or AZA
- Monitoring: clinic visits, serial PFTs, chest X-ray, bronchoscopy w/ transbronchial biopsy

Complications

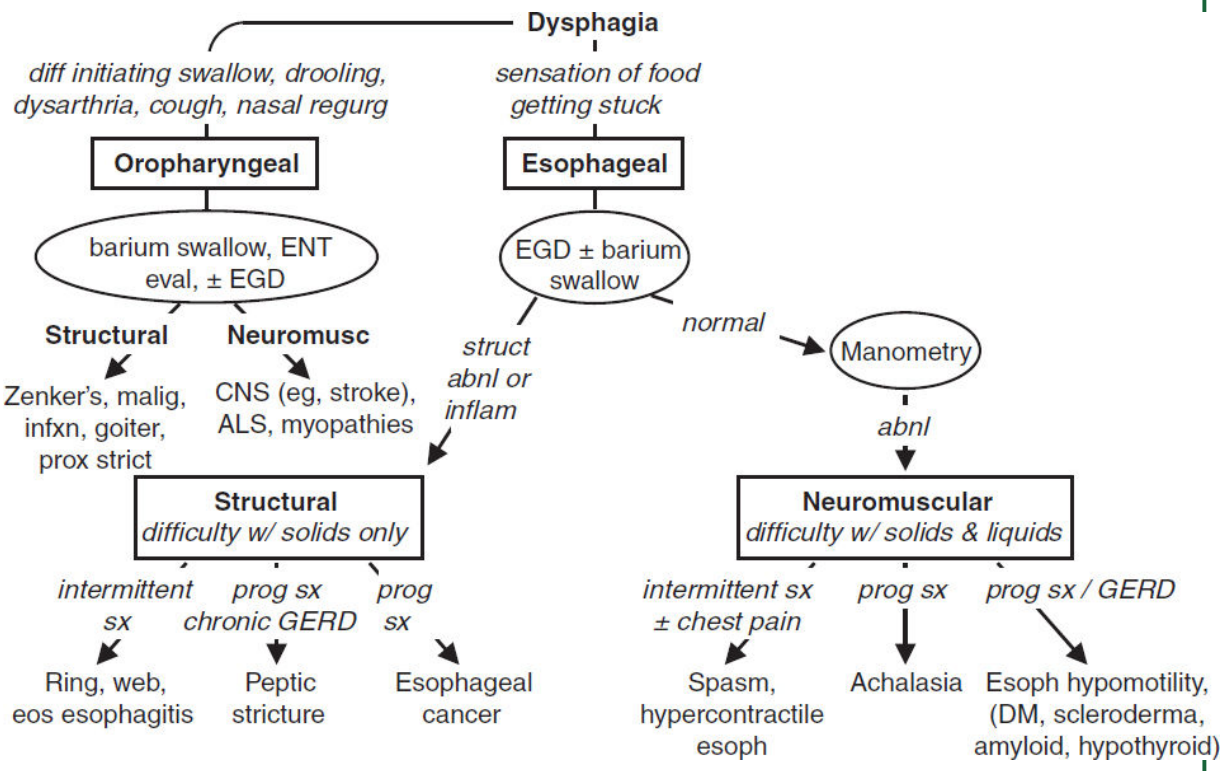
- Primary graft dysfunction (PGD): acute lung injury following txp; assoc w/ early mortality
- Anastomotic: vascular (stenosis, thrombosis) and airway (infection, necrosis, dehiscence, granulation tissue, tracheobronchomalacia, stenosis, fistula)
- Acute rejection: ↓ lung fxn, cough, SOB, fever; Dx w/ trans-bronch bx; Rx immunosupp
- Chronic rejection: bronchiolitis obliterans w/ obstruction; Dx w/ PFTs, trans-bronch bx; Rx limited (azithromycin, montelukast, Δ immunosuppressives)
- Infection: ↑ bacterial, fungal, viral pneumonia, systemic infections, CMV, OI
- Malignancy: 2× ↑ risk overall. 5.5× ↑ risk lung cancer. PTLD (assoc w/ EBV) common.
- Misc: GVHD, CKD, DM, CAD, CHF, stroke, encephalopathy, drug toxicity

ESOPHAGEAL AND GASTRIC DISORDERS

Dysphagia

- Oropharyngeal: inability to propel food from mouth through UES into esophagus
- Esophageal: difficulty swallowing & passing food from esophagus into stomach

Figure 3-1 Etiologies of and approach to dysphagia (*NCP Gastrohep* 2008;5:393; *Neurogastro* 2012;24:57)



Structural dysphagia (solids >liquids; *JAMA* 2015;313:18; *Gastro* 2018;155:1022)

- **Oropharyngeal**

Zenker's divertic. (pharyngeal pouch): in elderly, a/w aspir., dx w/ video fluoro, Rx endo/surg

Malignancy; proximal strictures/rings/webs; infection; radiation injury; goiter; osteophytes

- **Esophageal**

Rings (intermittent dysphagia, concentric obstructing tissue, Schatzki ring): near GE jxn, a/w food impaction, linked to GERD; Rx w/ PPI, dilation

Webs: thin, partially occlusive structure, proximal, a/w Fe defic. (Plummer-Vinson synd.)

Peptic or XRT strictures, foreign body, tumor, vascular rings (dysphagia lusoria), compression from dilated left atrium compression

Infxn esophagitis: odynophagia >dysphagia; often immunosupp w/ *Candida*, HSV, CMV

Pill esophagitis: odynophagia >dysphagia; NSAID, KCl, bisphosp., doxy & tetracycline

Eosinophilic esophagitis (*JAMA* 2021;326:1310): often young/middle-aged ♂. Dx: >15 eos/hpf on bx, esoph dysfxn (ie, dysphagia, food impaction). Rx: 1st line is PPI (½ respond); alternative (or if fail PPI) is **3Ds**: 1st elimination **D**iet (Ø milk, soy, eggs, wheat, nuts, fish); if no Δ, **D**rugs (swallow inh steroids); if ongoing sx & stricturing, **D**ilation (*Gastro* 2020;158:1776).

Neuromuscular dysphagia (solids & liquids; *Neurogastero Motil* 2021;33:e14058)

- Caused by aberrant motility or innervation of oropharynx/esophagus
- Oropharyngeal: consider CNS disorders (eg, stroke, ALS, myopathies, CNS tumors)
- Esophageal: motility disorder w/ dysphagia, chest pain, GERD; dx: conventional or high-res manometry w/ esophageal pressure topography. Chicago classification v4.0:

1. Disorders of EGJ Outflow: *Isolated EGJ outflow obstruction or achalasia. Achalasia:* simult. ↓ amp contractions & ↓ LES relaxation; barium swallow w/ dilated esophagus & distal "bird's beak" narrowing; mostly idiopathic, although can be a/w Chagas; Rx: pneumatic dilation as effective as Heller myotomy

(local expertise dependent) (*Gut* 2016;65:732); peroral endoscopic myotomy; CCB/nitrates/PDEi; botox if Ø surg cand.

2. Disorders of Peristalsis: *Absent contractility* (failed peristalsis)*; distal esophageal spasm* (uncord. peristalsis w/ simult. contractions); *hypercontractile esoph* (high amp contract.; Rx w/PPI, nitrates/CCB/PDEi, TCA); *ineffective esophageal motility* (↓ amp of distal esoph contractions; seen in scleroderma, DM, hypothyroid.; Rx w/ underlying disorder & w/ PPI)

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Pathophysiology (*JAMA* 2020;324:2536)

- ↑ acid exposure in esophagus, caused by ↑ transient LES relaxations. Worsened by ↑ intraabd pressure (eg, obesity, pregnancy), ↓ esophagogastric motility, hiatal hernia. Rarely caused by ↑ secretory states (eg, Zollinger-Ellison).
- Precipitants: supine, fatty foods, caffeine, alcohol, cigarettes, CCB, pregnancy, obesity

Clinical manifestations

- Esophageal: **heartburn**, atypical chest pain, regurgitation, sour taste, dysphagia
- Extraesophageal: **dry cough**, asthma (often poorly controlled), laryngitis, dental erosions

Diagnosis (*Annals* 2015;163:ITC1; *Nat Rev Gastro Hepatol* 2016;13:501)

- Clinical diagnosis based on sx and response to empiric trial of PPI ("PPI test")
- EGD if: Ø response to PPI or *alarm features*: dysphagia, vomiting, ↓ wt, anemia, age >60
- If dx uncertain & EGD nl → esoph manometry w/ 24-h pH monitoring ± impedance to dx:
  - "Nonerosive reflux disease": no erosion, ulceration or Barrett's; ½ abnl pH. Unpredictable response to PPI. Most will *not* progress to erosive esophagitis or Barrett's.
  - "Reflux hypersensitivity": nl acid exposure on pH/impedance w/ symptom–reflux assoc.
  - "Functional heartburn": nl acid exposure on pH/impedance w/o symptom–reflux assoc.

Treatment (*World J Gastrointest Endosc* 2018;10:175; *Am J Gastro* 2022;117:27)

- Lifestyle: avoid precipitants, lose weight, no eating 2 hrs before bed, exercise, Ø tobacco
- Medical: start low-dose PPI, uptitrate up to 40 mg bid; H2 blockers for intermittent sx
- Refractory (max dose ≥8 wks): confirm w/ pH testing on or off PPI, consider hernia repair
  - If acidic or sx correlate w/ reflux episodes: surgical fundoplication (emerging Rx: LES sphincter augmentation w/ radiofrequency, implantable magnetic or electrical devices)
  - If nl pH or no sx correlation = "fxnal dyspepsia" (*Gastro* 2020;158:2286); Rx w/ TCA, SSRI

Complications (*Gastro* 2020;158:760)

- Reflux esophagitis (erosions/ulcers above GE jxn), strictures (caused by chronic inflamm)
- Barrett's esoph. (BE): metaplastic columnar mucosa above GE jxn replaces squam epithel.
  - Screen if chronic (>5 y) and/or frequent GERD (≥1/wk) in ♂ w/ ≥2 risk factor for Barrett's/esophageal adeno: >50 y, white, hiatal hernia, central adiposity, smoking, FHx of Barrett's/esophageal adeno. In ♀, consider only if multiple RFs. 0.1–0.3%/y risk of esoph adenocarcinoma, ↑ if ↑ dysplasia (*Am J Gastro* 2016;111:30).
  - Mgmt: PPI. W/o dysplasia: surveillance EGD q3–5y. Low-grade dysplasia: EGD q12mo; possible endoscopic eradication. High-grade dysplasia: endoscopic eradication; consider chemoprophylaxis w/ high-dose PPI & ASA (*Lancet* 2018;392:400).

Peptic Ulcer Disease (PUD)

Definition & etiologies (*BMJ* 2019;367:5495)

- Ulcers (break in mucosal lining >5 mm) & erosions (<5 mm) in stomach and duodenum
- Principal risk factors: *H. pylori* infection >ASA/NSAID use
- ***H. pylori* infection:** causes ~80% of duodenal ulcers (DU) & ~30–40% of gastric ulcers (GU). ~50% of world colonized w/ *H. pylori*, but only 5–10% will develop PUD.

- **ASA/NSAIDs:** damage to mucosa caused by ↓ prostaglandin synthesis. Cause majority of non–*H. pylori*-related DU & GU. Regular use a/w 5–6× ↑ odds of GIB.
- Other: smoking, stress, excessive EtOH, gastric cancer/lymphoma, Crohn's, viral infxn (eg, CMV/HSV in immunosupp), bisphosphonates, steroids (in combo w/ NSAIDs, but not risk factor alone); rarely gastrinoma (Zollinger-Ellison synd.), mastocytosis, idiopathic
- Stress ulcer: risk factors = ICU & coagulopathic, mech vent, h/o GIB, steroid use; Rx w/ PPI

Clinical manifestations

- **Epigastric gnawing abdominal pain:** relieved with food (DU) or worsened by food (GU)
- Complic.: UGIB, perf. & penetration, gastric outlet obstruction (due to edema & dysmotility)

Diagnostic studies

- Testing for *H. pylori:* stool Ag, urea breath testing (UBT) or EGD + rapid urease test (RUT) False ⊖ Ag, UBT, RUT if on abx, bismuth, PPI; ∴ stop prior to testing if possible Serology: ↓ utility, useful only to exclude infection in lower prevalence areas
- EGD (definitive dx): if fail empiric Rx or alarm features (see "GERD"); bx GU to r/o malig & *H. pylori;* repeat EGD in 6–12 wk if >2 cm, malig features, risk factors for gastric cancer (ie, ⊕ FHx, ⊕ *H. pylori*, atrophic gastritis, metaplasia on bx, >50 y), or sx persist

Treatment (*Lancet* 2016;388:2355; *Gastro* 2016;151:51; *Gut* 2017;66:6; *AJG* 2017;112:212)

- **If *H. pylori*** ⊕ → **eradicate** ("test and treat"); if ⊖ → gastric acid suppression w/ PPI
  - 1st line: Quad. Rx: 14d x [MNZ + TCN + bismuth + PPI] or [MNZ + amox + clarith + PPI]
  - Besides PUD, test & Rx if: gastric MALT lymphoma, s/p resection for early gastric ca, FHx gastric ca, unexplained iron def. anemia, ITP, uninvestigated dyspepsia in Pt <60 y, or when initiating long-term NSAIDs
- "Test-of-cure": 4 wk after Rx, off PPI x 1–2 wk. Use stool Ag, EGD + RUT, or UBT.

- Lifestyle changes: d/c smoking and probably EtOH; diet does not seem to play a role
- Surgery: if refractory to med Rx (1st r/o NSAID use) or for complic. (see above)

GI prophylaxis if taking ASA/NSAID (*Am J Gastro* 2009;104:728)

- PPI if h/o PUD/UGIB and either (a) on $P2Y_{12}$ inhib or anticoag, or (b) ≥2 of the following: >60 y, steroids or dyspepsia. Low bleeding risk Pts unlikely to benefit (*Gastro* 2019;157:403).
- Consider Δ non-selective NSAID to selective COX-2 inhibitor (↓ PUD & UGIB but ↑ CV events), if low CV risk & not on ASA

GASTROINTESTINAL BLEEDING

Definition

- Intraluminal blood loss anywhere from the oropharynx to the anus
- Classification: **upper** = above the ligament of Treitz; **lower** = below the ligament of Treitz
- "Severe" GIB: defined as having associated shock, orthostatic hypotension, ↓ Hct by 6% (or ↓ Hb by 2 g/dL), or requiring transfusion ≥2U PRBCs. Requires hospitalization.

Clinical manifestations

- **Hematemesis** = blood in vomitus (UGIB)
- **Coffee-ground emesis** = emesis of blood exposed to gastric acid (UGIB)
- **Melena** = black, tarry stools from digested blood (usually UGIB, but can be SB or R colon)
- **Hematochezia** = bloody or maroon-colored stools (LGIB or rapid UGIB)

Initial management (*Am J Gastro* 2021;116:899)

- **Assess severity:** *VS including orthostatic Δs, JVP.* Tachycardia (can be masked by βB use) suggests 10% volume loss, orthostatic hypotension 20% loss, shock >30% loss. Scoring predicts rebleeding & mortality: AIMS65, ABC Score & Glasgow-Blatchford.
- **History:** prior GIB, tempo of current bleed, specific bleeding manifestations (see above), other GI s/s (eg, abd pain, Δ in bowel habits, weight loss, N/V), ASA/NSAID or EtOH use, anticoag/antiplt drugs, h/o or risk factors for cirrhosis, radiation, prior GI or aortic surgery
- **Physical exam:** localizable abd tenderness, peritoneal signs, masses, LAN, prior surgery, signs of liver disease (hepatosplenomegaly, ascites, jaundice, telangiectasias), rectal exam: masses, hemorrhoids, anal fissures, stool appearance, color
- **Resuscitation:** placement of 2 large-bore (18-gauge or larger) intravenous lines. Volume replacement: NS or LR to achieve

normal VS, UOP, & mental status.

- **Lab studies: Hct** (*may be normal* in first 24 h of acute GIB before equilibration) 2–3% → 500 mL blood loss; low MCV → Fe deficient and chronic blood loss; **plt**, **PT/INR**, **PTT;** BUN/Cr (ratio >36 in UGIB b/c GI resorption of blood ± prerenal azotemia); LFTs
- **Transfuse:** type & cross; use O-neg if emerg; for UGIB (esp. w/ portal HTN) transfuse w/ more restrictive Hb goal (eg, >7 g/dL or >8 g/dL if CAD) (*JAMA* 2016;316:2025)
- **Reverse coagulopathy:** consider FFP to normalize INR (however caution in ESLD where INR does not correlate with bleeding risk); plts >50k, ddAVP if uremic, consider reversal agents if on anticoagulants (qv)
- **Triage:** alert endoscopist. Consider ICU if unstable VS or poor end organ perfusion.
  Intubation for: emergent EGD, ongoing hematemesis, shock, poor resp status, Δ MS
  OutPt management if SBP ≥110, HR <100, Hb ≥13 (♂) or ≥12 (♀), BUN <18, Ø melena, syncope, heart failure, liver disease (*Clin Gastro Hepatol* 2015;13:115)

Diagnostic studies (*JACR* 2021;18:S139)

- UGIB: **EGD** w/in 24 h (*NEJM* 2020;382:1299). If severe bleed, ↑ dx/Rx yield if **erythro 250 mg IV given 30 min prior to endoscopy** to clear stomach contents.
- LGIB: **colonoscopy** (identifies cause in >70%); early colo (w/in 24 h) unlikely to improve outcome vs. late (24-96 h) (*Gastro* 2020;158:168). If hematochezia a/w orthostasis, concern for brisk UGIB → *exclude UGIB w/ EGD first.* Push enteroscopy, anoscopy, capsule endoscopy in combo w/ urgent colo results in dx >95% of cases (*GI Endo* 2015;81:889).
- Imaging: if too unstable for endo or recurrent bleeding, consider IR embolization or surgery
  tagged RBC scan: can identify general luminal location if bleeding rate ≥0.04 mL/min
  CT angiography: faster to obtain than RBC scan, detects bleeding ≥0.3 mL/min

arteriography: can localize exact vessel if bleeding rates ≥0.5 mL/min, *allows for IR Rx*

- Emergent exploratory laparotomy (last resort) if no localization and life-threatening bleed

Etiology UGIB	**Comment & Treatment** (*GI Endosc Clin N Am* 2015;25:415)
PUD (20–60%; duodenal>gastric) (*Am J Gastro* 2021;116:899) See "PUD"	*Treatment:* **PPI:** 40 mg PO or IV BID **Endoscopic therapy:** epi inj + bipolar cautery or hemoclip. Bx for *H. pylori* and treat if ⊕. *High-risk (for rebleeding) ulcer*: arterial spurting, adherent clot, visible vessel. Endo Rx, IV PPI × 72 h post EGD, then Δ to high-dose oral PPI. If fail, arteriography w/ embolization; surgery (last resort). *Intermediate-risk ulcer*: oozing, in o/w stable Pt. Endo Rx, can Δ to oral PPI after EGD and observe 24–48 h. *Low-risk ulcer:* clean-based or flat. Oral PPI & discharge. Hold anticoag & antiplatelet Rx until hemostasis; can resume after hemostasis & PPI on board (*Endoscopy* 2015;47:a1)
Erosive gastropathy (4–30%)	Precipitants: ASA/NSAID, EtOH, cocaine, gut ischemia, XRT Stress-related mucosal injury in ICU Pts. Risk factors include severe coagulopathy, mech vent >48 h, high-dose glucocorticoids Treatment: high-dose PPI
Esophagitis (15%)	Rx offending cause + high-dose PPI; repeat EGD to r/o Barrett's.
Esophageal or gastric varices (4–20%) (*Clin Gastro Hepatol* 2015;13:2109; *J Gastro Hepatol* 2016;31:1519; *Hep* 2017;65:310) See "Cirrhosis"	2° to portal HTN. If isolated gastric → r/o splenic vein thrombosis. *Pharmacologic* Start **octreotide** pending EGD if suspect varices: Rx for 2–5 d Abx: 20% cirrhotics p/w GIB have infxn, & ~50% develop infxn during hospitalization; Ppx w/ IV CTX, cipro, or levoflox × 7 d *Nonpharmacologic* Esophageal varices: **endoscopic band ligation** (>90% success). Covered esophageal stent placement or balloon tamponade if refractory as bridge to TIPS (consider early espec. if Child-Pugh C). Gastric varices: arteriography w/ coiling, or if available, endoscopic injection of cyanoacrylate (glue). If refractory: TIPS or balloon-retrograde transvenous obliteration (BRTO).
Portal HTN gastropathy	↑ portal venous pressure → ectatic vessels,

		hyperemia in gastric antrum. Rx: reduce portal HTN (octreotide), βB, TIPS.
Vascular (5–10%)	Angioectasia AVMs, HHT (see below)	AVMs congenital. Angioectasia (ectatic submucosal vessels) a/w ↑ age, CKD, cirrhosis, CTD, severe CV dis. *Heyde syndrome:* GIB due to angioectasias + aortic stenosis. Rx: endoscopic Rx.
	Dieulafoy's lesion	Large (1–3 mm) submucosal artery protruding through fundal mucosa → sudden, massive UGIB. *Difficult to identify.* Endo Rx.
	Gastric antral vasc. ectasia (GAVE)	"*Watermelon stomach*"; ectatic gastric vessels, often a/w cirrhosis, CTD, typically older ♀. Rx w/ EGD w/ thermal hemostasis, repeat q4–8wk to eradicate lesions. TIPS does *not* improve outcomes.
	Aortoenteric fistula	AAA or aortic graft erodes into 3rd portion of duodenum. P/w "herald bleed." If low suspicion → endoscopy; if high → CT angiography.
Malignancy (5%)		Endoscopic hemostasis of mass temporizing measure till cancer Rx
Mallory-Weiss tear (5–10%)		GE jxn lacerations due to vomiting → ↑ intraabd pressure & shearing Often self-resolve; Rx→ antiemetics, PPI, endoscopic therapy
Cameron's lesions		Linear erosions in hiatal hernia due to mech trauma of diaphragm
Post-sphincter- otomy bleeding		Occurs in ~2% of ERCP w/ sphincterotomy; ↑ risk w/ more complic. procedure. Bleeding into duodenum. Rx w/ endo hemostasis.

Etiology LGIB	**Comment & Treatment** (*NEJM* 2017;376:1054)
Diverticular bleed (30%)	*Pathophysiology:* Intimal thickening and medial thinning of vasa recta as they course over dome of diverticulum → weakening of vascular wall → arterial rupture. Diverticula more common in left colon; but *bleeding diverticula more often in right colon.* *Clinical:* older, ASA/NSAIDs, usually painless hematochezia ± abd cramping *Treatment:* Usually stops spontaneously (~75%); ~20% recur. Can perform endoscopic hemostasis. Surgery (partial colectomy) last resort.
Polyp/Tumor (20%)	Typically slow ooze, p/w fatigue, weight loss, iron deficiency, anemia
Colitis (20%)	Infectious (see "Acute Diarrhea"), IBD, ischemic colitis, XRT
Anorectal disorders (20%)	Internal, external hemorrhoids; anal fissures, rectal ulcers, rectal varices (Rx by ↓ portal venous pressure in cirrhosis), XRT
Vascular (<10%)	Angioectasia & AVMs. *Hereditary hemorrhagic telangiectasia* (Weber-Osler-Rendu): diffuse AVMs throughout GI mucosa (also involve lips, oral mucosa, fingertips).

Meckel's diverticulum	Congenital intestinal pouch due to incomplete obliteration of vitelline duct. 2% of pop, w/in 2′ of IC valve, 2″ long, ♂:♀ 2:1, can present as obscure GIB in adults. Dx w/ ^{99m}Tc-pertechnetate scintigraphy. Rx w/ angioembo, surgical resection.

Obscure GIB (*Am J Gastro* 2015;110:1265; *Gastro* 2017;152:497)

- **Definition:** continued bleeding (melena, hematochezia) despite ⊖ EGD & colo; 5% of GIB
- **Etiologies:** Dieulafoy's lesion, GAVE, small bowel angiodysplasia, ulcer or cancer, Crohn's disease, aortoenteric fistula, Meckel's diverticulum, hemobilia
- **Diagnosis:** repeat EGD w/ push enteroscopy/colonoscopy when bleeding is active
  - If ⊖, video capsule to evaluate small intestine (contraindic. if stricture) (*GIE* 2015;81:889)
  - If still ⊖, consider ^{99m}Tc-pertechnetate scan ("Meckel's scan"), enteroscopy (single-balloon, double-balloon, or spiral), tagged RBC scan and arteriography

DIARRHEA

ACUTE DIARRHEA (<4 weeks' duration)

Acute Infectious Etiologies (*Am J Gastro* 2016;111:602; *JAMA* 2019; 321:891)		
NONINFLAMMATORY		**Predom. disruption small intestine absorp. & secretion. Voluminous diarrhea, N/V. ⊖ Fecal WBC & FOB.**
Preformed toxin		"Food poisoning," <24 h dur. *S. aureus* (meats & dairy), *B. cereus* (fried rice), *C. perfringens* (rewarmed meats).
Viral (*Lancet* 2018; 392:175)	Rotavirus	Outbreak person to person (PTP), daycare; lasts 4–8 d.
	Norovirus	~50% of all diarrhea. Winter outbreaks; PTP & food/water; no immunity. Lasts 1–3 d. Vomiting prominent.
Bacterial	*E. coli* (toxigenic)	>50% of traveler's diarrhea; cholera-like toxin; <7 d.
	Vibrio cholerae	Contam H_2O, shellfish; "rice water" stools w/ dehydration
Parasitic (± malab for mos after Rx)	*Giardia*	Streams/outdoor sports, travel, outbreaks. Bloating. Acute (profuse, watery) → chronic (greasy, malodorous).
	Cryptosporidia	In soil; water-borne outbreak; usually self-limited, can → chronic infxn if immunosupp. Abd pain (80%), fever (40%).
	Cyclospora	Contaminated produce, intl travel (Latin America)
INFLAMMATORY		**Predom. colonic invasion. Small-vol diarrhea. LLQ cramps, tenesmus, fever, typically ⊕ fecal WBC or FOB.**
Bacterial	*Campylobacter*	Undercooked poultry, unpasteurized milk; carried by - puppies & kittens. Prodrome w/ abd pain, "pseudoappendicitis"; c/b GBS, reactive arthritis.
	Salmonella (nontyphoidal)	Eggs, poultry, milk, hamsters. Bacteremia in 5–10%. 10–33% of bacteremic Pts >50 y may develop aortitis.
	Shigella	Abrupt onset; no N/V; gross blood & pus in stool; ↑↑ WBC

Acute Infectious Etiologies (*Am J Gastro* 2016;111:602; *JAMA* 2019; 321:891)		
	E. coli (O157:H7 & inv/hemorrhagic non-O157:H7)	Undercooked beef, unpasteurized milk, raw produce; PTP. O157 & non-O157 sp. (40%) produce *Shiga* toxin → HUS (typically in children). Gross blood in stool.
	C. difficile	Vide infra
	Vibrio parahaem.	Undercooked seafood
	Salmonella typhi	Travel to Asia, Africa, South America. Systemic toxicity, relative bradycardia, rose spot rash, ileus → "pea-soup" diarrhea, bacteremia.
	Other	*Yersinia:* undercooked pork; unpasteurized milk, abd pain → "pseudoappendicitis" (aka mesenteric adenitis) *Aeromonas, Plesiomonas, Listeria* (meats & cheeses)
Parasitic	*E. histolytica*	Contaminated food/water, travel (rare in U.S.); liver abscess
Viral	CMV	Immunosuppressed; dx by shell vial cx of colon bx

Evaluation (*NEJM* 2014;370:1532; *Digestion* 2017;95:293; *PLOS One* 2017;12:11)

- **Ddx:** hyperthyroid, adrenal insufficiency, meds (abx, antacids, immune checkpt inhibitors), appendicitis, diverticulitis, radiation, 1st presentation of bowel disorder (eg, IBD, celiac)
- **History:** stool freq, blood, abd pain, duration of sxs [~1 wk for viral & bacterial (except *C. diff*), >1 wk for parasitic], travel, food, recent abx, immunocompromise
- **PEx:** vol depletion (VS, UOP, axillae, skin turgor, MS), fever, abd tenderness, ileus, rash
- **Laboratory:** calprotectin, stool cx, BCx, lytes, *C. diff* (if recent hosp/abx), stool O&P (if >10 d, travel to endemic area, exposure to unpurified H_2O, community outbreak, daycare, HIV ⊕ or MSM); ± stool ELISAs (viruses, *Crypto*, *Giardia*), serologies (*E. histolytica*); PCR available (but high ⊕ rate & unclear if true vs. colonized; consider if immunocompromised)
- **Imaging/endoscopy:** consider if ***warning signs (WS)*** of fever, severe abd pain, blood or pus in stool, >6 stools/d, severe dehydration, immunosupp, elderly, duration >7 d, hosp-acquired. CT/KUB if ? toxic megacolon; sig/colo if immunosupp or cx ⊖.

Treatment (*Am J Gastro* 2016;111:602; *Clin Infect Dis* 2017;65:e45)

- If no WS, nl PO intake → supportive: hydrate, loperamide, bismuth subsalicylate (Ø antichol)
- If mod. dehydration: 50–200 mL/kg/d of oral solution or Gatorade, etc. If severe: IV fluids.
- If suspect traveler's diarrhea → azithro 1 g x 1 d (due to FQ resistance in Asia), rifaximin, or rifamycin; if suspect protozoal → flagyl or nitazoxanide
- *Empiric* abx for non–*C. diff inflammatory* diarrhea reasonable for severe disease (fever, >6 BMs/d, hospitalization, bloody or mucoid stools or high-risk Pt [> 70 yrs, immunosupp]: azithro 1 g x 1 d (preferred if fever or dysentery) or FQ × 3–5 d (↑ resistance)
- *Avoid* abx if suspect *E. coli* O157:H7 (exposure hx, gross blood) as may ↑ risk of HUS

CLOSTRIDIOIDES DIFFICILE INFECTION (CDI)

Pathogenesis & epidemiology (*NEJM* 2015;372:825)

- Ingestion of *C. diff* spores → colonization when colonic flora Δ'd by abx or chemo → release of toxin A/B → colonic mucosal necrosis & inflammation → pseudomembranes
- Most frequently reported nosocomial infxn; community-acquired w/o abx ~⅓of new cases. A/w *any* abx during or up to 10 wks post Rx (esp. β-lactams, clinda, FQ).
- Elderly, immunocompromised, and IBD Pts can develop CDI w/o recent abx exposure

Clinical manifestations (a spectrum of disease)

- Asx colonization: <3% healthy adults; ~20% in hospitalized patients on antibiotics
- Acute watery diarrhea (>3 stool/d), occ bloody ± mucus, lower abd pain, fever, ↑↑↑ WBC
- Pseudomembranous colitis: above sx + pseudomembranes + bowel wall thickening
- Fulminant colitis (2–3%): **toxic megacolon** (colonic atony/absence of BMs, colon dilatation ≥6 cm on KUB, systemic toxicity) and/or bowel perforation

Diagnosis (*Ann Intern Med* 2018;169:49)

- Only test if *symptomatic* (diarrhea, s/s of colitis); test *liquid* stool (unless concern for ileus)
- **Stool toxin immunoassay** (high Sp) + **glutamate dehydrogenase** (GDH) (high Se)
- **Stool PCR:** has ↑ Se, but ⊕ if colonized in absence of active infxn; should not necessarily Rx if ⊕ PCR w/ neg toxin assay (*JAMA IM* 2015;175;1792)
- Obtain CT abdomen/pelvis if suspect complication (toxic megacolon). Consider flex sig if dx uncertain and/or evidence of no improvement on standard Rx.

Initial treatment (*CID* 2021;73:5; *Am J Gastro* 2021;116:1124)

- If possible, d/c abx ASAP; stop antimotility agents & cholestyramine if using (binds vanco)
- Fidaxomicin is now preferred over vancomycin regardless of severity; may be limited by $
- **Mild-mod:** fidaxomicin 200 mg BID (↓ recurrence rate) or vanco 125 mg PO q6h × 10 d
- **Severe** (any of the following: >12 BM/d, Temp >103°F, WBC >15, HoTN, ICU care required, ileus): as above; could consider PO+PR vanco
- **Fulminant disease**: vanco 500 mg PO qid + MNZ 500 mg IV q8h; consider FMT
- If **worsening** (ileus, ↑ WBC, ↑ lactate, shock, toxic megacolon, peritonitis): abd CT & urgent surgical consult - subtotal colectomy, diverting loop ileostomy or colonic lavage
- If need to cont abx, cont *C. diff.* Rx for ≥7 d post-abx cessation (*Am J Gastro* 2016;111:1834)
- Stool carriage 3–6 wk postcessation; retesting for *C. diff* of limited utility during this time

Recurrent infection (15–30% risk after d/c of abx, most w/in 2 wk of stopping abx)

- 1st recurrence: fidaxomicin 200 mg PO bid × 10 d or vanco 125 mg PO q6h × 10–14 d. Consider adding bezlotoxumab 10 mg/kg IV × 1 during abx Rx (mAb that binds toxin B) as ↓ recurrence; caution in CHF (*NEJM* 2017;376:305).
- Subsequent recurrences: fidaxomicin or vanco PO pulse → taper. Consult ID. Fecal microbial transplant (*JAMA* 2017;318:1985)

recommended after 3 CDI.
- Prevention: vanco 125 mg PO QD ↓ risk of recurrence (*CID* 2016;65:651); consider for Pts needing abx w/ h/o severe or recurrent CDI. Avoid acid suppression/abx as able.

CHRONIC DIARRHEA (>4 wk)

General evaluation (*JAMA* 2016;315:2712; *Gastro* 2019;157:3)
- Clinically can be classified as *watery*, *fatty*, *inflammatory*
- Additional hx: timing (freq, relation to meals; *nocturnal diarrhea* a/w organic causes like IBD rather than IBS), abd pain, wt loss, prior surg, chemo/XRT, diet (incl caffeine or poorly absorbed carbs/sugars), infectious sxs, immunocompromise, travel, laxative use, stress
- Hx offending meds: PPI, colchicine, abx, H2RA, SSRIs, ARBs, NSAIDs, chemo, caffeine
- PEx: gen appearance (BMI), signs of systemic disease, surgical scars, rectal tone/DRE
- Lab testing: CBC, metabolic profile, alb, TSH, Fe, fecal calpro; *see under each category*
- Imaging/endoscopy: colonoscopy for chronic diarrhea of unknown cause. Abd CT/MRI usually warranted if systemic problem suspected.

Osmotic (watery; ⊖ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)
- Caused by ingestion of poorly absorbed cations/anions (Mg, sulfate, phos; found in laxatives) or poorly absorbed carbs (eg, mannitol, sorbitol [found in chewing gum]) or lactose if lactose intolerant. *Diarrhea resolves w/ cessation of offending substance.*
- Dx: ↑ **stool osmotic gap** (see Figure); stool pH <6 if unabsorbed carbohydrates
- **Lactose intolerance**: can be acquired after gastroenteritis, med illness, GI surg. Clin: bloating, flatulence, discomfort, diarrhea. Dx: H^+ breath test or empiric lactose-free diet. Rx: lactose-free diet & lactase tablets.

Secretory (watery; nl osmotic gap, no **Δ** diarrhea w/ fasting, nocturnal, cramps)

- Caused by secretion of anions or K+ into lumen or inhib of Na absorption → ↑ H_2O in stool. Most commonly caused by bacterial toxins from **infxn** (see above). Other causes:
- **Endocrine:** Addison's, VIPoma, carcinoid, Zollinger-Ellison, mastocytosis, hyperthyroid (↑ motility). ✓ serum peptide levels (eg, gastrin, calcitonin, VIP) & urinary histamine.
- **GI neoplasm:** carcinoma, lymphoma, villous adenoma
- **Microscopic colitis:** common cause of chronic diarrhea w/ obscure origin. Often seen in middle-aged women w/ autoimmune disorders. NSAIDs, SSRIs, PPIs notable triggers. Grossly normal on colo but bx shows lymphocytic & plasmacytic infiltration of mucosa ± thickened submucosal collagen. Rx: budesonide (1st line), antidiarrheals, cholestyramine, bismuth; consider anti-TNFs if refractory (*Gastro* 2016;150:242).
- **Bile acid-induced diarrhea:** ileal resection or disease (eg, Crohn's) → bile acids in colon → electrolyte & H_2O secretion. Rx w/ empiric bile-acid binders (eg, cholestyramine).

Functional/IBS (normal osmotic gap, ↓ diarrhea with fasting): see "Dysmotility"

Malabsorption (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- Defective mucosal absorption of nutrients b/c Δs in: mucosal surface (surgical resection) or gen. mucosal dis. (celiac, IBD). Bloating, foul-smelling, floating stools (steatorrhea).
- **Celiac disease** (*JAMA* 2017;318:647; *Lancet* 2018;391:70; *Gastro* 2019;156:4)
  - Immune rxn in genetically predisposed Pts (~1% pop) to gliadin, a component of gluten (wheat protein) → small bowel inflammatory infiltrate → impaired absorption
  - Other s/s: Fe/folate/B_{12} defic anemia; osteoporosis; dermatitis herpetiformis; ↑ ALT/AST
  - Dx: best if eating gluten when tested; IgA anti-tissue transglutaminase Ab (most Se), IgA anti-deaminated gliadin peptide Ab; IgA α-endomysial Ab. Duodenal bx confirms dx (blunted villi, crypt hyperplasia, inflamm infiltrate); absence of HLA-DQ2/8 excludes dx.

Rx: gluten-free diet; 7–30% do not respond to diet → ? wrong dx or noncompliant

Complic: ~5% refractory sx, risk of T-cell lymphoma and small bowel adenocarcinoma

- **Whipple's disease:** infxn w/ *T. whipplei* (*Lancet* 2016;16:13)
  Other s/s: fever, LAN, edema, arthritis, CNS Δs, gray-brown skin pigmentation, AI & MS, oculomasticatory myorhythmia (eye oscillations + mastication muscle contract).
  Dx: bx/path, IHC, PCR. Rx: PCN + streptomycin or 3rd-gen ceph × 10–14 d → Bactrim ≥1 y.
- **Small intestinal bacterial overgrowth** (SIBO): colonic bacteria in SI → steatorrhea, B12/Fe defic, protein-losing enteropathy. A/w dysmotility (DM neuropathy, scleroderma), Δ'd anatomy (Crohn's, surgery, fistulae), immune deficiency, celiac, CF. Dx w/ H^+ or ^{14}C -xylose breath testing or empiric abx. Rx w/ 7–10 d abx (rifaximin, MNZ, or FQ).
- Other: s/p short bowel resection (short bowel syndrome), chronic mesenteric ischemia, eosinophilic gastroenteritis, intestinal lymphoma, tropical sprue, *Giardia* infection

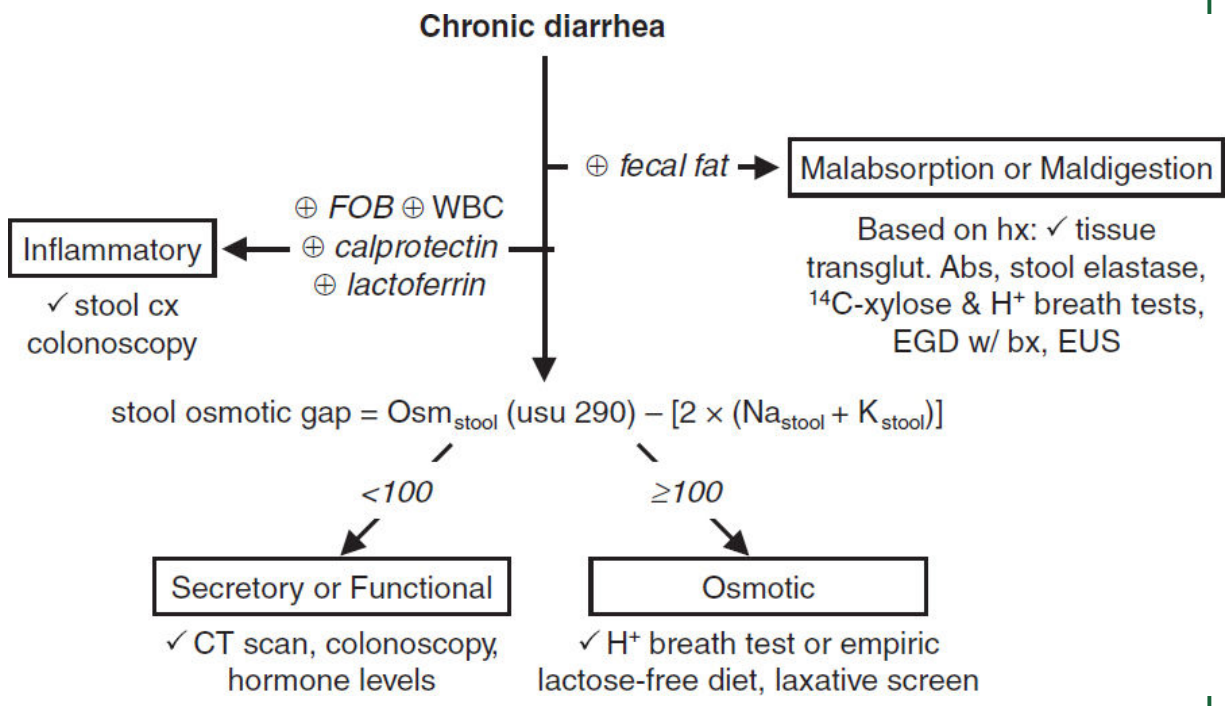
Maldigestion (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- Defective intraluminal hydrolysis of nutrients, typ. 2/2 pancreatic/hepatobiliary pathology
- **Pancreatic insufficiency:** most commonly from chronic pancreatitis or pancreatic cancer. Test w/ stool elastase, chymotrypsin levels, fecal fat, or empiric pancreatic enzyme Rx.
- ↓ **bile acids** due to ↓ synthesis (cirrhosis), cholestasis (PBC), or s/p ileal resection. Test w/ empiric bile acid replacement therapy.

Inflammatory (⊕ fecal WBC, calprotectin, lactoferrin; ⊕ FOB; fever, abd pain)

- **Infections:** chronic *C. diff*, *Entamoeba histolytica*, *Yersinia*, CMV, TB especially in immunocompromised hosts. CMV, *C. diff* notorious for causing exacerbations of IBD.
- **Inflammatory bowel disease** (Crohn's, UC); fecal calprotectin helpful for ruling out IBD
- Radiation enteritis, ischemic colitis, neoplasia (colon cancer, lymphoma)

Figure 3-2 Workup of chronic diarrhea



DYSMOTILITY & NUTRITION

Functional GI disease (~30 types per Rome IV criteria; *Gastro* 2016;150:1257)

- Recurrent GI sx caused by disorders of gut-brain interaction rather than structural cause
- **Irritable bowel syndrome (IBS)** (*JAMA* 2015;313:949; *Gastro* 2015;149:1399 & 2018;154:1140)
  - Abd discomfort for 6+ mos a/w ≥2: improves w/ defecation, Δ stool frequency, Δ stool form
  - **IBS-C** (constipation predominant) vs. **IBS-D** (diarrhea predominant) vs. IBS-M (mixed) vs. IBS-U (unclassified). Sx may be affected by stress, diet, lifestyle, probably microbiome.
  - **Treatment:** cog. behavior Rx, probiotics, anti-spasmodics, exercise, neuromodulators (eg, TCA, SSRI), Δ diet (↓ fermentable carbs w/ low FODMAP diet, lactose-free diet)
  - IBS-C: ↑ fiber, laxatives (lubiprostone, linaclotide, tegaserod, tenapanor), biofeedback
  - IBS-D: loperamide, rifaximin, eluxadoline, bile acid sequestrants, alosetron
- **Cyclic vomiting syndrome (CVS):** acute recurrent vomiting; a/w marijuana use, personal or FHx of migraine. Acute Rx: antiemetics, IVF, sumatriptan (1st line, followed by aprepitant x 3 d), BDZs; prevention: TCAs/AEDs; avoid marijuana.

Gastroparesis (*Nat Rev Dis Primers* 2018;4:41)

- Delayed gastric emptying w/o mechanical obstruction, typically p/w nausea (>90%), vomiting (>80%), early satiety (60%), postprandial fullness/pain
- Etiol: DM, post-surg, post-viral, crit. illness, Parkinson's, opiates, CCB, anti-cholin, idiopath
- Dx: r/o mechanical cause then gastric emptying scintigraphy; (⊕ if retained solids >4 h)
- Treatment: prokinetics (metoclopramide or erythromycin), antiemetics for sx; feeding tube if refractory; consider pyloromyotomy, botox

injection, pyloroplasty, or gastric stimulator

Paralytic ileus of the colon & small bowel (*Dis Colon Rectum* 2021;64:1046)

- Definition: loss of intestinal peristalsis in absence of mechanical obstruction
- Abd discomfort & distention, ↓ or absent bowel sounds, ± N/V, hiccups
- Typically in elderly, hospitalized, ill Pts; precipitated by: intra-abd process (surgery, pancreatitis, peritonitis, intestinal ischemia), severe illness (eg, sepsis), meds (opiates, CCB, anticholin.), metab/endo abnl (thyroid, DM, kidney failure, liver failure, hypoK), spinal cord compression/trauma, neurologic d/o (Parkinson's, Alzheimer's, MS)
- KUB/CT w/ colonic dilatation (in ileus, dilated loops of SB) w/o mech obstruction; cecal diam >12 cm a/w high-risk perf in Ogilvie's syndrome (colonic pseudo-obstruction)
- **Treatment:** NPO, avoid offending meds, IV **neostigmine** (monitor for bradycardia), methylnaltrexone; bowel decompression w/ NGT, rectal tube, nutrition support. Ogilvie's only: colonoscopic decompression; if refractory, colostomy or colectomy.

Constipation (*Annals* 2015;162:ITC1, *Nat Rev Dis Primers* 2017;3:17095; *JAMA* 2019;322:2239)

- Defined as dissatisfaction w/ defecation or (per Rome IV): ≥2 of following during last 3–6 mos ≥25% of the time: straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate defecation, stool frequency <3/wk
- **Primary etiologies:** slow transit vs. pelvic floor dyssynergia
- **Secondary etiologies** (4 Ms; *JAMA* 2016:315:185)
  - Mech obstruction: malignancy, compression, rectocele, strictures
  - Meds: opioids, TCAs, anticholinergics, CCB, NSAIDs, diuretics, Ca^{2+}, Fe, low fiber diet
  - Metabolic/endo: DM, hypothyroid, uremia, preg, panhypopit, porphyria, ↑ Ca, ↓ K, ↓ Mg
  - Myopathy/Neuro: Parkinson's, Hirschsprung's, amyloid, MS, spinal injury, dysautonomia
- **Dx:** H&P w/ DRE. Labs: consider CBC, electrolytes w/ Ca, TSH. Colonoscopy if alarm sx. Anorectal manometry/balloon expulsion

test; colonic transit study; defecography.

- **Treatment:** *1st line:* ↑ fluid, fiber, & exercise; emollient laxative (docusate) to soften stool.
  2nd line: Bulk laxatives (psyllium, methylcellulose) to ↑ colonic residue, ↑ peristalsis. Stimulant laxatives (senna, castor oil, bisacodyl) to ↑ motility & secretion. Osmotic laxatives (Mg, $NaPO_4$ [avoid in CKD], PEG) to ↑ H_2O in colon.
  3rd line: Enema/suppository (phosphate, mineral oil, tap water, soapsuds, bisacodyl)
  After above failed: linaclotide ↑ stool freq, ↓ straining/bloating (*Am J Gastro* 2018;113:105).
  Lubiprostone (↑ secretion); methylnaltrexone and alvimopan for opioid-induced.
  Plecanitide (cGMP agonist) for chronic idiopathic constipation (*Gastroenterol* 2016;150:S317)

Nutrition in critical illness (also see "Mech Ventilation") (*Crit Care* 2015;19:35)

- Enteral & parenteral with similar clinical outcomes (*Lancet* 2018;391:133)
- **Enteral** (EN): starting w/in 48 h of ICU admit may ↓ infection & mortality. Contraindic. if bowel obstruction, major GIB, uncontrolled shock. Possible complic: ischemic bowel b/c ↑ demand for splanchnic blood, aspiration PNA, metabolic abnormality.
- **Parenteral** (PN): start after 7 d if unable to tolerate EN; no clear benefit to early initiation. Contraindic: hyperosmolality, severe electrolyte disturbances, severe hyperglycemia; sepsis is *relative* contraindication. Complications: hyperglycemia, sepsis (↑ risk of fungal infections), catheter-associated thrombus, refeeding syndrome, abnl LFTs (steatosis, cholestasis, gallbladder sludge due to lack of enteric stimulation).

DISORDERS OF THE COLON

DIVERTICULOSIS

Definition & pathophysiology (*Aliment Pharm Ther* 2015;42:664)

- Acquired herniations of colonic mucosa & submucosa in areas where vasa recta penetrate
- Abnormal motility and ↑ intraluminal pressure cause protrusion of colonic wall

Epidemiology

- Risk factors: ↓ fiber, chronic constipation, obesity, smoking, physical inactivity, EtOH, NSAIDs, ↑ age (10% if <40 y; 50–66% if >80 y); ↑ red meat consumption
- **Left side** (90%, mostly sigmoid) >R side of colon (except in Asia where 75–85% R-sided)

Clinical manifestations

- Usually asx; 5–15% develop diverticular hemorrhage (see "GIB") and 10–25% diverticulitis
- Limited data for ↑ fiber diet or avoiding nuts/seeds (*Thera Adv Gastro* 2016;9:213)

DIVERTICULITIS

Pathophysiology (*NEJM* 2007;357:2057; *Gastro* 2015;149:1944)

- Retention of undigested food and bacteria in diverticulum → fecalith formation → obstruction → compromise of diverticulum's blood supply, infection, microperforation
- **Uncomplicated** (75%): microperforation → localized infection, LLQ pain, fever, ↑ WBC
- **Complicated** (25%): macroperf → abscess, peritonitis, fistula (65% w/ bladder), obstrxn

Clinical manifestations

- **LLQ abdominal pain**, **fever**, nausea, vomiting, constipation or diarrhea
- PEx ranges from LLQ tenderness ± palpable mass to peritoneal signs & septic shock
- Ddx includes IBD, infectious colitis, PID, tubal pregnancy, cystitis, colorectal cancer

Diagnostic studies

- **Abdominal CT** (I^+O^+): diverticula, bowel wall thickening, pericolic fat ± abscess, fistula
- Colonoscopy *contraindic.* acutely as ↑ risk of perforation; for Pts w/o colonoscopy in the past year, perform 6–8 wks after to r/o neoplasm

Treatment (*JAMA* 2017;318:291; *NEJM* 2018;379:1635; *Gastro* 2021;160:906)

- Mild: outPt Rx indicated if Pt has few comorbidities and can tolerate POs
  - PO abx: (MNZ + FQ) or amox/clav for 7 d; liquid diet until clinical improvement
  - No abx is noninferior to abx in uncomplicated diverti (*Clin Gastroenterol Hepatol* 2021;19:503)
- Severe: inPt Rx if cannot take POs, narcotics needed for pain, or complications
  - NPO, IVF, NGT (if ileus); IV abx (GNR & anaerobic coverage; eg, CTX/MNZ or pip-tazo)
- Abscesses >4 cm should be drained percutaneously or surgically
- Surgery: if progression despite med Rx, undrainable abscess, free perforation
  - After source control, 4 d abx may be sufficient (*NEJM* 2015;372:1996)
  - Resection for recurrent bouts of diverticulitis on a case-by-case basis
  - Consider lower threshold for urgent & elective surgery for immunocompromised Pts

Prevention (*Gastro* 2021;160:906)

- Avoid smoking and NSAIDs; insufficient evidence to recommend mesalamine or rifaximin
- Risk of recurrence 10–30% w/in 10 y of 1st episode; nuts, seeds ∅ increase risk

POLYPS

Pathophysiology & epidemiology (*NEJM* 2016;374:1065)

- Accumulation of mutations in colonic epithelial cell DNA affecting oncogenes & tumor suppressor genes → *tumor initiation* (formation of adenoma; *APC* loss of fxn) → *tumor progression* (adenoma → carcinoma; *K-ras* gain of fxn, *DCC, p53* loss of fxn)
- Risk factors: ↑ age, FHx (sporadic in 1° relatives, Lynch, FAP), IBD, ↑ dietary fat, central adiposity, ↑ EtOH, ↓ fiber, ↑ red meat, smoking, DM
- Protective factors: ↑ physical activity, ASA/NSAIDs, Ca^{2+} intake, HRT, ↓ BMI; possibly ↑ fiber, vitamin D, fish oil, statins, selenium
- **Neoplastic polyps**: adenomas (tubular, villous, tubulovillous dysplasia), sessile serrated adenomas/polyps (concern for interval CRC), carcinomas
- **Non-neoplastic polyps**: hyperplastic, juvenile, Peutz-Jeghers (can undergo malignant transformation), inflammatory

CRC screening (*JAMA* 2021;325:1978)

- *Colonoscopy* gold standard. Other options: FOBT/FIT yearly, flex sig q5y or flex sig q10y + FIT every year, fecal DNA testing (eg, Cologuard) q3y or CT colonography q5y
- Start screening in average risk Pts at age 45 (typically q10y unless abnl found)
- If ⊕ FHx, start age 40, or 10 y before age of dx in youngest family member, repeat q5y

INFLAMMATORY BOWEL DISEASE

Definition (*NEJM* 2020;383:2652)

- **Ulcerative colitis (UC):** inflammation of the colonic *mucosa; contiguous*, starting at rectum
- **Crohn's disease (CD):** *transmural* inflammation anywhere along GI tract, *skip lesions*

Epidemiology & pathophysiology (*Lancet* 2016;387:156 & 2017;390:2769)

- Age of onset 15–30 y; bimodal w/ 2nd peak at 50–70 y; 1:1 M:F in N America
- Genetic predisposition (↑ Caucasian/Jewish) + environmental risk factors (smoking ↑ risk for CD, defective mucosal barrier) → T cell dysregulation → inflammation

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ULCERATIVE COLITIS (*Lancet* 2018;389:1756; *Am J Gastro* 2019:114:384)

Clinical manifestations

- **Grossly bloody diarrhea**, lower abdominal cramps, tenesmus, small, frequent BM
- Extracolonic (>25%): erythema nodosum, pyoderma gangrenosum, aphthous ulcers, uveitis, episcleritis, thromboembolic events (esp. during a flare; *Lancet* 2010;375:657), AIHA, seroneg arthritis (most common), PSC (↑ risk cholangio CA, CRC)
- Several scores for severity assessment: Truelove & Witts; Mayo Score/DAI; Montreal

Diagnosis

- **Colonoscopy:** involves rectum (95%) & extends prox., circumfer., & *contig. w/in colon*
- Location: proctitis (30–60%), L-sided (15–45%) and extensive (pancolitis; 15–35%)
- Appearance: vascularity loss, friable mucosa, diffuse ulceration, *pseudopolyps* (chronicity)

- Histology: superficial chronic inflammation; crypt abscesses & architectural distortion
- Barium enema with featureless and tubular appearance of colon (*leadpipe appearance*)
- Flares: ↑ ESR & CRP (not Se or Sp); ⊕ fecal calprotectin helpful in distinguishing IBD vs. IBS and monitoring for IBD flare (*Gastro Hep* 2017;13:53); must rule out infection

Complications

- **Toxic megacolon** (5%): colon dilatation (≥6 cm on KUB), colonic atony, systemic toxicity, & ↑ risk of perf. Rx w/ IV steroids & broad-spectrum abx; surgery if needed.
- Stricture (rectosigmoid), dysmotility, anorectal dysfxn after recurrent inflammation
- ↑ Risk of CRC and dysplasia (*see below*) after 8 years of active disease
- For Pts s/p surgery w/ ileal pouch, may develop *pouchitis* (inflammation of ileal pouch, up to ½ of Pts). Rx w/ abx (MNZ, cipro), probiotics.

Prognosis

- 50% in remission at any given time. Intermittent exacerbations in 90%; continual active disease in ~18%. Prox progression in 25% at 10 y. Rate of colectomy at 10 y is 24%.
- Mortality rate of severe UC flare is <2%, & overall life expectancy in UC = non-UC Pts

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CROHN'S DISEASE (*Lancet* 2017;389:1741)

Clinical manifestations (*Nat Rev Gastro Hep* 2016;13:567)

- **Abdominal pain**, loose/frequent stools (up to 50% ⊕ FOBT), malaise, wt loss
- Mucus-containing, **often nonbloody diarrhea**
- N/V, bloating, obstipation if presence of obstruction; extracolonic manifestations as in UC
- Several scoring systems: CD Activity Index (CDAI), Harvey-Bradshaw Index

Diagnosis

- **Ileocolonoscopy** + **bx along w/ small bowel assessment** (eg, MR-enterography)
- Small bowel/ileitis (~25%), ileocolonic (~50%), colonic (~25%); isolated upper tract rare
- Appearance: nonfriable mucosa, cobblestoning, aphthous ulcers, deep & long **fissures**
- Histology: **transmural inflammation** with mononuclear cell infiltrate, **noncaseating granulomas** (seen in <25% of mucosal biopsies), fibrosis, ulcers, fissures, skip areas
- Montreal classification: age at dx, disease location & behavior (stricturing vs. nonstricturing, penetrating vs. nonpenetrating), plus modifiers for upper tract & perianal disease

Complications

- **Perianal disease:** fissures, fistulas, skin tags, perirectal abscesses (in 24% of Pts; perianal disease *precedes* intestinal symptoms)
- **Stricture:** small bowel, postprandial abd pain; can lead to complete SBO & require surgery
- **Fistulas:** perianal, enteroenteric, rectovaginal, enterovesicular, enterocutaneous
- **Abscess:** fever, tender abd mass, ↑ WBC; *steroids mask sx*, ∴ need high level of suspicion
- **Malabsorption:** ileal disease/resection: ↓ bile acids abs → gallstones; ↓ fatty acid abs → Ca oxalate kidney stones; ↓ fat-soluble vitamin abs → vit D deficiency → *osteopenia*

Prognosis

- Variable at 1 y: ~50% in remission, ~20% flare, ~20% low activity, ~10% chronic active
- At 20 y, majority will have required some surgery; overall life expectancy is slightly ↓

MANAGEMENT (*Lancet* 2017;398:1756; *Mayo* 2017;92:1088)

Initial evaluation

- **H&P** (✓ for intestinal & extraintestinal manifestations) and **dx studies** as above
- **Lab:** consider CBC/diff, LFTs, iron studies, B12, folate, vit D, ESR, CRP, fecal calprotectin

- **Exclude other etiologies:** infectious (espec. TB), ischemic colitis, intestinal lymphoma, CRC, IBS, vasculitis, Behçet's, celiac disease, small intestinal bacterial overgrowth
- **R/o infection** (esp. TB, HBV, CMV, O&P) before treating with immunosuppressants and biologics (although not all acutely hospitalized Pts w/ IBD need infxn r/o prior to Rx)

Goals of treatment (*Ther Adv Gastro* 2015;8:143)

- Induce remission of acute flare → maintain remission; mucosal healing 1° goal
- Step-up Rx (least → most toxic) vs. top-down; (strongest → de-escalate) approach; consider early biologic if severe disease

Medical Therapy for IBD (*NEJM* 2021;385:1302)	
Ulcerative Colitis (*Am J Gastrol* 2019:114:384)	
Mild	**Rectal mesalamine** or **glucocorticoids** as suppository or enema
Mild- moderate	**Oral 5-ASA:** many formulations (sulfasalazine, mesalamine, olsalazine, balsalazide) depending on disease location. Used for induction & maintenance of remission. Complications: pancreatitis, abd pain, diarrhea. **MMX-budesonide:** PO budesonide released throughout colon for flare. 1st-pass metab ↓ systemic steroid adverse effects of steroid.
Moderate- severe	**PO prednisone:** 40–60 mg w/ taper over several wks to induce remission **AZA/6-MP:** 0.5–1 mg/kg and uptitrate over several wks for maintenance Complications: BM suppression, lymphoma, pancreatitis, hepatitis ✓ TPMT levels prior to dosing to ↓ risk of generation of toxic metabs. In selected cases, add allopurinol to boost activity in non-responders. **Anti-TNF:** ↑ remission rate when AZA combined w/ IFX (*Gastro* 2014;146:392)

Medical Therapy for IBD (*NEJM* 2021;385:1302)	
Severe or refractory disease (*Lancet* 2017; 389:1218; *NEJM* 2016; 374:1754 & 2017; 76:1723; *JAMA* 2019; 321:156)	**IV steroids:** 100 mg hydrocort q8h or 16–20 mg methylpred q8h to induce remission w/ plan to taper & switch to non-steroid maintenance. **Cyclosporine:** for severe flares refractory to steroids, 2–4 mg/kg infusion × 7 d w/ goal to Δ to maintenance medication (eg, AZA/6-MP) **Anti-TNF** (infliximab, adalimumab & golimumab): for steroid-refractory flares or to maintain remission. Complic: reactivation of TB (✓ PPD prior to Rx) or viral hepatitis; small ↑ risk NHL; lupus-like rxn, psoriasis, MS, CHF. **Alternative agents:** vedolizumab (α4β7 integrin inhibitor); tofacitinib (JAK inhibitor); ustekinumab (IL-12/23 inhibitor); ozanimod (sphinosine-1- phosphate receptor agonist) *Investigational:* fecal microbiota transplant; etrolizumab (α4β7 inhibitor)
Crohn's Disease (*JAMA* 2021;325:69)	
Mild	**Oral 5-ASA:** for colonic Crohn's disease **Symptom control:** loperamide/cholestyramine for diarrhea management.
Mild-mod	**PO budesonide:** enteric-coated for ileal release (taper over 3 mos)
Moderate- severe	**PO prednisone:** same as UC, for inducing remission, not maintenance **AZA/6-MP:** same as UC; ↑ remission w/ AZA+IFX (*NEJM* 2010;362:1383) **MTX:** 15–25 mg IM/SC or PO qwk for maintenance; 1–2 mo to take effect
Severe or refractory disease (*NEJM* 2016; 375:1946)	**IV steroids:** same as UC, for inducing remission, not maintenance **Anti-TNF:** infliximab, adalimumab or certolizumab (pegylated); consider combination therapy with AZA/6-MP **Alternative agents:** vedolizumab (α4β7 integrin inhibitor); ustekinumab (IL-12/23 inhibitor); natalizumab (α4 integrin inhibitor) *Investigational*: tofacitinib (JAK inhibitor); ozanimod (S-1-P receptor agonist)

Surgery

- **UC:** colectomy if sx refractory to or intolerable side effects from meds, CRC, perforation, toxic megacolon, uncontrolled hemorrhage. Often *ileal pouch-anal anastomosis* (IPAA).
- **CD:** resection if refractory; surgery for strictures; diverting ileostomy for perineal disease

Cancer screening (*NEJM* 2015;372:1441)

- **Colon cancer:** risk in UC ~2% at 10 y, ~8% at 20 y, ~18% at 30 y. Similar for pancolonic CD, plus risk of small bowel cancer as well.

Dysplasia best marker for risk. Other risk factors include: PSC, ⊕ FHx, greater extent of disease, stricture, & pseudopolyps.

- **Surveillance:** *colonoscopy* w/ random bx 8 y after dx to eval for dysplasia, q1–3y thereafter based on risk factors. *Chromoendoscopy* using dye to stain high-risk lesions for targeted bx may be preferable. If high-grade dysplasia or dysplasia-assoc. lesion/mass → colectomy.

INTESTINAL ISCHEMIA

ACUTE MESENTERIC ISCHEMIA

Definition and causes (*NEJM* 2016;374:959)

- Reduced or absent blood flow to small intestine, typically caused by *arterial* (ie, SMA or its branches) occlusion or transient hypoperfusion or less often by *venous* occlusion
- **Arterial embolism** (~40–50%): embolic occlusion to SMA (has narrow take-off angle), often in setting of AF, valvular disease incl. endocarditis, atherosclerotic plaque in aorta
- **SMA thrombosis** (~20–30%): typically due to atherosclerosis at origin of SMA; other risk factors incl. vascular injury from abd trauma, infxn, or mesenteric dissections/aneurysms
- **Nonocclusive mesenteric ischemia** (~10%): transient intestinal hypoperfusion due to ↓ CO, athero, sepsis, drugs that ↓ gut perfusion (pressors, cocaine, amphetamines)
- **Mesenteric venous thrombosis** (MVT, ~5%): a/w hypercoag. states, portal hypertension, IBD, malignancy, inflammation (pancreatitis, peritonitis), pregnancy, trauma, surgery
- **Focal segmental ischemia of small bowel** (<5%): vascular occlusion to small segments of small bowel (vasculitis, atheromatous emboli, strangulated hernias, XRT)

Clinical manifestations

- Arterial occlusion: **sudden intense abd pain out of proportion to tenderness on exam**
- Venous occlusion: *often more insidious in onset*, intermittent pain with peaks and valleys
- Nonocclusive: abd distention & pain, n/v, **lower GI bleeding** due to mucosal sloughing; often occurring after episode of hypoperfusion (eg, cardiac event or shock)
- Exam ranges: unremarkable ± abd distention to peritoneal (infarction); ⊕ **FOBT ~75%**

Diagnostic studies

- Dx relies on high level of suspicion; rapid dx essential to avoid infarction (occurs w/in hrs)
- Mortality 20 to >70% if bowel infarcted; dx prior to infarction strongest predictor of survival
- Laboratory: often nl; ~75% ↑ WBC; ↑ amylase, LDH, PO_4, D-dimer; ~50% ↑ lactate (late)
- KUB: nl early before infarct; "thumbprinting," ileus, pneumatosis in later stages
- **CT angiography** (arterial phase): noninvasive test of choice; *venous* phase for dx MVT
- **Angiography:** gold standard; potentially therapeutic; indicated if vasc occlusion suspected

Treatment (*NEJM* 2016;374:959; *World J Emerg Surg* 2017;12:38)

- IVF, NPO, **optimize hemodynamics** (minimize pressors), **broad-spectrum abx**, **anticoagulation** w/ heparin ± **tPA** (for occlusive disease), **IV papaverine** (vasodilator; for non-occlusive mesenteric ischemia)
- If evidence of peritonitis: to OR for surgical endovascular therapies & bowel resection
- **SMA thrombosis:** percutaneous (stenting) or surgical revascularization
- **SMA embolism:** embolectomy (catheter-based aspiration vs. surgical)
- **Nonocclusive:** correct underlying cause (esp. cardiac)
- **Mesenteric venous thrombosis:** 3–6 mo anticoag after initial heparinization. Fibrinolysis or thrombectomy typically reserved for Pts w/ hemodynamic instability or refractory sx.
- **Focal segmental ischemia:** typically surgical resection

Chronic Mesenteric Ischemia

- Pathophysiology: ↓ blood flow to gut typically because of mesenteric atherosclerosis
- Sx: "intestinal angina" = **postprandial abd pain**, early satiety, & ↓ wt due to fear of eating. If pain becomes constant → could represent acute thrombosis (see above).

- Dx: duplex U/S or CTA; angiography gold stnd; gastric tonometry exercise testing
- Treatment: surgical revascularization (1st line); angioplasty ± stenting; TPN for nutrition

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ISCHEMIC COLITIS

Definition & pathophysiology

- Nonocclusive disease 2° to Δs in systemic circulation or anatomic/fxnal Δs in local mesenteric vasculature; often underlying etiology unknown, frequently seen in elderly
- "Watershed" areas (splenic flexure & rectosigmoid) most susceptible; 25% involve R side; confers worse prognosis (*Clin Gastroenterol Hepatol* 2015;13:1969)

Clinical manifestations, diagnosis, & treatment

- Usually p/w **cramping LLQ pain w/ overtly bloody stool;** fever and peritoneal signs should raise clinical suspicion for infarction
- Disease spectrum: reversible colopathy (35%), transient colitis (15%), chronic ulcerating colitis (20%), resulting stricture (10%), gangrene (15%), fulminant colitis (<5%)
- Dx: **flex sig/colonoscopy** or **CT abd/pelvis** to make diagnosis; r/o IBD, infectious colitis
- Treatment: bowel rest, IV fluids, broad-spectrum abx, serial abd exams; **surgery** for infarction, fulminant colitis, hemorrhage, failure of med Rx, recurrent sepsis, stricture
- Resolution w/in 48 h w/ conservative measures occurs in >50% of cases

PANCREATITIS

ACUTE PANCREATITIS (*Lancet* 2020; 396:726; *JAMA* 2021;325:382)

Pathogenesis

- Pancreatic duct and acinar injury via direct or indirect toxicity → impaired secretion and premature activation of digestive enzymes → autodigestion and acute inflammation

Etiologies (*JAMA* 2021;325:382)

- **Gallstones** (40%): ♀ > ♂; usually due to small stones (<5 mm) or microlithiasis/sludge
- **Alcohol** (30%): ♂ > ♀; 4–5 drinks/day over ≥5 yrs; usually chronic w/ acute flares
- Metabolic: hypertrig. (2–5%; TG >1000; type I & V familial hyperlipemia); hyperCa
- Drugs (<5%): 5-ASA, 6-MP/AZA, ACEI, cytosine, didanosine, dapsone, estrogen, furosemide, isoniazid, MNZ, pentamidine, statins, sulfa, thiazides, tetracycline, valproate
- Anatomic: divisum, annular pancreas, duodenal duplication cysts, Sphincter of Oddi dysfxn
- Autoimmune (vide infra)
- Familial: suspect if age <20 y; (often a/w mutation in PRSS1, SPINK1 or CFTR gene)
- Infections: ascaris, clonorchis, coxsackie, CMV, EBV, HIV, mumps, mycoplasma, TB, toxo
- Ischemia: shock, vasculitis, cholesterol emboli
- Neoplastic: panc/ampullary tumors, mets (RCC most common, breast, lung, melanoma)
- Post ERCP (5%): Ppx w/ PR indomethacin can ↓ sx; temporary panc duct stent if high risk
- Trauma: blunt abdominal trauma, post-pancreatic/biliary surgery

Clinical manifestations

- **Epigastric abdominal or LUQ pain (90%)**, only ½ w/ bandlike pain radiating to back
- 10% pain-free (due to analgesic/steroid use, immunosuppressed, ΔMS, ICU); ∴ ✓ lipase in unexplained shock, periumbilical or flank (Cullen or Grey Turner signs) bruising
- **N/V (90%),** abd tenderness/guarding, ↓ bowel sounds, jaundice if biliary obstruction
- Ddx: acute cholecystitis, perforated viscus, SBO, mesenteric ischemia, IMI, AAA leak, distal aortic dissection, ruptured ectopic pregnancy
- **Early phase** (<1 wk): possible SIRS ± organ failure; **late** (>1 wk): local complications (qv)

Diagnostic studies (*Am J Gastro* 2013;108:1400)

- **Dx requires 2 of 3:** characteristic abd pain; lipase or amylase >3× ULN; ⊕ imaging
- Laboratory: levels of amylase & lipase do *not* correlate w/ severity of disease
  - ↑ **amylase**: rises w/in hrs, normalizes w/in 3–5 d (faster than lipase)
  - false ⊖: 20% EtOH pancreatitis; 50% hypertriglyceridemia (assay interference)
  - false ⊕: other abd or salivary gland process, acidemia, ↓ GFR, macroamylasemia
  - ↑ **lipase**: longer $t_{½}$ than amylase
  - >3× ULN 99% sensitive, 99% specific for acute pancreatitis
  - >10k has 80% PPV for biliary dx, 99% NPV for EtOH (*Dig Dis Sci* 2011;56:3376)
  - false ⊕: renal failure, other abd process, DKA, HIV, macrolipasemia
  - ALT >3× ULN has 95% PPV for gallstone pancreatitis (*Am J Gastro* 1994;89:1863)
- Imaging studies (*Am J Gastro* 2013;108:1400)
  - **Abd U/S:** bowel gas often obscures pancreas visualization; however *should be ordered to r/o biliary etiology* (ie, gallstones, BD dilatation)
  - **Abd CT:** not rec for first 3 days (local complic. not yet visible & concern for AKI w/ IV contrast). However, if persistent pain

and/or clinical deterioration after 48–72 h, CT(I^+) useful to r/o local complications (necrosis, fluid collections).

MRI/MRCP: Can detect necrosis, assess for stones & ductal disruption earlier than CT

Endoscopic U/S (EUS): useful for occult biliary disease (microlithiasis)

Severity (*Gut* 2013;62:102; *Gastro* 2018;154:1096)

- Severity defined by presence of organ failure (AKI, resp failure, GIB, shock) & local or systemic complic. (panc necrosis, fluid collections, gastric outlet obstrxn, splenic & PVT).
  - **Mild:** 80% of cases; no organ failure or local/systemic complications; low mortality
  - **Moderate:** transient (<48 h) organ failure ± local/systemic complications, high morbidity
  - **Severe:** persistent (>48 h) organ failure, very high mortality

Prognosis (*NEJM* 2016;375:1972)

- **Ranson's, APACHE II:** predict severity at 48 h using multiple physiolog. criteria; poor PPV
- **BISAP:** simple 5-point scoring system (BUN >25, impaired MS, SIRS, age >60 y, pleural effusion) used w/in first 24 h; score ≥3 predicts ↑ risk of organ failure, mortality
- **CTSI:** CT data at 48–72 h (fluid collect., necrosis) to predict mortality; lags behind clinical sx

Treatment (*Am J Gastro* 2017;112:797; *JAMA* 2020;323:2331)

- **Fluid resusc.:** *aggressive in 1st 24 hrs, even if mild.* 20 mL/kg IVB → 3 mL/kg/hr. Goal ↓ BUN & Hct over 12–24 h. ✓ UOP (goal 0.5–1 cc/kg/hr); LR superior to NS (↓ SIRS; avoid if ↑ Ca).
- **Nutrition** (*NEJM* 2014;317:1983)
  - Early enteral feeding encouraged, though not superior to oral feeding at 72 h
  - Mild: Start feeding once without N/V or ileus; may not need to be completely pain free. Low-fat low-residue diet as safe as liquid diet and a/w shorter LOS.
  - Severe: early (w/in 48–72 h) enteral nutrition indicated and preferred over TPN b/c ↓ infectious complications. Nasogastric non-inferior to nasojejunal feeding.

- **Analgesia:** IV opioids (monitor respiratory status, adjust dosing if ↑ renal impairment)
- **Gallstone pancreatitis:** urgent (w/in 24 h) ERCP w/ sphincterotomy if cholangitis, sepsis, or Tbili ≥5. If mild, CCY during initial hosp. to ↓ risk of recurrence (*Lancet* 2015;386:1261); defer surgery if necrotizing panc. until improvement in inflam. & fluid collections.
- **Hypertriglyceridemia:** insulin gtt (activates lipoprotein lipase), fibrates, ± apheresis
- No role for Ppx abx in absence of infectious complications (*World J Gastro* 2012;18:279)

Complications

- Systemic: ARDS, abdominal compartment syndrome, AKI, GIB (pseudoaneurysm), DIC
- Metabolic: hypocalcemia, hyperglycemia, hypertriglyceridemia
- Fluid collections:
  - **Acute fluid collection:** seen early; not encapsulated; asymptomatic; resolve in 1–2 wk
  - **Pseudocyst:** ~4 wk after initial attack, encapsulated. No need for Rx if asx (regardless of size/location). If sx → endoscopic (*Gastro* 2013;145:583) vs. perc/surg drainage.
- Pancreatic necrosis: Nonviable pancreatic tissue. CT-guided FNA if infection suspected.
  - **Sterile necrosis:** if asx, can be managed expectantly, no role for Ppx abx
  - **Infected necrosis**: most often GN gut organism; high mortality. Rx w/ carbapenem, pip/tazo, or [(3rd gen ceph or FQ) + MNZ]. If stable, defer drainage to >4 wk to allow liquefication & WOPN (qv). If sx or unstable, perc. drainage & minimally invasive surgical debridement or endoscopic necrosectomy superior to open necrosectomy.
  - **WOPN** (walled off panc. nec.): fibrous wall surrounds necrosis over ≥4 wk; endoscopic or perc. drainage (preferred over open necrosectomy) if infected or symptomatic
- Peripancreatic vascular complications: pseudoaneurysm, abdominal compartment syndrome, **splanchnic venous thrombosis** (splenic vein most common site)

CHRONIC PANCREATITIS (*Lancet* 2020;396:499)

Pathogenesis & etiology (*Gastro* 2013;144:1292; *JAMA* 2019;322:2422)

- Often recurrent acute attacks → inflam infiltrate → fibrosis → loss of exocrine & endocrine tissue. Pancreatic insufficiency (DM, fat/protein malabsorption) when 90% panc fxn lost.
- TIGAR-O: **T**oxins (60–80% due to EtOH; smoking), **I**diopathic, **G**enetic (PRSS1, SPINK1, CFTR, CTRC, CASR), **A**utoimmune, **R**ecurrent panc., **O**bstruction

Clinical manifestations

- Epigastric pain, N/V; over time can be painless; signs of exocrine insuff (steatorrhea, wt loss) or endocrine insuff (DM: polydipsia, polyuria); 13× ↑ risk of pancreatic cancer

Diagnostic studies (*Pancreas* 2014;43:1143; *Am J Gastro* 2020;115:322)

- Labs: amylase/lipase ↑ early, may be nl later. ⊕ fecal fat, ↓ stool elastase & A1AT. Mixed TG breath test alternative to stool elastase. ✓A1c, consider IgG4/ANA & genetic testing if young or ⊕ FHx. If dx w/ CP, measure baseline fat-soluble vitamins (ADEK).
- Imaging: Ca^{2+} on KUB/CT. ERCP/MRCP/EUS: high sens for dx; may show stricture, dilated ducts. IV secretin stim w/ MRI may ↑ dx yield. Panc fxn testing not widely available.

Treatment (*JAMA* 2019;322:2422; *Lancet* 2020;396:499)

- Pancreatic enzyme replacement (may ↓ pain by reducing CCK). Rx routine vitamin D & Ca.
- Pain control: smoking & EtOH cessation, analgesics (start with non-opioids; eg, pregabalin), endoscopy (stone removal or stenting strictures), celiac nerve plexus block, surgery

AUTOIMMUNE PANCREATITIS

Pathogenesis (*Am J Gastro* 2018;113:1301)

- Type 1: lymphoplasmacytic sclerosing panc. w/ dense fibrosis; ↑ IgG4; high relapse
- Type 2: idiopathic duct-centric pancreatitis; minimal ↑ IgG4; a/w IBD; fewer relapses

Clinical manifestations

- **Abdominal pain**, can p/w obstructive jaundice and panc mass mimicking panc Ca
- Can be primary, or in a/w IgG4 cholangiopathy, salivary gland disease (eg, Sjögren's), mediastinal or RP fibrosis, interstitial nephritis, autoimmune thyroiditis, UC/PSC, RA

Diagnosis

- Labs: cholestatic LFTs (↑ Aϕ >AST/ALT), ↑ γ-globulins and IgG4, ⊕ ANA, RF
- HISORt criteria: Histology, Imaging ("sausage pancreas," bile duct stricture), Serology, other Organ involvement, Response to therapy

Treatment

- Glucocorticoids 1st-line; immunomod. (AZA, MMF, cyclophosphamide, rituximab) if relapse

ABNORMAL LIVER TESTS

Tests of hepatocellular injury or cholestasis (*J Clin Transl Hepatol* 2017;5:394)

- **Aminotransferases** (AST, ALT): intracellular enzymes released 2° necrosis/inflammation
  - ALT more specific for liver than is AST (heart, skeletal muscle, kidney, brain, RBC/WBC)
  - ↑ levels seen w/ most types of hepatocellular injury; AST >ALT → MSK injury, MI
- **Alkaline phosphatase** (Aϕ): enzyme bound in hepatic canalicular membrane ↑ levels seen w/ biliary obstrxn, intrahepatic cholestasis or infiltration of the liver also found in bone, intestines, kidney, placenta; confirm from liver w/: ↑ GGT (or ↑ 5′-NT)
- **Bilirubin:** product of heme metab (unconjugated, "indirect") carried by alb to liver where taken up for conjugation ("direct") to make soluble, then excreted into bile.
  - ↑ indirect hyperbili seen with hemolysis, enzymatic disorders (eg, Crigler-Najjar, Gilbert's)
  - ↑ direct hyperbili seen with cholestasis, enzymatic disorders (eg, Dubin-Johnson, Rotor's)
  - jaundice seen when bili >2.5 mg/dL (esp. in sclera or under tongue); direct ↑ urine bili

Tests of hepatic function

- **Albumin:** marker for liver protein synthesis, can help differentiate acute vs. chronic liver failure, may be normal in acute hepatocellular injury ($t_{1/2}$ ~15–18 d)
- **Prothrombin time** (PT): depends on synthesis of coag factors by liver (except FVIII); b/c $t_{1/2}$ of some factors (eg, V, VII) is short, ↑ PT can occur w/in hrs of liver dysfxn

Patterns of LFTs				
Pattern	**ALT**	**AST**	**Aϕ**	**Bilirubin**
Hepatocellular	↑↑	↑↑	±↑	±↑ (direct)
Viral hepatitis, NAFLD	Often ALT >AST		±↑	±↑ (direct)
Alcoholic hepatitis	AST:ALT ≥2:1		±↑	±↑ (direct)
Ischemic injury	↑↑↑	↑↑↑	↑↑	↑↑ (direct)
Wilson disease	↑	↑	Aϕ:Tbili <4 (if fulminant)	
Cholestatic	±↑	±↑	↑↑	↑↑ (direct)
Infiltrative	near nl	near nl	↑↑	±↑
Nonhepatic				
Skeletal muscle injury	AST >>ALT (early)		nl	nl
Bone disease	nl	nl	↑ (w/ nl GGT)	nl
Hemolysis	nl	nl	nl	↑ (indirect)

- **R-value** = ratio of ALT:Aϕ normalized to ULN for each = (ALT/ULN) ÷ (Aϕ/ULN)
  R >5 suggests hepatocellular injury, <2 suggests cholestatic injury, 2–5 suggests mixed

Acute mild-to-moderate elevation in ALT/AST (<15× ULN)

- Assess risk of **EtOH/drug/toxin**: H&P; in EtOH AST:ALT ratio >2:1
- Obtain abdominal imaging to r/o cirrhosis, congestion, or biliary obstruction (mixed LFTs)
- Other infectious etiologies: tick borne illnesses, CMV/EBV, COVID-19, others
- Can be initial manifestation of chronic etiologies noted below

Chronic mild-to-moderate elevation in ALT/AST (<15× ULN)

- **Viral hepatitis**: ✓ HBsAg, anti-HBs, anti-HBc, anti-HCV, IgM anti-HAV
- **NAFLD**: consider BMI, ✓ lipid panel, Hb_{A1c}, liver U/S or elastography
- Other etiologies of cirrhosis (qv)
  Hemochromatosis: ✓ TIBC, serum iron, serum ferritin
  Wilson disease: serum ceruloplasmin, urine Cu
  α-1 antitrypsin (can cause liver disease w/o lung involvement)
- Chronic autoimmune hepatitis ✓ ANA, ASMA, anti-LKMA, IgG, SPEP
- TSH (both hypo & hyperthyroidism associated with abnormal LFTs), celiac disease

• If workup negative, consider biopsy

Acute severe elevation in ALT/AST (>1000)

• Massive elevations (>5000) usually due to ischemic injury or drug-induced hepatitis
• **Ischemia**: hypotension, shock or severe HF (often >50× ULN), Budd-Chiari: usually diagnosed based on clinical hx, U/S w/ Doppler; ratio ALT:LDH <1.5 if ischemic because of concomitant ↑ LDH (vs. ratio >1.5 w/ toxins, viruses)
• **Meds/toxins**: acetaminophen, meds (eg, INH, amio, nitrofuratonin), OTC/herbal, cocaine (nb, EtOH should not produce this degree of elevation). Obtain acet. level, tox screen.
• **Acute viral infection**: hepatitis A–E or reactivation of HBV, EBV/CMV
• Acute autoimmune hepatitis (qv): ✓ IgG, ANA, ASMA
• Acute biliary obstruction (often with sig drop in ALT/AST the next day, Aϕ takes longer to rise & fall): start w/ liver U/S, if unrevealing obtain CT or MRCP
• Rhabdomyolysis and heat stroke

Figure 3-3 Approach to abnormal liver tests with cholestatic pattern

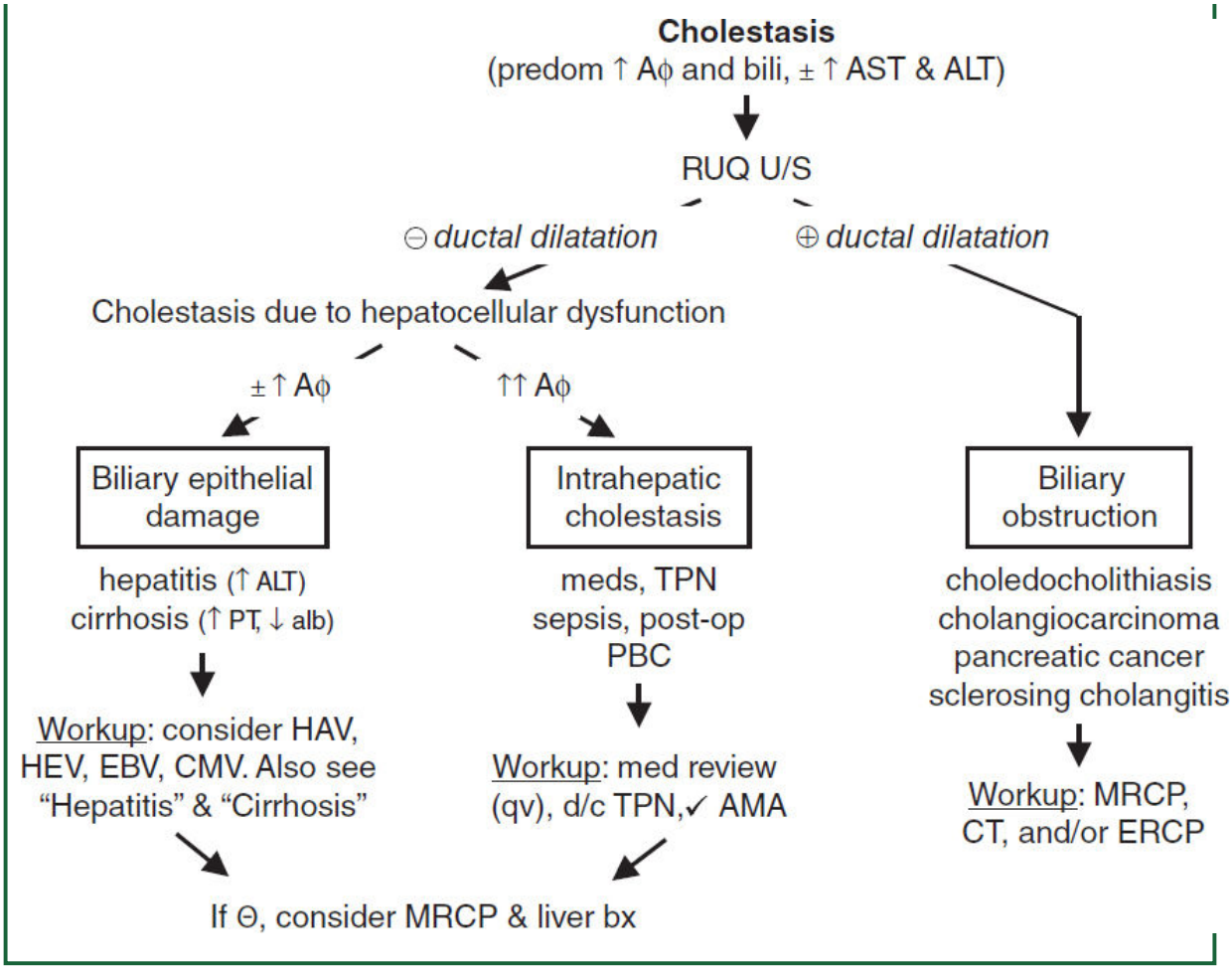
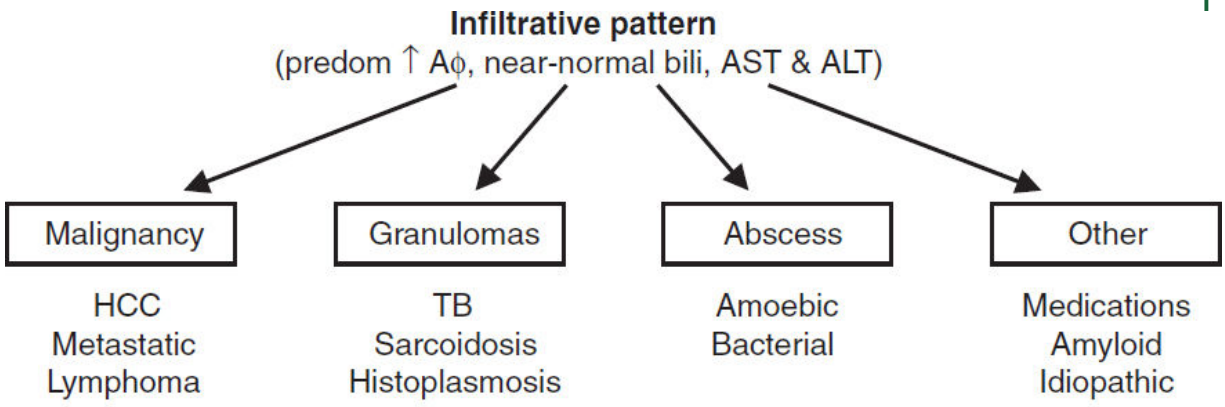


Figure 3-4 Approach to abnormal liver tests with infiltrative pattern



Medication causes of abnormal LFTs (http://livertox.nlm.nih.gov; *NEJM* 2019;381;264)				
Hepatocellular		**Cholestatic**		**Mixed**
acarbose acetaminophen allopurinol amiodarone azathioprine clindamycin fibrates hydralazine isoniazid ipilimumab (and other checkpt inhibitors) ketoconazole methotrexate mirtazapine nitrofurantoin (some) NSAIDs phenytoin	prednisone protease inhibitors pyrazinamide risperidone statins sulfonamides tamoxifen tetracyclines TNF-alpha inhibitors trazodone tricyclics valproic acid	ACE inhibitors anabolic *steroids* azathioprine cephalosporins chlorpromazine estrogens macrolides methimazole	6-MP OCP penicillins protease inhibitors sulfonamide terbinafine tricyclics	amox-clav azathioprine carbamazepine clindamycin mirtazapine nitrofurantoin penicillins phenobarbital phenytoin protease inhibitors sulfonamides trazodone tricyclics valproic acid verapamil

HEPATITIS

VIRAL

Hepatitis A (ssRNA; 30–45% of acute viral hepatitis in U.S; *MMWR* 2018;67:1208)

- Transmission & RFs: fecal–oral route; contam. food, water, shellfish; daycare ctr; intl travel
- Incubation: 2–6 wk; no chronic carrier state; once antibody forms → lifelong immunity
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, jaundice; rarely ALF (↑ w/ chronic HCV)
- Diagnosis: acute hepatitis = ⊕ IgM anti-HAV; past exposure = ⊕ IgG anti-HAV (⊖IgM)
- Rx for acute HAV: supportive care; refer to liver txplnt center if acute liver failure
- Vaccinate if: MSM, IVDU, chronic liver disease, international travel; Havrix (2 doses)

Hepatitis B (dsDNA; ~45% of acute viral hepatitis in U.S.; *JAMA* 2020;324:2452)

- Transmission: blood (IVDU, transfusion), sexual, perinatal (vertical)
- Incubation: 6 wk–6 mo (mean 12–14 wk)
- Acute infxn: 70% subclinical, 30% jaundice, <1% acute liver failure (up to 60% mortality)
- Chronic infxn: HBsAg ⊕ >6 mo in <5% of adult-acquired (↑ if immunosupp), >90% of perinatal; ~40% chronic HBV → cirrhosis (↑ risk w/ HCV, HDV, or HIV coinfxn, EtOH)
- HCC: ↑ risk if cirrhosis, ⊕ FHx HCC, African >20 y old, Asian ♂ >40 y old or ♀ >50 y old, or >40 y old w/ ↑ ALT ± HBV DNA >2000. Screen w/ AFP & U/S q6mo.
- Extrahepatic syndromes: PAN (<1%), membranous nephropathy, MPGN, arthritis

- Serologic and virologic tests (screening guidelines: *Hepatology* 2018:67:1560)
  - HBsAg: appears before sx; used to screen blood donors; persists >6 mo = chronic HBV
  - HBeAg: evidence of viral replication and ↑ infectivity
  - IgM anti-HBc: 1st Ab to appear; indicates acute infection window period = HBsAg becomes ⊖, anti-HBs not yet ⊕, anti-HBc only clue to infxn
  - IgG anti-HBc: indicates previous (HBsAg ⊖) or ongoing (HBsAg ⊕) HBV infection
  - anti-HBe: indicates waning viral replication, ↓ infectivity
  - anti-HBs: indicates resolution of acute disease & immunity (sole marker after vaccination)
  - HBV DNA: presence in serum correlates w/ active viral replication in liver

Diagnosis	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV DNA
Acute hepatitis	⊕	⊖	IgM	⊕	⊖	⊕
Window period	⊖	⊖	IgM	±	±	⊕
Resolved	⊖	⊕	IgG	⊖	±	⊖
Immunization	⊖	⊕	⊖	⊖	⊖	⊖
Chronic hepatitis *HBeAg* ⊕	⊕	⊖	IgG	⊕	⊖	⊕
Chronic hepatitis *HBeAg* ⊖	⊕	⊖	IgG	⊖	⊕	±*

*Precore mutant: HBeAg not made, but anti-HBe can develop due to x-reactivity w/ HBcAg; a/w ↑ HBV DNA

- **Treatment for acute HBV:** supportive; hospitalize for Δ MS or ↑ INR (liver transplant center); consider antiviral therapy if severe or protracted course

Phases of Chronic HBV Infection						
Phase	**ALT (ULN*)**	**sAg**	**DNA (IU/mL)**	**eAg**	**Liver histology (inflam/fibrosis)**	**Rate of cirrhosis**
HBeAg ⊕ HBV infxn (Immune tolerant)	Nl	High	$\geq 10^6$	⊕	Minimal	<0.5%/y
HBeAg ⊕ hepatitis (Immune active)	≥2×	High	≥20k	⊕	Moderate to severe	2–5.5%/y
HBeAg ⊖ HBV infxn (Inactive carrier)	Nl	Low	≤2k	⊖	Min necroinflam; variable fibrosis	0.05%/y
HBeAg ⊖ hepatitis (Chronic hep B)	≥2×	Inter	≥2k	⊖	Moderate to severe	8–10%/y
Resolved	Nl	⊖	⊖	⊖	No inflam	Variable

*ALT ULN <35 U/L for ♂, <25 U/L for ♀. Adapted from *Hepatology* 2018;67:1560

- **When to treat chronic HBV with anti-virals?** (1) immune active phase; (2) HBeAg ⊖ chronic hepatitis B; (3) cirrhosis w/ HBV DNA ≥2K; (4) decomp. cirrhosis due to hep B; (5) acute liver failure due to acute hepatitis B; (6) special pop: preg (3rd trimester w/ HBV DNA ≥200k), inactive carriers treated w/ immunosuppression, HCC, HCV co-infection
- **Entecavir** or **tenofovir:** nucleo(s/t)ide analogs, well tolerated, low resistance; at 5 y, HBeAg seroconversion is 30–40% & loss of HBsAg is 5–10% (*Lancet Gastro Hep* 2016;1:185). Tenofovir preferred if h/o lamivudine resistance; no known tenofovir resistance to date.
- Rx duration: (1) HBeAg ⊕ immune active w/o cirrhosis: if seroconversion (HBeAg ⊖, anti- HBe ⊕), can stop after 1 y if ALT nl & HBV DNA suppressed or until HBsAg clears; (2) HBeAg ⊖ immune reactivation: indefinite; (3) cirrhosis: indefinite
- If undergo liver transplant: HBIG + nucleo(s/t)ide analogue effective in preventing reinfection
- HIV/HBV *coinfection:* Rx w/ 2 drugs active against both HBV & HIV (https://aidsinfo.nih.gov)
- Immunosuppression: prior to initiating chemoRx, anti-TNF, rituximab, steroids (>20 mg/d >1 mo), screen for HBV; Rx if mod-to-high risk of reactive (incl anti-HBs ⊕ getting rituximab)
- Postexposure (risk infxn ~30%) Ppx: HBIG → vaccine (if unvac or known nonresponder)

Hepatitis C (ssRNA; ~10% of acute viral hepatitis in U.S.; *Lancet* 2015;385:1124)

- Transmission: blood (IVDU, transfusion before 1992) >sexual; 20–30% w/o clear precipitant
- Incubation: 1–5 mo; mean 6–7 wk
- Acute infxn: 80% subclinical; 10–20% sx hepatitis w/ jaundice; acute liver failure rare; prob of spont clearance a/w *IL28B* & HLA class II genotypes (*Annals* 2013;158:235)
- Chronic: up to 85% → chronic hepatitis, 20–30% of whom develop cirrhosis (after ~20 y)
  - ↑ risk of cirrhosis in men, EtOH, HIV; HCC in 1–4% of Pts w/ cirrhosis per year
- Extrahepatic syndromes: mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, leukocytoclastic vasculitis, thyroiditis, MPGN, IPF, NHL and monoclonal gammopathies
- Serologic, virologic, & genetic tests (screen all adults [✓ anti-HCV] *JAMA* 2020;323:970)
  - anti-HCV (ELISA): ⊕ in 6 wk, does *not* = recovery or immunity; can be ⊖ after recovery
  - HCV RNA: ⊕ w/in 2 wk, marker of active infection
  - HCV genotype (1–6): guides duration & predicts response to Rx; geno. 3 a/w ↑ risk HCC
- Dx: *acute* hepatitis = ⊕ HCV RNA, ± anti-HCV; *resolved* = ⊖ HCV RNA, ± anti-HCV; *chronic* = ⊕ HCV RNA, ⊕ anti-HCV
- Treatment indications (www.hcvguidelines.org) (*Lancet* 2019;393:1453; *Hepatology* 2020;71:686)
  - Acute: if no spont. clearance at 12–16 wk, can Rx w/ same regimens for chronic HCV
  - Chronic: ↓ HCC & mortality. Recommended for all except if ↓ life expectancy.

Recommended First-Line Oral Direct-Acting Antiviral (DAA) Regimens	
Regimen (simplified)	**Indication**
Sofosbuvir & velpatasvir	Genotypes 1–6, 12 weeks Rx
Glecaprevir & pibrentasvir	Gentotypes 1–6; 8 weeks Rx

Recommended First-Line Oral Direct-Acting Antiviral (DAA) Regimens
Simplified treatment: adults w/ HCV w/o cirrhosis or w/ compensated cirrhosis & no prior HCV treatment; cannot have HIV, HBsAg ⊕, pregnancy, HCC, ESRD, or liver transplant; if decompensated or previously treated, refer to GI for assistance.

Based on *Hepatology* 2020;71:686. Antiviral classes: RNA *polymerase inhibitor* ("…buvir"); *NS5a inhibitor* ("…asvir"); *NS3/4A protease inhibitor* ("…previr").

- Monitoring on Rx: CBC, INR, LFTs, GFR, HCV VL prior to starting Rx. PIs contraindicated if decomp. liver dx (ascites, encephalopathy) or CPS ≥7. D/c Rx if jaundice, N/V, weakness, 10x ↑ in ALT, or significant ↑ in bili, Aϕ, INR after 4 wks.
- Goal is *sustained virologic response* (SVR) = Ø viremia 12 wks after completion of Rx. Success depends on genotype but SVR rates >90% with current regimens.
- Special populations (HCV/HIV coinfection, decompensated cirrhosis, s/p liver transplant, renal impairment): www.hcvguidelines.com for updated recs on mgmt
- Vaccinate all chronic HCV patients against HBV and HAV if not immune
- Postexposure (needlestick risk ~3%) Ppx: none, although sofosbuvir-velpatasivir under investigation in clinical trial; if HCV RNA → ⊕, consider Rx w/in 3 mos

Hepatitis D (RNA; *Gastro* 2019:156;461)

- Transmission: blood or sexual; endemic in Africa & E. Europe. Generally requires host to already have HBV infxn in order to cause co-infection or superinfection; in rare cases (immunosupp s/p liver transplant) can replicate autonomously.
- Natural hx: acute HBV–HDV coinfection resolves in >80% of cases; however, acute HDV superinfection leads to chronic HBV–HDV in most cases (↑ progression to cirrhosis, HCC)
- Dx: ✓ total anti-HDV once in all HBV-infected patients, if antibody ⊕, confirm w/ HDV RNA

Hepatitis E (ssRNA; *World J Gastro* 2016;22:7030; *Gastro Clin N Am* 2017;46:393)

- Most common cause of acute viral hepatitis in endemic areas
- Transmission: fecal–oral; travelers to central & SE Asia, Africa and Mexico, exposure to swine. ↑ rates of cases in Europe.

- Natural hx: often asx, sometimes causes acute hepatitis w/ ↑ mort. (10–20%) if pregnant; rarely can become chronic in transplant Pts
- Dx: IgM anti-HEV (through CDC), HEV RNA; treatment is generally supportive only
- Extrahepatic sx: arthritis, pancreatitis, anemia, neuro (GBS, meningoencephalitis)

Other viruses (human pegivirus, CMV, EBV, HSV, VZV)

AUTOIMMUNE HEPATITIS (AIH)

Classification (*J Hep* 2015;62:S100, *World J Gastro* 2015;21:60)

- Type 1: anti-smooth muscle Ab (ASMA), ANA; anti-soluble liver antigen (anti-SLA), a/w more severe disease and relapsing disease (found in 10–30% Pts), IgG often ↑
- Type 2: anti-liver/kidney microsome 1 (anti-LKM1); anti-liver cytosol type 1 (anti-LC-1)
- Overlap syndrome: AIH + PBC (suspect if ⊕ AMA or ⊕ histology → "autoimmune cholangitis")
- Drug-induced: minocycline, nitrofurantoin, infliximab, hydralazine, α-methyldopa, statins

Diagnosis and treatment (*J Hepatol* 2015;63:1543, *Clin Liver Dis* 2015;19:57)

- 70% female; bimodal presentation in the second and fifth decades of life
- 40% present w/ severe AIH (3% ALF) w/ ALT >10 × ULN; 34–45% asx
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs' ⊕ anemia, celiac
- Dx: scoring system combining serologies, ↑ IgG, Ø viral hepatitis, & liver bx (interface hepatitis & lymphoplasmacytic infiltrate) has high Sp & mod Se (*Dig Dis* 2015;33[S2]:53)
- Rx: (1) ALT or AST >10× ULN (2) IgG >2× ULN + ALT >5× ULN (3) bridging/multiacinar necrosis (4) cirrhosis w/ inflammation on biopsy (5) AST/ALT >2x ULN + symptoms
- Induction Rx: (1) prednisone monoRx; (2) prednisone + AZA, or (3) budesonide (if non-cirrhotic) + AZA → 65–80% remission (asx, nl LFTs, bili, & IgG, none-to-minimal interface hepatitis); taper steroids as able; relapse rate of 50–80% (*J Hep* 2015;62:S100)

- Nonresponders or AZA intolerant: cyclosporine, tacrolimus, MMF, rituximab, infliximab

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OTHER CAUSES OF HEPATITIS OR HEPATOTOXICITY

Alcohol-associated hepatitis (*J Hepatol* 2016;69:154; *Am J Gastro* 2018;113:175)

- Sx: progressive jaundice, tender hepatomegaly, fever, ascites, GIB, encephalopathy
- Labs: ALT usually <300–500 w/ AST:ALT > 2:1, ↓ plt, ↑ Tbili & INR indicate severe hepatitis
- Prognosis: scoring systems include Maddrey's discriminant fxn (MDF), Lille model, MELD
  - MDF (4.6 × [PT – control] + Tb) ≥32 w/ 30–50% 1-mo mortality if unRx'd (*Gastro* 1996;110:1847)
  - Lille model: predicts nonresponse to steroids after 1st week of Rx; score >0.45 predicts poor response to further steroid Rx and a/w ↓ in 6-mo survival (*Hep* 2007;45:1348)
  - Combination of Lille + MELD scores best predictor of mortality (*Gastro* 2015;149:398)
- Rx: consider if MDF ≥32, MELD >18, or presence of encephalopathy
  - Glucocorticoids (eg, methylprednisolone 32 mg/d or prednisolone 40 mg/d × 4 wk → 4–6 wk taper) may ↓ 1-mo but not 6-mo mortality, a/w ↑ infection (*NEJM* 2015;372:1619, CD001511)
  - Contraindic: active GIB, pancreatitis, untreated HBV, uncontrolled bact/fungal/TB infxn
  - Addition of NAC to steroids ↓ 1-mo but not 6-mo mortality (*NEJM* 2011;365:1781)
- Consider early transplantation in carefully selected Pts (*Gastro* 2018;155:422)

Acetaminophen hepatotoxicity (*Clin J Transl Hepatol* 2016;4:131; *BMJ* 2016;353:i2579)

- Pathophysiology: >90% of acetaminophen (N-acetyl-p-aminophenol, APAP) metab into nontoxic metab, but ~5% metab by CYP2E1 into NAPQI, a hepatotoxic metab detoxified by glutathione conjugation; APAP overdose (>10 g) depletes glutathione stores → injury
- CYP2E1 *induced* by fasting, alcohol, certain anticonvulsants and anti-TB drugs, resulting in injury with even low doses (2–6 g) of

acetaminophen
- Liver dysfunction may not be apparent for 2–6 d; nausea, vomiting & abdominal pain 1st sx
- Rx: NG lavage, activated charcoal if w/in 4 h. Consider early transfer to transplant ctr
  - ***N*-acetylcysteine:** administer up to 72 h after ingestion, if time of ingestion unknown or chronic ingestion >4g/d; low threshold to start NAC w/ low or undetectable APAP levels
  - PO NAC (preferred): 140 mg/kg loading dose → 70 mg/kg q4h × 17 additional doses
  - IV NAC: 150 mg/kg × 1 h → 50 mg/kg × 4 h → 100 mg/kg × 16 h; risk of anaphylaxis (↓ w/ 12-h regimen; *Lancet* 2014;383:697); use if unable to tolerate POs, GIB, pregnancy, liver injury

Ischemic hepatitis

- "Shock liver" w/ AST & ALT >1000 + ↑↑ LDH (ALT:LDH ratio often <1:5); delayed ↑↑ Tbili
- Seen in HoTN & CHF; often requires ↑ venous + ↓ portal/arterial pressure + hypoxia

Nonalcoholic fatty liver disease (NAFLD) (*JAMA* 2020;323:1175; *Lancet* 2021;397:2212)

- Definition: fatty infiltration of liver + absence of EtOH or other cause of steatosis (HCV, etc.)
  - **NAFL** = steatosis, Ø inflam; **NASH** = steatosis + inflam ± fibrosis on bx
- NAFLD: 25% of U.S. pop. & over 60% in T2DM & obesity
- NASH: 2–5% of NAFLD & risk of cirrhosis in NASH w/ fibrosis on bx is 30% at 10 y
- Clinical: 80% asx, ↑ ALT > AST, but nl ALT/AST does not exclude poss. of NASH on bx
- Dx: liver bx remains gold standard. VCT elastography emerging alternative (*J Hepatol* 2017;66:1022). FIB-4/NAFLD fibrosis score predicts NASH w/ advanced fibrosis w/ PPV >80%.
- Rx (*Gastro* 2021;161:1657): wt loss (≥10%), exercise, DM control, liraglutide (*Lancet* 2016;387:679), statins (*Metabolism* 2017;71:17), vit E in Pts w/o DM (*Hepatol* 2018;67:328), bariatric surgery (*World J Hepatol* 2019;11:138). New therapies (eg, PPAR agonist lanifibranor, *NEJM* 2021;385:1547)

emerging. HCC a complication of NAFLD, usually in setting of NASH cirrhosis.

ACUTE LIVER FAILURE (ALF)

Definition

- Acute liver injury + coagulopathy + encephalopathy w/o preexisting liver dis. (<26 wks)
- Fulminant if encephalopathy <8 wks from jaundice onset, subfulminant if 8–26 wks
- Acute on chronic liver failure: acute insult to liver in Pt w/ underlying chronic liver disease

Etiology (*J Hepatol* 2015;62:S112)

- **Drugs/toxins** (nearly 80% of cases in U.S.; *Gastro* 2015;148:1353, *Clin Liver Dis* 2017;21:151)
  Dose-dependent: acetaminophen (most common cause; >40% of cases in U.S.)
  Idiosyncratic, not dose related: anti-TB drugs (INH, RIF, PZA); AEDs (phenytoin, valproate, carbamazepine); NSAIDs; abx (eg, fluoroquinolones, macrolides, nitro-furantoin); drugs of abuse (MDMA & cocaine); others (amiodarone, TCAs)
  Toxins: *Amanita phalloides* (mushroom sp. in West Coast), certain herbal preparations
- **Viral**: HAV, HBV, HCV (rare), HDV + HBV, HEV (esp. if pregnant). In immunosupp: HSV (50% have skin lesions), EBV, VZV, CMV, HHV6
- **Vascular:** Budd-Chiari, ischemic hepatitis, hepatic sinusoidal obstruction syndrome
- **Other:** Wilson disease, pregnancy-related ALF (acute fatty liver, preeclampsia, HELLP), initial presentation of autoimmune hepatitis; idiopathic

Clinical manifestations

- Initial presentation: N/V, malaise, RUQ pain, jaundice, encephalopathy, multiorgan failure
- Neurologic: **encephalopathy:** grade 1 = attn deficit, disordered sleep; grade 2 = *asterixis*, confusion; grade 3 = somnolence,

rigidity; grade 4 = coma; ↑ ICP w/ bradycardia & HTN
cerebral edema: astrocyte swelling related in part to ↑ ammonia levels

- Cardiovascular: **hypotension** with low SVR, shock
- Pulmonary: **respiratory alkalosis**, impaired peripheral O_2 uptake, pulm edema, ARDS
- GI: GI tract bleed common (need PPI Ppx), pancreatitis (due to ischemia, drugs, infxn)
- Renal: ATN, **hepatorenal syndrome**, hyponatremia, hypokalemia, hypophosphatemia
- Hematology: **bleeding diathesis** w/ thrombocytopenia, ↑ PT/PTT, ↓ fibrinogen, ↓ synthesis of coag factors balanced by ↓ protein C/S; bleeding mostly due to low platelet count, DIC
- **Infection**: espec. with *Staph*, *Strep*, GNRs, and fungi (↓ immune fxn, invasive procedures); *fever and ↑ WBC may be absent, most common sites are respiratory, urinary & blood*
- Endocrine: **hypoglycemia** (↓ glc synthesis), metabolic acidosis (↑ lactate), adrenal insuf.

Workup (*Clin Liver Dis* 2017;21:769)

- CBC, PT/PTT, LFTs, lytes, BUN/Cr, NH_3, pH, *arterial* lactate, acetaminophen level, HIV, amylase/lipase, viral serologies (qv) in all Pts, with additional labs as below if suspected
- Autoimmune hep serologies & IgG levels, ceruloplasmin & serum/urine copper, preg test
- Imaging studies (RUQ U/S or abd CT, Doppler studies of portal and hepatic veins)
- Liver biopsy if underlying etiology remains elusive after initial testing

Management (*J Clin Exp Hepatol* 2015;5:S104; *Gastro* 2017;152:644)

- **ICU care at liver transplant center** for hemodynamic & ventilatory support; CVVH for AKI
- Early listing for liver transplantation in selected Pts (see below)
- Cerebral edema: consider ICP monitoring if grade 3/4 enceph; if ↑ ICP → mannitol 0.5–1.0 mg/kg; if arterial NH_3 >150, grade 3/4 enceph, AKI or on vasopressors → prophylactic 3% saline with goal Na 145–155 mEq/L; barbiturates & hypothermia if refractory ↑ ICP

- Encephalopathy: intubate for grade 3 or 4; lactulose is of little benefit & may be detrimental
- Coagulopathy: vit K, FFP/plts/cryo only if active bleeding (↑ risk of volume overload)
- Infection: low threshold for abx (broad spectrum, eg, vancomycin & 3rd-gen ceph.) if suspect infection; anti-fungal coverage in high-risk Pts (TPN, CVVH)
- Rx of specific causes: NAC if acetaminophen; antiviral for HBV; plasma exchange can be temporizing measure for Wilson disease; IV acyclovir for HSV; PCN-G for *A. phalloides;* delivery of child for pregnancy-related; TIPS, anticoag for Budd-Chiari. Lack of data for use of steroids in autoimmune, but often given (*Hepatology* 2014;59:612).
- NAC may benefit Pts w/ non-APAP ALF but data inconclusive (*Clin Drug Investig* 2017;37:473)
- **King's College Criteria for Liver Transplantation consideration:**
  Acetaminophen ALF: arterial pH <7.30 or Grade III/IV enceph + INR >6.5 + Cr >3.4
  Non-acetaminophen ALF: PT >100 or any 3: age <10 or >40 y, jaundice >7 d prior to onsent of encephalopathy, PT >50 or INR >3.5, Tbili >18, unfavorable disease (viral hepatitis, DILI, Wilson's disease, or low factor V level)

Prognosis (*Ann Intern Med* 2016;164:724; *World J Gastro* 2016;22:1523)

- Non-acetaminophen ALF mortality ~70%, acetaminophen-induced ALF mortality ~25–30%
- HBV, Wilson's, AIH, DILI, Budd-Chiari ~ associated with ↓ prognosis
- Factor V level <20% in Pts <30 yrs or <30% in >30 yrs associated w/ poor prognosis

CIRRHOSIS

Definition (*Dig Dis* 2016;34:374; *NEJM* 2016;375:767; *J Hep* 2016;64:717)

- Definition **fibrosis & regenerative nodules** causing distortion of hepatic architecture
- **Decompensated** = complication due to ↑ portal pressure such as: variceal bleed, HCC, SBP, encephalopathy, ascites, hepatorenal or hepatopulmonary syndrome

Etiologies

- **Alcohol**, toxins (eg, arsenic)
- **Nonalcoholic fatty liver disease (NAFLD**) is the cause of most "cryptogenic cirrhosis"
- **Viral hepatitis**: chronic HBV, HCV, HDV infection
- **Autoimmune hepatitis:** ♀, ↑ IgG, ⊕ ANA, ASMA, anti-LKM-1, anti-LC1
- **Metabolic diseases**: hemochromatosis, Wilson disease, α_1-AT deficiency
- **Biliary tract diseases**: primary biliary cholangitis, secondary biliary cirrhosis (calculus, neoplasm, stricture, biliary atresia), primary sclerosing cholangitis
- **Vascular diseases:** Budd-Chiari syndrome, R-sided CHF, constrictive pericarditis, SOS
- **Medications:** amiodarone, methotrexate, vitamin A, valproic acid, isoniazid

Clinical manifestations

- Nonspecific sx (anorexia, fatigue) or jaundice, encephalopathy, ascites, variceal bleeding

Physical exam

- Liver: *initially* enlarged, palpable (L lobe predom), firm; *eventually* shrunken, nodular
- Signs of liver failure: jaundice (bili >2.5), spider angiomata & palmar erythema (↑ estra- diol), Dupuytren contractures, white nail lines

(Muehrcke lines) & proximal nail beds (Terry nails), ↑ parotid & lacrimal glands, gynecomastia, testicular atrophy, asterixis, encephalopathy, clubbing, hypertrophic osteoarthropathy, anovulation in women
- Signs of portal HTN: splenomegaly, ascites, dilated superficial abd veins (caput medusae), epigastric Cruveilhier-Baumgarten venous hum (flow through recanalized umbilical vein)

Laboratory studies
- LFTs: ↑ **bili**, ↑ **PT/INR** (poor correlation w/ bleeding; factor VIII nl b/c not synthesized by liver), ↓ **alb**, ± ↑ aminotransferases (AST >ALT if late) and ↑ Aϕ (variable)
- Hematologic tests: anemia (marrow suppress., hypersplenism, Fe ± folate defic.), neutro-penia (hypersplenism), thrombocytopenia (hypersplenism, ↓ Tpo production, EtOH tox)
- Chem: ↓ Na (↑ ADH due to ↓ EAV); ↑ Fe/TIBC, ↑ ferritin (released from hepatocytes)
- Lab indices predictive of cirrhosis: AST/plt >2; Lok index; Bonacini score (*JAMA* 2012;307:832)
- Indirect markers of fibrosis: FibroTest/FibroSURE, Hepascore (good at differentiating significant fibrosis F2 to F4), FIB-4 index (NAFLD, HCV), NAFLD fibrosis score, APRI (HCV), non-invasive imaging (eg, U/S or MR elastography)

Workup (*Am J Gastro* 2017;112:18; *Lancet* 2021;398:1359)
- Abd **U/S w/ Doppler:** liver size & echotexture, r/o HCC, ascites, ✓ patency of vasculature
- Determine etiology: hepatitis serologies (HBsAg, anti-HBs, anti-HCV), autoimmune hepatitis studies (IgG, ANA, ASMA), Fe and Cu studies, α_1-AT, AMA
- Assess fibrosis: biomarkers (FibroSURE = panel of 5 markers validated in HCV, ↑ score predictive of fibrosis); elastography (U/S or MR-based; measurement of liver stiffness)
- Liver bx (gold standard): percutaneous or transjugular (consider if ascites or coagulopathy), used to confirm presence of cirrhosis and dx etiology, not always needed

Prognosis (www.mdcalc.com/child-pugh-score-cirrhosis-mortality)

- **Modified Child-Turcotte-Pugh (CPS)** score based on ascites, enceph., & labs (bili, alb & INR; see Appendix). CPS A (5–6 pts): 1-y survival 100%, B (7–9): 80%; C (10–15): 45%.
- **MELD-Na** (**M**odel for **E**nd-Stage **L**iver **D**isease; *Gastro* 2011;14:1952): used to stratify liver Tx list & predict 3-mo survival in cirrhosis and some acute forms of liver dis. Based on Cr, INR, total bili, Na. Calculator: https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/.
  - If MELD <21, additional predictors of mortality include refractory ascites, ↑ HVPG & ↓ QoL.
  - MELD-Plus includes alb, chol, LOS, age, WBC (*PLOS One* 2017;12:e0186301).

Ascites (see "Ascites" for diagnostic eval; *Dig Dis* 2017;35:402; *Hepatology* 2021;74:1014)

- Due to portal HTN (defined as hepatic venous pressure gradient [HVPG] >5 mmHg)
- Develops in 60% w/in 10 y; often first decompensating event
- Treatment: ↓ **Na intake** (1–2 g/d); restrict intake of free water if Na <125
  - **Diuretics:** goal diurese ~1 L/d. Use spironolactone ± furosemide in 5:2 ratio (uptitrate as able); urine Na/K >1 implies effective natriuresis if Pt compliant w/ low-Na diet
  - Avoid NSAIDs/ACEI/ARBs in cirrhosis because interfere w/ diuretic action
  - Long-term albumin infusions ↓ mortality (*Lancet* 2018;391:2417), but not widely adopted
- **Refractory ascites:** seen in 5–10% of Pts; 2-y survival 25%
  - Defined as diuretic-resistant if on 2-g Na diet w/ minimal weight loss on max diuretics, or diuretic-induced complications (AKI, Na <125, ↑ K, encephalopathy)
  - Conflicting evid. for d/c'ing βB (*Hep* 2016;63:1968; *J Hepatol* 2016;64:574). Discontinue if SBP <90 or MAP ≤82 mmHg, serum Na <120 mEq/L, AKI, HRS, SBP, sepsis, severe alcohol-assoc hepatitis, or poor follow-up. If limited by HoTN, can add midodrine.
  - **Large-volume paracenteses** (LVP; >5 L fluid removal): give 6–8 g albumin per L fluid removed (above 5 L) as colloid replacement a/w ↓ risk of post-para circulatory dysfxn & possibly ↓ mortality

(*Hep* 2012;55:1172). Avoid LVP if SBP present because ↑ risk of AKI.

Transjugular intrahepatic portosystemic shunt (TIPS) (*Gastro* 2017;152:157)

↓ ascites in 75%; ↑ CrCl, ↑ enceph, survival benefit over LVP remains controversial

Contraindic: grade II enceph, CHF or pulm HTN, active infxn or biliary obstruction

Complications: bleeding, fistula; stent thrombosis (1-y patency w/ coated stents ~80%); infxn ("endotipsitis"); new or ↑ enceph in 20–30% (*Am J Gastro* 2016;111:523), hemolysis

Consider for liver transplant if above fail

- **Hepatic hydrothorax:** 2° diaphragmatic defect; often unilateral, R >L, ± ascites

  Treatment: avoid chest tube (↑ complications); Rx same as ascites (TIPS if refractory). Indwelling pleural catheter potential option if refractory for palliation (*Chest* 2019;155:307)

  Spontaneous *empyema* can occur (even w/o SBP) → dx thoracentesis; Rx abx

Spontaneous bacterial peritonitis (SBP; see "Ascites"; *Hepatology* 2021;74:1014)

- High mortality rate; risk factors include ascitic TP <1 g/dL, hx of SBP, current GIB
- Can p/w encephalopathy, abd pain, fever, *but often* (*25%*) *asx;* perform diagnostic paracentesis in all hospitalized patients with cirrhosis and ascites
- Micro: typically, monobacterial GNRs (*E. coli, Klebs*) >GPCs (*S. pneumo, enterococcus*)
- Rx: 3rd-gen. ceph is 1st line; consider pip/tazo or mero if ↑ risk of MDRO; vanc if prior MRSA ⊕; IV albumin 1.5 g/kg at time of dx & 1 g/kg on day 3 → ↑ survival (*NEJM* 1999;341:403)
- Repeat paracentesis at 48 h: expect 25% ↓ in PMNs if Rx working.
- Indefinite Ppx if (1) h/o SBP or (2) ascitic TP <1.5 plus: Na ≤130 or Cr ≥1.2 or BUN ≥25 or [CPS ≥9 + Tbili ≥3] (*Am J Gastro* 2009;4:993) → cipro 500 mg qd or Bactrim DS qd. Short-term Ppx: CTX 1 g IV × 7d if GIB (Δ to cipro 500 bid/Bactrim DS bid when eating).

Gastroesophageal varices ☐ UGIB (see also "GIB"; *Hepatology* 2017;65:310)

- Presence of varices correlates w/ severity of liver dis (40% of Child A Pts → 85% Child C)
- ↑ varix size, child B/C, & red wale marks assoc w/ ↑ risk of bleeding
- UGIB 1° prevention: screen at time of dx w/ EGD; data best for Pts w/ med-large varices
  - **Nonselective β-blockers:** ~50% ↓ risk of bleeding & ↓ mortality if med-large varices. Nadolol, propranolol, or carvedilol; latter ↓ MAP & HVPG more than propranolol; delays progression of varices (*Gut* 2017;66:1838); may use in Pts w/ HTN. Titrate to max tolerated dose; EGD not req. to document improvement. Hold for criteria listed above.
  - **Endoscopic variceal ligation** (EVL): superior to βB in ↓ risk of 1st bleed but no diff in mortality (*Ann Hep* 2012;11:369); risk of serious complications (esoph perf, ulcers). Repeat q1–4wk until varices gone, w/ f/u EGD at 3 mo then q6–12mo.
  - βB vs. EVL: choice based on Pt/physician preference; βB often 1st for small varices; larger varices may benefit more from EVL; both for 1° Ppx currently not recommended
- 2° prevention: for all Pts after 1st bleed, given ~50% risk of rebleed & ~30% mortality; βB + EVL >either alone; TIPS if refractory, or consider in child B/C w/in 72 h of admission for EV bleed (↓ rebleeding, ↑ enceph., Ø Δ mort.) (*Hepatology* 2017;65:310)

Hepatic encephalopathy (HE) (*NEJM* 2016;375:1660; *Hepatology* 2014; 60:715)

- Pathogenesis: failure of liver to detoxify NH_3 + other substances (eg, ADMA; *J Hepatol* 2013;58:38) that cause cerebral edema, ↓ O_2 consumption, ↑ ROS → brain dysfxn
- Precipitants: bleeding, infxn, med nonadherence, ↓ K, ↓ Na, dehydration, hypoxia, portosystemic shunt (eg, TIPS), meds (eg, sedatives), acute insult to liver (eg, PVT)
- Stages: see section in "Acute Liver Failure"
- Dx: serum NH_3 levels have poor Se for dx & monitoring Rx; remains a *clinical dx*
- Rx*:* identify/correct precipitants; **lactulose** (acidification of colon: NH_3 → NH_4^+) w/ goal 2–4 stools/d (PEG may be as effective; *JAMA IM*

2014;174:1727); add **rifaximin** 550 mg bid (↓ gut bacteria → ↓ NH_3 prod) if refractory or after 2nd recurrence HE on lactulose (NNT=3) (*Am J Gastro* 2013;108:1458); FMT, oral branched-chain AAs, probiotics may have a role (Cochrane Reviews 2017;2; *Gastro* 2019;156:1921); maintain K >4, avoid alkalosis as able

Hepatorenal syndrome (HRS) (*Hepatology* 2021;74:1014, *Gastro* 2016;150:1525)

- Pathophys: splanchnic vasodilation and renal vasoconstriction w/ ↓ renal blood flow
- Criteria: (1) cirrhosis w/ ascites; (2) **acute kidney injury** (serum Cr ↑ ≥0.3 mg/dL w/in 48 h or ≥50% ↑ in serum Cr from baseline; *Gut* 2015;64:531); (3) Ø improvement in Cr after d/c diuretic & volume expansion (1 g/kg/d of albumin × 2 d); (4) Ø shock (prerenal azotemia/ATN); (5) Ø nephrotoxic meds; (6) Ø intrinsic kidney disease
  - **HRS-AKI:** development in <2 wk; usually occurs in severe liver failure, often following precipitating event (see later); median survival 2 wk
  - **HRS-CKD:** more indolent, median survival 6 mo; liver failure present <than in HRS-AKI
- Precipitants: GIB, overdiuresis, infection, serial LVP, drugs (aminoglycosides, NSAIDs)
- Rx: *if critically ill* → vasopressor (eg, norepinephrine or vasopressin) + albumin (1 g/kg, max 100 g, bolus daily) to ↑ MAP 10 mmHg. *If not critically ill* → octreotide (100–200 mcg SC tid) + midodrine (max 15 mg PO tid) + 1 g/kg (max 100 g) albumin on day of presentation followed by 20–60 g albumin qd to ↑ MAP. Terlipressin + albumin ↑ 10 d survival (not yet approved in U.S. but now recommended by AASLD) (*NEJM* 2021;384:818). May need dialysis or TIPS as bridge to liver transplant.

Hepatocellular carcinoma (HCC; qv in Heme-Onc) (*Nature Reviews* 2021;7:6)

- ↑ risk w/ cirrhosis of any type (leading cause of death in cirrhosis, 1–6%/y) but esp. ↑ w/ viral (Hep B/C~3–8%/y), concomitant EtOH use, obesity related NASH, HFE or diabetes
- Clinical: asx vs. hepatic decompensation (eg, ascites, HE), PVT w/ tumor thrombus

- Dx: screen Pts w/ cirrhosis q6mo w/ U/S ± AFP; alternative is dual-phase CT/MRI
- Rx: see "HCC" in Heme-Onc

Other complications

- **Hepatopulmonary syndrome** (HPS) (*Dig Dis Sci* 2015;60:1914, *Hepatology* 2021;74:1014)
  - Abnl gas exchange (A-a gradient ≥15 or P_aO_2 <80) caused by intrapulmonary vascular dilatations leading to intrapulmonary shunting (improves with O_2)
  - S/S: platypnea-orthodeoxia (dyspnea & hypoxia w/ sitting up), clubbing, spider angiomas
  - Dx w/ contrast echo showing "late" A-V shunting (contrast in LA 3–6 cycles after RA)
  - Rx: O_2; potential embolization if large vessel on CT, TIPS, liver tx only definitive Rx
- **Portopulmonary hypertension** (POPH) (*Expert Rev Gastro Hepatol* 2015;9:983)
  - Pulm HTN in Pt w/ portal HTN w/o other cause. ESLD→ ↑ endothelin→ pulm vasoconst.
  - Rx w/ same therapies as for idiopathic PAH, incl prostacyclin analogs, endothelin receptor antagonists, sildenafil; liver transplant is often curative
- **Cirrhotic cardiomyopathy:** ↓ inotropic & chronotropic response, ↓ systolic & diastolic fxn, ↑ QT, hyperkinetic circulation, high output; ↑ troponin & BNP
- **Infxns:** unless immune, vaccinate for HAV, HBV, PCV13, PPSV23, COVID-19; flu yearly. Cellulitis in ~20% of Pts hospitalized w/ cirrhosis, often in abd or LE a/w edema.
- **Endocrine:** diabetes (15–30%), ↑ frequency of adrenal insuffic. (*Dig Dis Sci* 2017;62:1067)
- **Coagulopathy:** balanced defects w/ ↓ synth of coag factors, hyperfibrinolysis, ↓ plt balanced by ↓ synthesis anticoag factors (protein C/S), defic. of profibrinolytic factors, ↑ levels of vWF. No support for routine administration of FFP, plt, cryo unless DIC.
- **Nutrition:** monitor and supplement fat-soluble vitamins, zinc, screen for malnutrition, sarcopenia & frailty; ensure protein intake 1.2–1.5 g/kg/d (*Hepatology* 2021;74:1611)

- Meds: acetaminophen can be used up to 2 g/d; avoid ASA/NSAIDs; aminoglycosides contraindicated; oral hypoglycemics if compensated but insulin if decompensated

Liver transplantation (*Hepatology* 2014;59:1144)

- Undertake evaluation when MELD ≥15. Exception points added if HCC, HPS
- Indic: recurrent/severe enceph, refractory ascites, recurrent variceal bleeding, HRS, HPS, PPH, HCC (if no single lesion is >5 cm *or* ≤3 lesions with largest ≤3 cm), ALF
- Contraindic: inadequate social support, active substance abuse (some exception), sepsis, advanced cardiopulm dis., extrahepatic Ca, cholangio Ca, hemangiosarcoma, persistent noncompliance, AIDS, ALF w/ sustained ICP >50 mmHg or CPP <40 mmHg
- Survival: 1-y up to 90%, 5-y up to 80**%**, though lower with autoimmune liver disease, such as AIH/PBC/PSC may recur in 10–30% (or more) of allografts

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Other Etiologies of Cirrhosis

Hemochromatosis & iron overload syndromes (*Am J Gastro* 2019;114:1202)

- Recessive disorder of iron sensing or transport leading to tissue **iron deposition**
- **HFE** mutations (85% of cases): typically C282Y homozyg. (~0.5% of N. Europeans), rarely C282Y/H63D compound heterozyg. C282Y homozygotes: 28% of ♂ & 1% of ♀ develop sx (delayed since menses ↓ Fe load). C282Y/H63D: only 1.5% manifest dis.
- Non-HFE mutations: hemojuvelin, hepcidin, transferrin receptor 2, & ferroportin
- 2° causes of iron overload: iron-loading anemias (eg, thalassemia major, sideroblastic anemia, aplastic anemia), parenteral iron overload (RBC transfusions, long-term HD), chronic liver disease (due to EtOH, HBV, HCV, NASH, etc.), dietary iron overload
- Sx: fatigue & arthralgias, loss of libido in ♂. In *advanced disease* (rare): bronze skin (melanin + iron), hypogonadism (esp. in juvenile onset), DM, arthropathy (MCP), CHF, infxns (↑ risk *Vibrio*, *Listeria*,

Yersinia), cirrhosis (↑ risk if EtOH/fatty liver disease; 15% risk of HCC). Disease also a/w ALS (H63D homozygotes) & porphyria.

- Dx: iron sat >45% (iron/TIBC × 100%); ↑ ferritin (acute phase reactant, so poor Sp; often nl in young Pts). If ↑ iron sat. → ✓ HFE to confirm dx, imaging by MRI (black liver). If HFE ⊕ & ferritin >1000 ng/mL or ↑ LFTs → liver bx for quant Fe index & to stage fibrosis
- Treatment: phlebotomy (250 mL = 1 unit, ~250 mg of Fe) qwk until Fe sat <50% & ferritin 50–100 μg/L, then q3–4mo; PPI ↓ intestinal Fe absorption & may ↓ need for phlebotomy; avoid vit C & uncooked seafood; deferoxamine if phleb. contraindic.; genetic counseling

Wilson disease (*World J Hepatol* 2015;7:2859)

- Recessive disorder of copper transport (mutation in *ATP7B*) → **copper overload**
- Epidemiology: 1 in ~30,000 w/ age of presentation generally ranging from 3 to 55 y
- Extrahepatic s/s: neuro ψ disease, parkinsonism, movement disorder (hepatolenticular disease), Kayser-Fleischer rings (⊕ in 99% w/ neuro ψ but in <50% w/ hepatic disease), Coombs ⊖ hemolytic anemia, renal disease
- Dx: ↑ 24-h urine Cu, ↓ serum ceruloplasmin (Se 90%), liver bx w/ hepatic Cu content, genetic testing for ATP7B gene helpful if unclear dx. In *acute liver failure*, Aϕ/bili <4 + AST/ALT >2.2 better Se & Sp than urine Cu or ceruloplasmin (*Hepatology* 2008;4:1167).
- Treatment: **chelation** w/ D-penicillamine (supplement B6 as D-pen inactivates); alternative is trientine (↓ toxicity w/ ≈ efficacy, but $$), ammonium or bis-choline tetrathiomolybdate (investigational) may ↓ neurologic deterioration compared to trientine. **Zinc:** ↓ intestinal Cu transport & can help delay disease; best used in conjunction w/ chelation (give 5 h after chelators). Eliminate Cu-rich foods. Transplant for ALF or unresponsive to Rx.

α_1-antitrypsin deficiency (α_1-AT) (*J Hepatol* 2016;65:413; *NEJM* 2020;382:1443)

- Abnl α_1-AT → polymerization in liver (cirrhosis) & uninhibited protease activity in lung (emphysema). Affects 1/3000 of European

ancestry. Varied presentations: neonatal hepatitis; cholestatic jaundice in children; ↑ AST/ALT or cirrhosis in children/adults.
- Extrahepatic disease: panlobular emphysema, necrotizing panniculitis, ANCA vasculitis
- Dx: serum α_1-AT (acute phase reactant) w/ CRP level (to ensure not ↑ due to inflamm.)
  gold standard = phenotyping of protease inhibitor (Pi). Alleles most a/w hepatic dis.: Z (63% of ZZ adults have chronic liver dis. and liver fibrosis, may be present in 35% of ZZ individuals w/o overt liver disease) & M (malton) (*J Hepatol* 2018;69:1357). Liver bx shows characteristic PAS ⊕ cytoplasmic inclusion bodies.
- Treatment: ↓ risk by avoiding EtOH, maintaining a normal BMI; liver transplant if severe

Primary biliary cholangitis (PBC) (*Hep* 2019;69:394; *Nat Rev* 2020;17:93; *Lancet* 2020;396:1915)

- Autoimmune destruction of *intrahepatic* bile ducts
- Epi: ♀ 40–60 y; a/w Sjögren's (50%), Raynaud's, scleroderma, celiac & thyroid disease; may be triggered by infxns or toxins; a/w X monosomy, variants in IL12α & IL12R genes
- Sx: fatigue/sleep disturbance, pruritus, jaundice, 50% asx w/ only LFT abnormalities
- Ddx: PSC, AIH, hepatic sarcoidosis, meds, idiopathic adult ductopenia, biliary stricture/Ca
- Dx: ↑ Aϕ, ↑ bili, ↑ IgM, ↑ chol (mainly HDL-C), ⊕ (AMA) in 95%. If ⊕ AMA, liver bx not needed due to high Se & Sp. 0.5% gen pop ⊕ AMA & nl LFTs → 10% develop PBC at 6 y. If AMA ⊖, liver bx (Pts often ⊕ ANA, smooth muscle Ab; same prognosis as ⊕ AMA).
- Rx: **ursodeoxycholic acid** (UDCA) (13–15 mg/kg bid), monitor for 3–6 mos → ~25% complete response, ↑ survival & ↓ histologic change & ↓ complications (varices). Biochemical response predicts clinical outcome.
  Obeticholic acid (FXR agonist): monoRx if cannot tolerate UDCA (but not in decompen cirrhosis) or if no Δ w/ UDCA after 1 y; found to ↓ Aϕ, ↑ pruritus (*NEJM* 2016;375:631)
  Bezafibrate (not available in U.S. but fenofibrate similar) appears to be effective 2nd-line agent in combo w/ UDCA if inadequate response to UDCA (*NEJM* 2018;378:2171)

Pruritus: cholestyramine (give 2–4 h after UDCA); if refractory sx: naltrexone, rifampin

If ESLD: liver tx; ~20% recur but no impact on long-term survival

Primary sclerosing cholangitis (PSC) (*NEJM* 2016;375:1161; *Clin Liver Dis* 2020;15:125)

- Diffuse inflammation of *intrahepatic and extrahepatic* bile ducts leading to fibrosis & stricturing of biliary system. A/w HLA-B8 and -DR3 or -DR4, frequent ⊕ autoantibodies.
- Epi: ♂ >♀ (20–50 y) ~70% Pts w/ PSC have IBD (usually UC); only 1–4% w/ UC have PSC. ⊕ prognostic factors: ♂, absence of IBD, small duct PSC (*Gastro* 2017;152:1829).
- Symptoms: fatigue, pruritus, jaundice, fevers, RUQ pain, IBD; 50% of Pts asymptomatic
- Ddx: extrahepatic obstruction, PBC, overlap w/ AIH, IgG4 autoimmune cholangitis, etc.
- Dx: cholangiography (MRCP ± ERCP) → *multifocal beaded bile duct strictures*; exclude 2° cause; may miss dx if confined to small intrahepatic ducts ("small duct PSC").

  Liver bx if unclear: "onion-skin" fibrosis around bile ducts + some findings similar to PBC.
- Treatment: supportive care, fat-soluble vitamins; no meds have improved survival

  UDCA may ↓ Aϕ & improve Sx, but unclear if beneficial

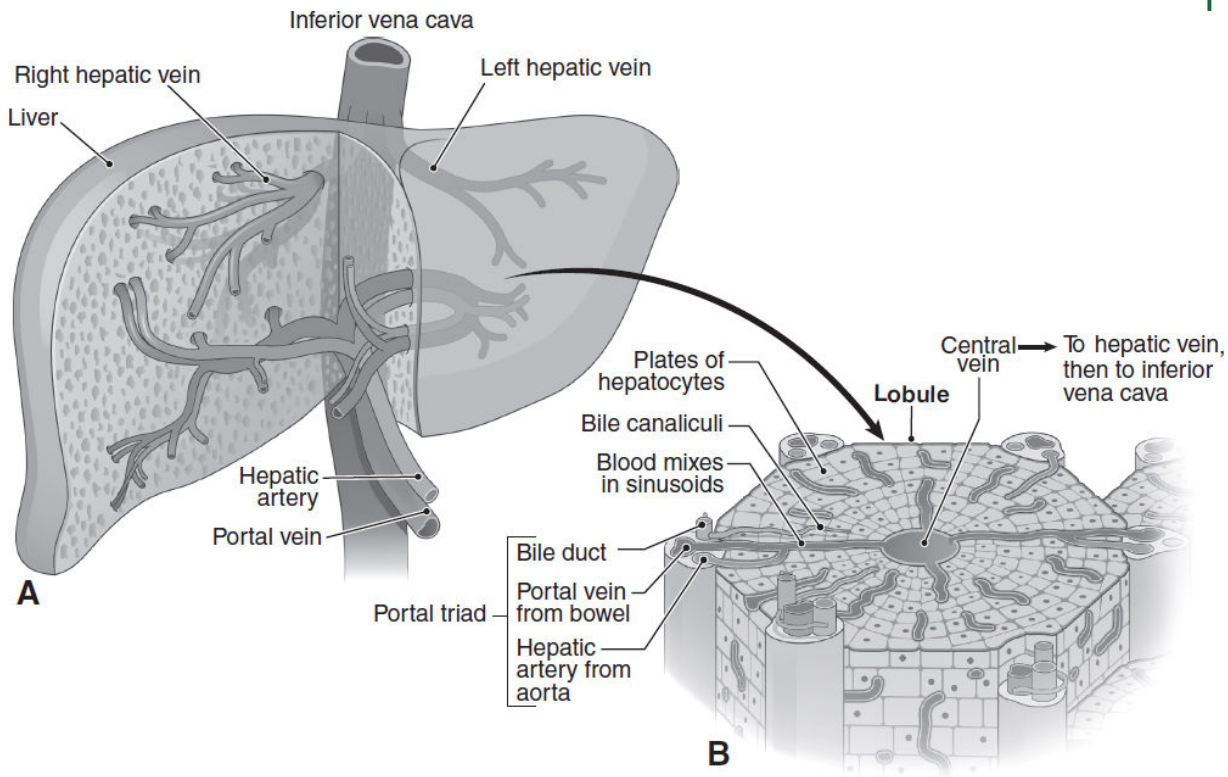
  If dominant stricture → endoscopic dilation, stenting or surgical resection can help

  Cholangiocarcinoma: 15% lifetime risk; annual surveillance w/ MRCP or U/S & CA19-9

  Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence

HEPATIC VASCULAR DISEASE

Figure 3-5 Normal hepatic vasculature



(Modified from *The Nature of Disease Pathology for the Health Professions, 2007. Hepatology* 2009;49:1729.)

Portal vein thrombosis (PVT) (*Clin Liver Dis* 2017;10:152; *Gastro* 2019;156:1582)

- Definition: thrombosis of portal vein often w/ extension into mesenteric vein/splenic vein
- Etiologies: commonly due to cirrhosis or hypercoaguable state (cancer, infection, OCP, collagen vascular diseases, Behçet's, IBD, surgery, trauma, OCPs, preg)
- Clinical manifestations
  - **acute:** abd pain, fever, variceal bleed or asx w/ incidental finding on U/S or CT. If mesenteric vein involved may p/w intestinal infarct. If fever, consider pylephlebitis.

chronic: asx/incidental finding; may p/w s/s of **portal HTN** → hematemesis 2° variceal bleeding, splenomegaly, encephalopathy; ascites uncommon unless cirrhosis

- Dx: LFTs usually nl; begin w/ U/S w/ Doppler, confirm w/ MRA or CT (I^+), angio; consider hypercoag w/u. "Portal cavernoma": network of hepatopetal collaterals in chronic PVT—can rarely cause biliary obstruction & cholestatic LFTs = portal cholangiopathy.
- Treatment: **Acute:** If noncirrhotic, LMWH → warfarin or DOAC × 6 mo, or indefinitely if irreversible cause. If cirrhotic, anticoag ↑ recanalization w/o ↑ bleeding (*Gastro* 2017;153:480); screen for high-risk varices prior to Rx (*Nat Rev Gastro Hep* 2014;11:435).
  Chronic: Anticoag if noncirrhotic or hypercoag state. If cirrhotic, consider txp if sx or progression. In all, screen for varices; if present, variceal bleed Ppx prior to anticoag.

Splenic vein thrombosis

- Can occur 2/2 local inflam. (eg, panc.). Can p/w isol. gastric varices. Splenectomy curative.

Budd-Chiari syndrome (*World J Hepatol* 2016;8:691)

- Hepatic outflow obstruction 2/2 occlusion of hepatic vein(s) or IVC → sinusoidal congestion and portal HTN. Can be 1° (eg, thrombosis) or 2° (eg, extravascular compression).
- Etiol.: ~50% due to myeloprolif. d/o a/w *JAK2* mutations (*P. vera*, etc.), hypercoag states (systemic, OCP, pregnancy), tumor invasion (HCC, renal, adrenal), trauma, idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals, acute liver failure
- Dx: ± ↑ AST, ALT & Aϕ; Doppler U/S of hepatic veins (85% Se & Sp); CT (I^+) or MRI/MRV → vein occlusion or ↑ caudate lobe (separate venous drainage); hepatic venography gold standard w/ "spider- web" pattern + assess venous pressure; biopsy only if unclear
- Treatment: Rx underlying condition, anticoag (LMWH → warfarin); consider thrombolysis if acute; angioplasty & stent if short stenosis; consider TIPS or DIPS (U/S-guided direct intrahepatic portosystemic shunt) (if other methods fail to treat sx of portal HTN); liver transplant if ALF or failed other options

Sinusoidal obstruction syndrome (SOS) (*Bone Marrow Transplant* 2020:55:485)

- Occlusion of hepatic venules & sinusoids (formerly veno-occlusive disease) 2/2 toxic insult
- Etiologies: post HSCT (15%), chemo (cyclophosphamide, cytarabine), XRT, bush tea
- Clinical manifestations: painful hepatomegaly, RUQ pain, ascites, weight gain, ↑ bilirubin
- Dx: U/S w/ reversal of portal flow; dx made clinically (early weight gain, ↓ plt refractory to transfusion, ↑ bili, hx of recent toxins); if necessary, liver bx or HVPG (>10 mmHg)
- Rx: supportive, diuretics; if severe → early defibrotide ↑ survival, but side effects & expensive
- Ppx: defibrotide; ursodeoxycholic acid for high-risk HSCT pop; ? use of low-dose heparin

ASCITES

Pathophysiology (*Hepatology* 2021;74:1014)

- Portal HTN → ↑ NO & prostaglandins → splanchnic vasodilatation → ↓ effective arterial volume → ↑ RAAS & ADH → renal Na & H_2O retention → volume overload and ascites
- In malignant or inflammatory ascites, leaking of proteinaceous material occurs from tumor or from inflamed/infected/ruptured intraabdominal structures

Symptoms

- ↑ abd girth, wt gain, new abd hernia, abd pain, dyspnea, nausea, early satiety

Evaluation (*World J Hepatol* 2013;5:251; *JAMA* 2016;316:340)

- Physical exam: **flank dullness** (>1500 mL needed), shifting dullness (Se ~83%)
- Radiologic: **U/S** detects >100 mL fluid; MRI/CT (also help with Ddx)
- **Paracentesis**: perform in all Pts w/ new ascites, suggested in all hosp. Pts w/ cirrhosis + ascites. Low complic. rate (~1% hematoma formation). Prophylactic FFP or plts does *not* ↓ bleeding complic. Most useful tests: cell count, alb, total protein (for SAAG), & culture
- **Serum-ascites albumin gradient (SAAG):** serum alb (g/dL) – ascites alb (g/dL)
  SAAG ≥1.1 diagnoses portal HTN with ~97% accuracy (*Ann Intern Med* 1992;117:215)
  If portal HTN + another cause (seen in ~5% of cases) SAAG still ≥1.1

Etiologies	
Portal HTN Related (SAAG ≥1.1)	**Non–portal HTN Related (SAAG <1.1)**

Etiologies	
Presinusoidal obstruction portal or splenic vein thrombosis, schisto- somiasis, sarcoidosis *Sinusoidal* obstruction: **cirrhosis**, acute hepatitis (including EtOH), malignancy (HCC or mets) *Postsinusoidal* obstruction right-sided **CHF** (ex: constriction, TR), Budd-Chiari syndrome, SOS	Malig: **peritoneal carcinomatosis**; chylous ascites from malignant lymphoma (↑ TG); Meigs' syndrome (ovarian tumor) Infection: TB, chlamydia/gonorrhea (ie, Fitz-Hugh-Curtis syndrome) Inflam: pancreatitis, ruptured pancreatic/biliary/lymph duct; bowel obstrxn, serositis (SLE) Hypoalbuminemic states: nephrotic syndrome, protein-losing enteropathy

- Ascites fluid total protein (**AFTP**): useful when SAAG ≥1.1 to distinguish cirrhosis (AFTP <2.5 g/dL) from cardiac ascites (AFTP ≥2.5 g/dL). Low AFTP (<1 g/dL) assoc. w/ ↑ risk of SBP (see "Cirrhosis" for guidelines on SBP Ppx based on AFTP).
- **Cell count:** normal limit of PMNs in ascitic fluid up to 250 PMNs/mm^3. Bloody tap (typically from traumatic para) can skew cell count; subtract 1 PMN for every 250 RBCs to correct PMN count. Ascitic PMNs ≥250 suggest infection.
- Other tests: amylase (pancreatitis, gut perforation); bilirubin (test in dark brown fluid, suggests bile leak or proximal intestinal perf); TG (chylous ascites); BNP (HF); cytology (peritoneal carcinomatosis, ~95% Se w/ 3 samples). SBP a/w ↓ glc & ↑ LDH. Ascites culture (prior to abx if possible, should have both aerobic & anerobic w/ 10 cc per bottle)

Treatment (see "Cirrhosis" for details)

- If 2° to portal HTN: ↓ **Na intake** (<2 g/d) + **diuretics**; if refractory → LVP (serial) or TIPS
- If non–portal HTN related: depends on underlying cause (TB, malignancy, etc.)

Bacterial peritonitis (*Gut* 2012;61:297; *Hepatology* 2021;74:1014)

Ascites PMN	⊕ Ascites Culture	⊖ Ascites Culture
≥250/ μL	**Spontaneous bacterial peritonitis (SBP):** gut bacterial translocation to ascites. In cirrhosis, ↓ ascites opsonins (esp. if ↓AFTP) ↑ risk of infxn. Infection usually monomicrobial: most common → *E. coli*, *Klebs*, *S. pneumo*; rarely *Staph* & *Pseudo*. Rx 3rd-gen ceph; carbapenem if critically ill.	**Culture-⊖ neutrocytic ascites (CNNA):** cell counts suggest infxn but cx ⊖. No recent abx, w/o other explan. for counts. Often do have SBP and

	2° bacterial peritonitis: 2/2 intra-abd abscess, perf. Runyon's criteria: AFTP >1 g/dL, glc <50 mg/dL, LDH >ULN for serum. Cx polymicrobial. Rx 3rd-gen ceph. + MNZ; urgent abd imaging ± ex lap.	should be treated with empiric regimen.
<250/ μL	**Nonneutrocytic bacterascites (NNBA):** ⊕ cx w/o ↑ PMNs. Natural course may resolve w/o Rx. Start abx if symptomatic; if asymptomatic repeat para in 48 hrs. Cx w/ 1 org.: Misc. GPC, *E. coli*, *Klebs*, misc. GNR.	(Normal)
Peritoneal dialysis-associated: cloudy fluid, abd pain, fever, nausea. Dx can be made with >50 PMNs. Culture most often GPC (50%) or GNR (15%). Rx: vanc + gent (IV load, then administer in PD).		

BILIARY TRACT DISEASE

CHOLELITHIASIS (GALLSTONES)

Epidemiology & pathogenesis (*J Hepatol* 2016;65:146; *Gastro* 2016;151:351)

- Affects ~10% of Western populations, 15–25% of people develop sx over 10–15 y
- Bile = bile salts, phospholipids, cholesterol; ↑ cholesterol saturation in bile + accelerated nucleation + gallbladder hypomotility → gallstones
- Risk factors: ♀; South, Central, Native American; ↑ age (>40 y); obesity, TPN, rapid ↓ wt; dyslipidemia; preg., drugs (OCPs, estrogen, clofibrate, octreotide); ileal dis., genetics
- Statin use ↓ risk of sx gallstones & cholecystectomy (*Hepatol Res* 2015;45:942)

Types of gallstones (*J Hepatol* 2016;65:146)

- Cholesterol (90%): 2 subtypes
  mixed: contain >50% cholesterol; typically smaller, multiple stones
  pure: 100% cholesterol; larger, yellow, white appearance
- Pigment (10%)
  Black: unconjugated bili & calcium; seen w/ chronic hemolysis, cirrhosis, CF, Gilbert synd
  Brown: stasis & infxn in bile ducts → bacteria deconjugate bilirubin → precipitates w/ Ca; found pred in bile ducts; seen w/ biliary strictures, parasites, post-cholecystectomy

Clinical manifestations

- Asx in ~80%. Biliary pain develops in 1–4%/y. Once sx, rate of complications ~1–3%/y.
- **Biliary pain = episodic RUQ or epigastric pain;** begins abruptly, continuous, resolves slowly and lasts 30 min–3 h; ± radiation to scapula; precip by **fatty foods**; **nausea**
- Physical exam: afebrile, ± RUQ tenderness or epigastric pain

Diagnostic studies

- Labs normal in most
- RUQ U/S: Se & Sp >95% for stones >5 mm; should be performed after ≥8 h fast for distended, bile-filled gallbladder. If ⊖, repeat in 1 mo to detect missed stones
- Endoscopic U/S (EUS): Se 94–98% in Pts w/ biliary pain but nl U/S (*J Hepatol* 2016;65:146)
- CT scan/KUB is less Se; stones often isodense w/o enough calcium & will be missed

Treatment (*Am Fam Physician* 2014;89:795; *J Hepatol* 2016;65:146)

- Cholecystectomy (CCY), usually laparoscopic, if symptomatic (earlier is better)
- CCY in *asx* Pts if: GB calcification (↑ risk of cancer), GB polyps >10 mm, stones >3 cm; Pts undergoing bariatric surgery, cardiac Tx candidates, hemolytic anemia (sickle cell)
- Options if ↑ risk for surgery: percutaneous drainage, endoscopic transpapillary drainage
- UDCA can be trialed for cholesterol stones w/ biliary pain or if poor surgical candidate, but takes ~3 mo to work; ↓ risk of gallstone formation that occurs w/ rapid wt ↓
- Pain: NSAIDs drugs of choice, efficacy ≈ opiates & avoids ↑ sphincter of Oddi pressure

Complications

- Cholecystitis: 20% of Pts with symptomatic biliary pain progress to cholecystitis w/in 2 y
- Choledocholithiasis → cholangitis or gallstone pancreatitis
- Mirizzi syndrome: hepatic duct compression by GB stone → jaundice, biliary obstruction
- Cholecystenteric fistula: stone erodes through gallbladder into bowel, ~15% w/ colon
- Gallstone ileus: SBO (usually at term ileum) due to stone in intestine that passed thru fistula
- Gallbladder carcinoma: ~1% in U.S., often found late stage, a/w poor prognosis

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CHOLECYSTITIS (*JAMA* 2022;327:965)

Pathogenesis

- Acute cholecystitis: stone impaction in cystic duct → inflammation behind obstruction → GB swelling ± secondary infection (50%) of biliary fluid
- Acalculous cholecystitis: GB stasis & ischemia (w/o cholelithiasis) → necroinflammation. Occurs in critically ill. A/w postop major surgery, TPN, sepsis, trauma, burns, opiates, immunosuppression, infxn (eg, CMV, *Candida*, *Crypto, Campylobacter*, typhoid fever).

Clinical manifestations

- History: RUQ/epigastric pain ± radiation to R shoulder/back, nausea, vomiting, fever
- Physical exam: **RUQ tenderness**, **Murphy's sign** = ↑ RUQ pain and inspiratory arrest with deep breath during palpation of R subcostal region, ± palpable gallbladder
- Laboratory evaluation: *may* see ↑ WBC, ± mild ↑ bilirubin, Aϕ, ALT/AST, amylase; if AST/ALT >500 U/L, bili >4 mg/dL or amylase >1000 U/L → choledocholithiasis

Diagnostic studies

- **RUQ U/S:** high Se & Sp for stones, but need *specific signs of cholecystitis:* GB wall thickening >4 mm, pericholecystic fluid and a sonographic Murphy's sign
- **HIDA scan:** most Se test (80–90%) for acute cholecystitis. IV inj of HIDA (selectively secreted into bile). ⊕ if HIDA enters BD but not GB. 10–20% false ⊕ (cystic duct obstructed 2/2 chronic cholecystitis, lengthy fasting, liver disease).

Treatment (*Ann Surg* 2013;258:385; *NEJM* 2015;373:357)

- NPO, IV fluids, nasogastric tube if intractable vomiting, analgesia
- **Antibiotics** (*E. coli*, *Klebsiella* and *Enterobacter* sp. are usual pathogens) ([2nd- or 3rd-generation cephalosporin or FQ] + MNZ) or piperacillin-tazobactam
- **CCY** (typically laparoscopic) w/in 24 h ↓ morbidity vs. waiting 7–45 d
- If unstable for surgery, EUS-guided transmural, ERCP-guided transcystic duct drainage, or percutaneous cholecystotomy (if w/o ascites or coagulopathy) are alternatives to CCY
- Intraoperative cholangiogram or ERCP to r/o choledocholithiasis in Pts w/ jaundice, cholangitis or stone in BD on U/S (see below)

Complications
- Gangrenous cholecystitis: necrosis w/ risk of empyema and perforation
- Emphysematous cholecystitis: infection by gas-forming organisms (air in GB wall)
- Perforation: ~10% of cases, due to delay in diagnosis; pericholecystic abscess forms
- Post CCY: bile duct leak, BD injury or retained stones, cystic duct remnant, sphincter of Oddi dysfxn

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CHOLEDOCHOLITHIASIS

Definition
- Gallstone lodged in common bile duct (CBD)

Epidemiology
- Occurs in 15% of Pts w/ gallbladder stones; can form de novo in CBD due to biliary stasis

Clinical manifestations
- RUQ/epigastric pain 2° obstrxn of bile flow → ↑ CBD pressure, jaundice, pruritus, nausea
- Rarely asymptomatic

Diagnostic studies (*J Hepatol* 2016;65:146; *Gastrointest Endosc* 2019;89:1075)
- Labs: ↑ bilirubin, Aϕ; transient spike in ALT or amylase suggests passage of stone
- RUQ U/S: BD stones seen ~50–80% of cases; usually inferred from dilated CBD (>6 mm)
- ERCP preferred modality when likelihood high (eg, visualized stone, cholangitis, bili >4, *or* dilated CBD on U/S + bili 1.8–4 mg/dL); cholangiogram (percutaneous, operative) if ERCP unavailable or unsuccessful; EUS/MRCP to exclude BD stones if suspicion intermediate (eg, no stone, dilated ducts on U/S, bili 1.8–4 mg/dL, gallstone panc., age >55, or abnl non-bili LFT)

Treatment
- ERCP & papillotomy w/ stone extraction (± lithotripsy)
- CCY w/in 6 wk unless contraindication (>15% Pts develop indication for CCY if unRx'd)

Complications
• Cholangitis, cholecystitis, pancreatitis, stricture

CHOLANGITIS

Definition & etiologies (*World J Gasrointest Pathophysiol* 2018:9:1)
• Bile duct obstruction causes stasis → infection proximal to the obstruction
• Etiologies: **BD stone** (~85%); malignant (biliary, pancreatic) or benign stricture; infection w/ fluke (*Clonorchis sinensis, Opisthorchis viverrini*); recurrent pyrogenic cholangitis

Clinical manifestations
• Charcot's triad: RUQ pain, jaundice, fever/chills; present in ~70% of Pts
• Reynolds' pentad: Charcot's triad + shock and Δ MS; present in ~15% of Pts

Diagnostic studies
• RUQ U/S: often demonstrates dilation of bile ducts
• Labs: ↑ WBC (with left shift), bilirubin, Aϕ, amylase; may see ⊕ BCx
• ERCP; percutaneous transhepatic cholangiogram if ERCP unsuccessful

Treatment
• **Antibiotics** (broad spectrum) to cover common bile pathogens (see above) ampicillin + gentamicin (or levofloxacin) ± MNZ (if severe); carbapenems; pip/tazo
• ~80% respond to conservative Rx and abx → biliary drainage on elective basis
• ~20% require **urgent biliary decompression** via ERCP (papillotomy, stone extraction, and/or stent insertion). If sphincterotomy cannot be performed (larger stones), decompression by biliary stent or nasobiliary catheter can be done; otherwise, percutaneous transhepatic biliary drainage or surgery.

ACID-BASE DISTURBANCES

GENERAL

Definitions

- **Acidemia** → pH <7.36, **alkalemia** → pH >7.44; pH = 6.10 + log([HCO_3]/[0.03xPCO_2])
- **Acidosis** → process that ↑ [H^+] or ↓ pH by ↓ HCO_3 or ↑ $PaCO_2$
- **Alkalosis** → process that ↓ [H^+] or ↑ pH by ↑ HCO_3 or ↓ $PaCO_2$
- Primary disorders: metabolic acidosis or alkalosis, respiratory acidosis or alkalosis
- Compensation
  - Respiratory: hyper/hypoventilation alters P_aCO_2 to counteract 1° metabolic process
  - Renal: excretion/retention of H^+/HCO_3^- to counteract 1° respiratory process
  - Respiratory compensation occurs in mins-hrs; renal compensation takes days
  - *Compensation usually never fully corrects pH*; if pH normal, consider mixed disorder

Consequences of Severe Acid-Base Disturbances (*NEJM* 1998;338:26 & 107)		
Organ System	**Acidemia (pH <7.20)**	**Alkalemia (pH >7.60)**
Cardiovascular	↓ contractility, arteriolar vasodilation ↓ MAP & CO; ↓ response to catecholamines ↑ risk of arrhythmias	Arteriolar vasoconstriction ↓ coronary blood flow ↑ risk of arrhythmias
Respiratory	Hyperventilation, ↓ resp. muscle strength	Hypoventilation
Metabolic	↑ K (resp. > metab.), insulin resistance	↓ K, Ca, Mg, PO_4
Neurologic	Δ MS	Δ MS, seizures, tetany

Workup (*NEJM* 2014;371:1434)

- **Traditional or physiologic approach** (Brønsted-Lowry definition of acids & bases)

Determine **primary disorder:** ✓ pH, P_aCO_2, HCO_3
Determine if **degree of compensation** is appropriate

Primary Disorders				
Primary Disorder	**Problem**	**pH**	**HCO_3**	**P_aCO_2**
Metabolic acidosis	Gain of H^+ or loss of HCO_3	↓	⇓	↓
Metabolic alkalosis	Gain of HCO_3 or loss of H^+	↑	⇑	↑
Respiratory acidosis	Hypoventilation	↓	↑	⇑
Respiratory alkalosis	Hyperventilation	↑	↓	⇓

Compensation for Acid-Base Disorders (*NEJM* 2014;371:1434)	
Primary Disorder	**Expected Compensation**
Metabolic acidosis	↓ $P_aCO_2 = 1.2 \times \Delta HCO_3$ or $P_aCO_2 = (1.5 \times HCO_3) + 8 \pm 2$ (Winters' formula) (also, $P_aCO_2 \approx$ last 2 digits of pH)
Metabolic alkalosis	↑ $P_aCO_2 = 0.7 \times \Delta HCO_3$ or $P_aCO_2 = 0.7\ (HCO_3–24) + 40 \pm 2$ or $HCO_3 + 15$
Acute respiratory acidosis	↑ $HCO_3 = 0.1 \times \Delta P_aCO_2$ (also, ↓ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory acidosis	↑ $HCO_3 = 0.35 \times \Delta P_aCO_2$ (also, ↓ pH = $0.003 \times \Delta P_aCO_2$)
Acute respiratory alkalosis	↓ $HCO_3 = 0.2 \times \Delta P_aCO_2$ (also, ↑ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory alkalosis	↓ $HCO_3 = 0.4 \times \Delta P_aCO_2$

- **Alternative approaches**
  Base excess/deficit (*NEJM* 2018;378:1419)
  Strong ion difference or "Stewart Method" (*NEJM* 2014;371:1821)

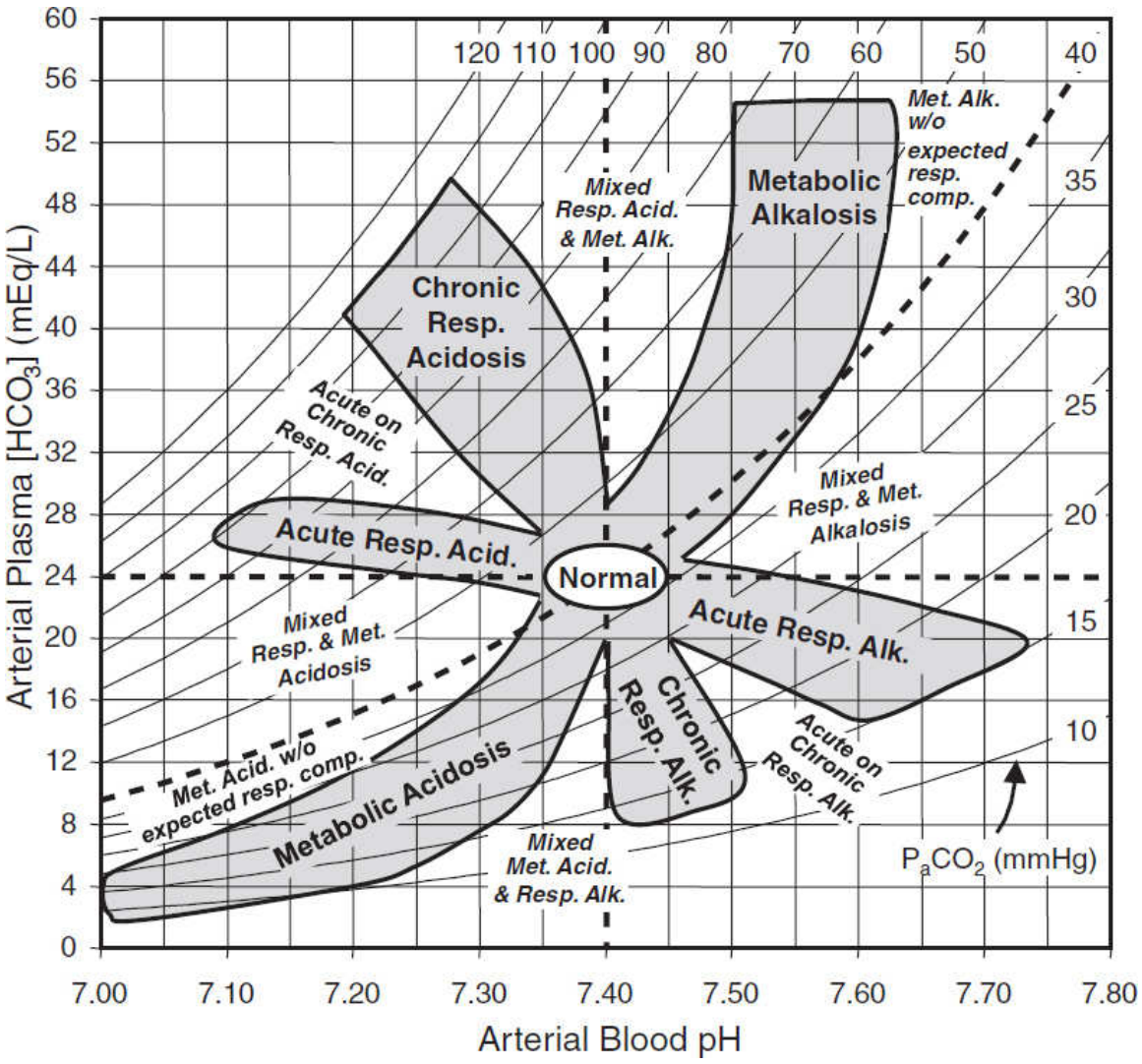
Mixed disorders (more than one primary disorder at the same time)

- If compensation less or greater than predicted, may be two disorders:
  P_aCO_2 too low → concomitant 1° resp. alk.; P_aCO_2 too high → concomitant 1° resp. acid.
  HCO_3 too low → concomitant 1° met. acid.; HCO_3 too high → concomitant 1° met. alk.
- Normal pH, *but...*
  ↑ P_aCO_2 + ↑ HCO_3 → resp. acid. + met. alk.
  ↓ P_aCO_2 + ↓ HCO_3 → resp. alk. + met. acid.
  Normal P_aCO_2 & HCO_3, *but* ↑ AG → AG met. acid. + met. alk.

Normal P_aCO_2, HCO_3, & AG → no disturbance *or* non-AG met. acid. + met. alk.

- *Cannot* have resp. acid. (hypoventilation) and resp. alk. (hyperventilation) simultaneously

Figure 4-1 Acid-base nomogram



(Adapted from Brenner BM, ed., *Brenner & Rector's The Kidney*, 8th ed., 2007; Ferri F, ed. *Practical Guide to the Care of the Medical Patient*, 7th ed., 2007)

- **ABG vs. VBG:** concordant for pH (~0.04), HCO_3 (~2 mEq) but **not** PCO_2 (~8±17 mmHg)
  VBG can be used to *screen* for hypercarbia w/ PCO_2 cutoff ≥45 mmHg (100% Se),

but may not accurately assess *degree* of hypercarbia (*Am J Emerg Med* 2012;30:896)

METABOLIC ACIDOSIS

Initial workup (*NEJM* 2014;371:1434)

- ✓ **anion gap** (AG) = $Na^+ – (Cl^– + HCO_3^–)$ = unmeasured anions – unmeasured cations
  If ↑ glc, use measured *not* corrected Na
  Expected AG is [albumin] × 2.5 (ie, 10 if albumin is 4 g/dL, 7.5 if albumin is 3 g/dL)
  ↑ AG → ↑ unmeasured anions such as organic acids, phosphates, sulfates
  ↓ AG → ↓ alb or ↑ unmeasured cations (Ca, Mg, K, Li, Ig), bromide/iodine toxicity
- If ↑ AG, ✓ **delta-delta** (Δ/Δ = $\Delta AG/\Delta HCO_3$) to assess if there is an additional metabolic
  acid-base disturbance; ΔAG = (calculated AG – expected AG), ΔHCO_3 = $(24 – HCO_3)$
  Δ/Δ = 1–2 → pure AG metabolic acidosis
  Δ/Δ <1 → AG metabolic acidosis *and* simultaneous non-AG acidosis
  Δ/Δ >2 → AG metabolic acidosis *and* simultaneous metabolic alkalosis
  For pure lactic acidosis Δ/Δ 1.6 b/c of slow lactate clearance

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	**Diabetes mellitus,** alcoholism, starvation (*NEJM* 2015;372:546)
Lactic acidosis (*NEJM* 2014; 371:2309)	**Type A:** hypoxic (eg, shock, mesenteric ischemia, CO poisoning, cyanide) **Type B:** nonhypoxic. ↓ clearance (eg, hepatic dysfxn) or ↑ generation [eg, malig, EtOH, thiamine def., meds (metformin, NRTIs, salicylates, propylene glycol, propofol, isoniazid, linezolid)] **D-lactic acidosis:** short bowel syndrome → precip by glc ingest → metab by colonic bacteria to d-lactate; not detected by standard lactate assay
Renal failure	Accumulation of organic anions (eg, phosphates, sulfates, etc.)

Etiologies of AG Metabolic Acidosis	
Ingestions (*NEJM* 2020; 382:2544)	**Glycols:** *Ethylene* (antifreeze) → metab to glycolic and oxalic acids *Propylene* (pharmaceutical solvent, eg, IV diazepam, lorazepam, and phenobarbital; antifreeze) → lactic acidosis *Diethylene* (brake fluid) → diglycolic acid **5-oxoproline** (pyraglutamic acid): acetaminophen → ↑ organic acid 5-oxoproline in susceptible Pts (malnourished, female, renal failure) **Methanol** (windshield fluid, antifreeze, solvents, fuel): metab to formic acid **Aspirin**: early resp alkalosis (CNS stim) + late metab acidosis (impairs oxidative phosphorylation → inorganic acids (eg, ketones, lactate)

"GOLD MARK" = Glycols, Oxoproline, Lactic, D-Lactic, Methanol, ASA, Renal, Ketoacidosis

Workup for AG metabolic acidosis (*AJKD* 2021;78:A16)

- ✓ for **ketonuria** (dipstick acetoacetate) or plasma β-hydroxybutyrate (βOHB)
  nb, urine acetoacetate often not present in early ketoacidosis due to shunting to βOHB; ∴ acetoacetate may later turn ⊕ but does not signify worsening disease
- If ⊖ ketones, ✓ **renal function, lactate, toxin screen, and osmolal gap**
- If obtunded or ↑↑ AG, check **osmolal gap** (OG) = measured osmoles – calculated osmoles
  Calculated osmoles = (2 × Na) + (glucose/18) + (BUN/2.8) (+ [EtOH/4.6] if ↑ EtOH level and want to test if other ingestions)
  OG >10 → suggests ingestion (see below) but lacks specificity (can be elevated in lactic acidosis, DKA, and alcoholic ketoacidosis due to acetone)
  High-dose lorazepam (>10 mg/h) a/w propylene glycol intoxication
  OG & AG vary based on timing, initially OG ↑, then ↓ w/ metabolism as AG ↑

Ingestions (*NEJM* 2018;378:270) Call poison control for guidance (800-222-1222)			
AG	**OG**	**Ingestion**	**Other Manifestations**
↑	nl	Acetaminophen	Hepatitis
		Salicylates	Fever, tachycardia, tinnitus; met. acid. + resp. alkalosis
↑	↑	Methanol	ΔMS, blurred vision, pupillary dilation, papilledema
↑	↑	Ethylene glycol	ΔMS, cardiopulm. failure, hypoCa. **Ca oxalate crystals** → AKI. Urine fluoresces under UV light.
nl/↑	↑	Propylene glycol	AKI, liver injury

Ingestions (*NEJM* 2018;378:270) Call poison control for guidance (800-222-1222)			
↑	nl/↑	Diethylene glycol	AKI, N/V, pancreatitis, neuropathy, lactic acidosis
nl/↑	↑	Isopropyl alcohol	ΔMS, fruity breath (acetone), pancreatitis, lactic acidosis
		Ethanol	Alcoholic fetor, ΔMS, hepatitis; keto + lactic acidosis ± met. alk. (vomiting)

Etiologies of Non-AG Metabolic Acidosis	
GI losses of HCO_3	Diarrhea, intestinal or pancreatic fistulas or drainage
RTAs	*See section on renal tubular acidoses below*
Early renal failure	Impaired generation of ammonia
Ingestions	Acetazolamide, sevelamer, cholestyramine, toluene
Dilutional	Due to rapid infusion of bicarbonate-free IV fluids
Posthypocapnia	Respiratory alkalosis → renal wasting of HCO_3; rapid correction of resp. alk. → transient acidosis until HCO_3 regenerated
Ureteral diversion	Colonic Cl^-/HCO_3^- exchange, ammonium reabsorption

Workup for non-AG metabolic acidosis

- Evaluate history for causes (see above)
- ✓ **urine anion gap** (UAG) = $(U_{Na} + U_K) - U_{Cl}$
  UAG = unmeasured anions – unmeasured cations; NH_4^+ is primary unmeasured cation (represented by U_{Cl}). UAG is indirect assay for renal H^+ excretion.
- ⊖ UAG → ↑ renal NH_4^+ excretion → appropriate renal response to acidemia
  Ddx: GI causes (diarrhea, fistulas, ureteral diversion), IV NS, ingestions
- ⊕ UAG → failure of kidneys to generate NH_4^+
  Ddx: distal (type 1, usually ↓ K) or hypoaldo (type IV, usually ↑ K) RTA, early renal failure
- UAG unreliable in AKI/CKD, polyuria, Na depletion (U_{Na} <20), U_{pH} >6.5 & HAGMA (causes ⊕ UAG b/c excretion of organic anions) and less useful in prox RTA as variable. Then use U_{Osm} gap = measured U_{Osm} – [2×($Na^+ + K^+$) + BUN + glc (mmol/L)]. U_{Osm} gap <40 mmol/L indicates impaired NH_4^+ excretion

Renal tubular acidoses (RTAs) (*Adv Ther* 2021;38:949)

- **Proximal** (Type II): ↓ proximal reabsorption of HCO_3

1° (Fanconi's syndrome) = ↓ proximal reabsorption of HCO_3, PO_4, glc, amino acids

Acquired: paraprotein (MM, amyloidosis), metals (Pb, Cd, Hg, Cu), ↓ vit D, PNH, renal Tx

Meds: acetazolamide, aminoglycosides, ifosfamide, cisplatin, topiramate, tenofovir

- **Distal** (Type I): defective distal H^+ secretion
  1°, autoimmune (Sjögren's, RA, SLE), hypercalciuria, meds (ampho, Li, ifosfamide); normally a/w ↓ K; if with ↑ K → sickle cell, obstruction, renal transplant
- **Hypoaldo** (Type IV): hypoaldo → ↑ K → ↓ NH_3 synthesis → ↓ urine acid-carrying capacity
  ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, calcineurin inh, HIV
  ↓ aldo production: 1° AI, ACEI/ARBs, heparin, severe illness, inherited (↓ 21-hydroxylase)
  ↓ response to aldosterone
  Meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors
  Tubulointerstitial disease: sickle cell, SLE, amyloid, DM
- Combined (Type III): rarely discussed or clinically relevant, also called juvenile RTA, has distal & proximal features, can be due to carbonic anhydrase II deficiency

Renal Tubular Acidosis

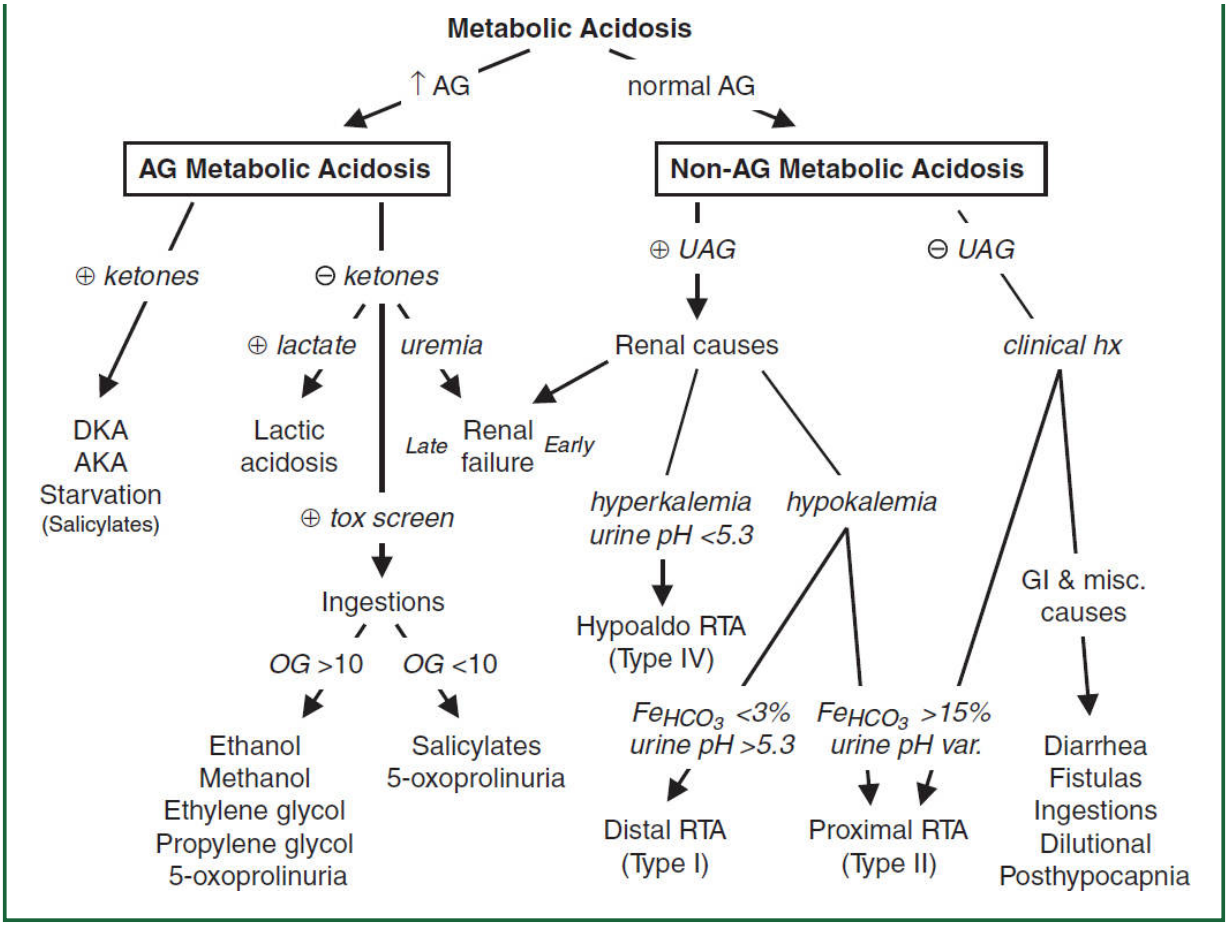
Location	Type	Acidosis	UAG	HCO_3^-	UpH	FE_{HCO3}[b]	K	Complications
Proximal	II	Moderate	±	12–20	<5.3[a]	>15%	↓	Osteomalacia
Distal	I	Severe	⊕	<10	>5.3	<3%	↓[c]	Kidney stones
Hypoaldo	IV	Mild	⊕	>17	<5.3	<3%	↑	Hyperkalemia

[a]Urine pH will rise above 5.3 in the setting of HCO_3 load

[b]Fe_{HCO3} should be checked after an HCO_3 load

[c]See above for causes of distal RTA (Type I) associated with hyperkalemia

Figure 4-2 Approach to metabolic acidosis



Treatment of severe metabolic acidoses (pH <7.2) (*Nat Rev Nephrol* 2012;8:589)

- DKA: insulin, IVF, K repletion (*NEJM* 2015;372:546); AKA: dextrose, IVF, replete K, Mg, PO_4
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors, avoid "Type B" meds
- Renal failure: hemodialysis
- Methanol & ethylene glycol: fomepizole (20 mg/dL), vit. B_1 & B_6 (ethylene glycol), folate (methanol), dialysis (if AKI, VS unstable, vision Δ or >50 mg/dL) (*NEJM* 2018;378:270)
- Alkali therapy: if pH <7.1 or <7.2 and co-existing AKI (may ↓ mortality; *Lancet* 2018;392:31)
- $NaHCO_3$: amps by IV push or infusion of three 50-mmol amps in 1 L D_5W if less urgent
  Can estimate mmol of HCO_3 needed as $[\text{desired-current } HCO_3]_{serum} \times$ wt (kg) × 0.4

Side effects: ↑ volume, ↑ Na, ↓ ICa, ↑ P_aCO_2 (& ∴ intracellular acidosis; ∴ *must ensure adequate ventilation* to blow off CO_2)

METABOLIC ALKALOSIS

Pathophysiology (*CJASN* 2020;15:1848)

- Saline-responsive etiologies require *initiating event* and *maintenance phase*
- *Initiating event:* net HCO_3^- reabsorption (due to loss of volume, Cl^-, and/or K^+) or loss of H^+
  - **Loss of H^+** (± Cl^-) from GI tract, kidneys, or transcellular shift in hypokalemia
  - **Contraction alkalosis:** loss of HCO_3^--poor fluid → extracellular fluid "contracts" around fixed amount of HCO_3^- → ↑ HCO_3^- concentration
  - **Exogenous alkali:** iatrogenic HCO_3^- (with renal impairment), milk-alkali syndrome
  - **Posthypercapnia:** resp. acidosis → compensation with H^+ excretion and HCO_3^- retention; rapid correction of hypercapnia (eg, intubation) → transient excess HCO_3^-
- *Maintenance phase*
  - **Volume depletion** → ↑ ATII → ↑ PCT reabsorption of HCO_3^- & ↑ aldosterone (see below)
  - **Cl^- depletion** → ↓ Cl^- uptake in macula densa → ↑ RAS & ↑ CCD Cl^-/HCO_3^- exchanger
  - **Hypokalemia** → transcellular K^+/H^+ exchange; intracellular acidosis → HCO_3^- reabsorption and ammoniagenesis & ↑ distal H^+-K^+-ATPase activity → HCO_3^- retention
  - **Hyperaldosteronism** (1° or 2°) → ↑ CCD α-intercalated H^+ secretion w/ HCO_3^- retention & Na^+ reabsorption in principal cell → H^+ secretion (for electrical neutrality)

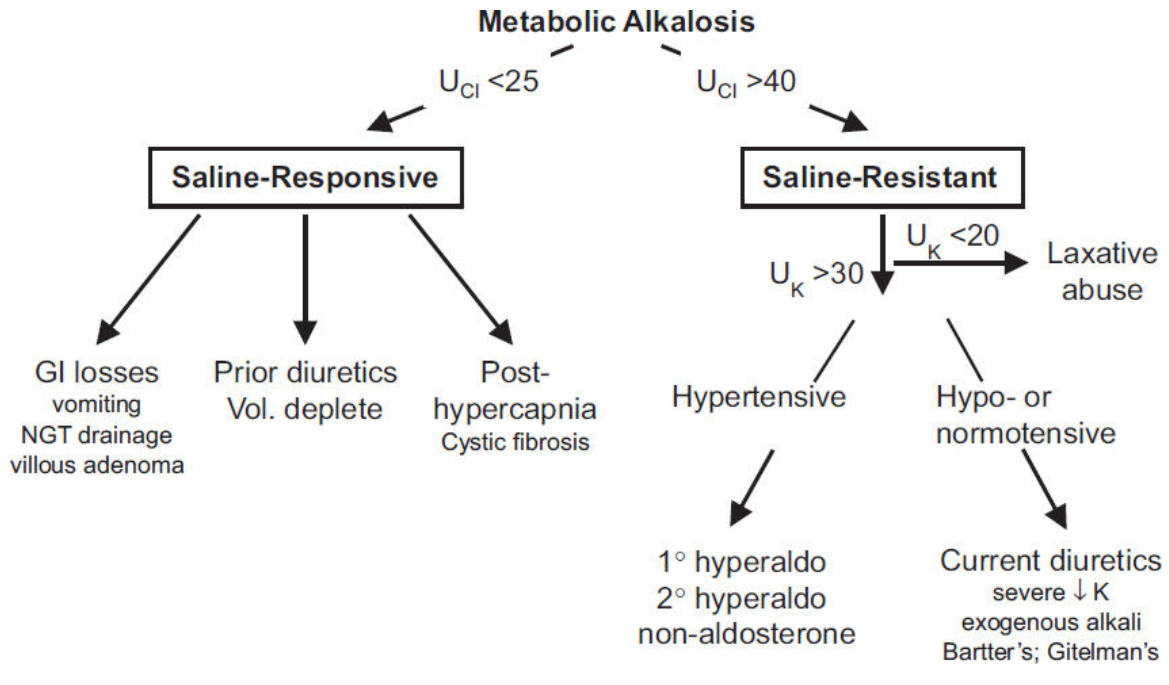
Etiologies of Metabolic Alkalosis	
Saline responsive UCl <25	**GI loss of H^+**: emesis, NGT suction, villous adenoma, chloridorrhea **Renal loss**: loop/thiazide, ↓ Cl intake, milk-alkali, Pendred syndrome Posthypercapnia, sweat losses in cystic fibrosis

Etiologies of Metabolic Alkalosis	
Saline resistant UCl >40	*Hypertensive* **(mineralocorticoid excess)** 1° hyperaldosteronism (eg, Conn's) 2° hyperaldosteronism (eg, renovascular dis., renin-secreting tumor) Non-aldo (Cushing's, Liddle's, exogenous mineralocorticoids, licorice) *Normotensive* Severe hypokalemia (K<2); exogenous alkali load (w/ AKI or ↓ vol) Bartter's syndrome (loop-like); Gitelman's syndrome (thiazide-like)

Workup

- Check **volume status** and **U_{Cl}**
  - U_{Cl} <25 mEq/L → saline responsive
  - U_{Cl} >40 mEq/L → saline resistant (unless currently receiving diuretics)
  - (U_{Na} unreliable determinant of volume status in alkalemia → ↑ HCO_3^- excretion → ↑ Na excretion; negatively charged HCO_3^- w/ Na^+ maintaining electrical neutrality)
  - If U_{Cl} >40 and volume replete, ✓ U_K; U_K <20 laxative abuse; U_K >30, ✓ **blood pressure**

Figure 4-3 Approach to metabolic alkalosis



Treatment of severe metabolic alkalosis (pH >7.6) (*JASN* 2012;23:204)

- If saline responsive: resuscitate with Cl-rich solution (NS), replete K, d/c diuretics cardiopulmonary disease precludes hydration, can use KCl,

acetazolamide, HCl
- Hyperaldosteronism: treat underlying condition, K-sparing diuretic, resect adenoma if 1°

RESPIRATORY ACIDOSIS (*NEJM* 1989;321:1223; *Crit Care* 2010;14:220)

Etiologies (also see "Hypercapnia"; $P_aCO_2 = VCO_2/V_E(1\text{-}V_D/V_T)$; $V_E = RR \times V_T$)

- ↑ **CO_2 production** (↑ VCO_2): fever, thyrotoxicosis, sepsis, steroids, overfeeding (carbs)
- **CNS depression** (↓ RR and/or V_T): sedatives (opiates, benzos, etc.), CNS trauma, central sleep apnea, obesity, hypoventilation, hypothyroidism
- **Neuromuscular disorders** (↓ V_T)**:** Guillain-Barré, poliomyelitis, ALS, MS, paralytics, myasthenia gravis, muscular dystrophy, severe ↓ P & K, high spinal cord injury
- **Chest wall** (↓ V_T): PTX, hemothorax, flail chest, kyphoscoliosis, ankylosing spondylitis
- **Upper airway** (↓ V_T)**:** foreign body, laryngospasm, OSA, esophageal intubation
- **Lower airway (gas exchange)** (↑ V_D and/or ↓ V_T): asthma, COPD, pulm edema, IPF
  Often hypoxia → ↑ RR → resp. alk., but muscle fatigue → resp. acid
- Post infusion of bicarbonate in acidemic Pt w/ limited ability to ↑ minute ventilation

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RESPIRATORY ALKALOSIS

Etiologies (*NEJM* 2002;347:43; *Crit Care* 2010;14:220)

- **Hypoxia → hyperventilation:** pneumonia, CHF, PE, restrictive lung disease, anemia
- **Primary hyperventilation**
  CNS stimulation, pain, anxiety, trauma, stroke, CNS infection, pontine tumors
  drugs: salicylates toxicity (early), β-agonists, progesterone, methylxanthines, nicotine
  pregnancy, sepsis, hepatic failure, hyperthyroidism, fever

- **Pseudorespiratory alkalosis:** ↓ perfusion w/ preserved ventilation (eg, CPR, severe HoTN) → ↓ delivery of CO_2 to lungs for excretion; low P_aCO_2 but ↑ tissue CO_2

SODIUM AND WATER HOMEOSTASIS

OVERVIEW

General (*NEJM* 2015;372:55 & 373:1350)

- Disorders of serum sodium are generally due to Δs in *total body water*, not sodium
- Hyper- or hypo-osmolality → rapid water shifts → Δs in brain cell volume → Δ MS, seizures

Key hormones

- **Antidiuretic hormone (ADH):** primary hormone that regulates *sodium concentration*
  Stimuli: hyperosmolality (290–295 mOsm), ↓↓ effective arterial volume, angiotensin II
  Action: insertion of aquaporin-2 channels in principal cells → passive water reabsorption
  urine osmolality is an indirect functional assay of the ADH-renal axis
  U_{osm} range: 50 mOsm/L (no ADH) to 1200 mOsm/L (maximal ADH)
- **Aldosterone:** primary hormone that regulates *total body sodium* (and ∴ volume)
  Stimuli for secretion: hypovolemia (via renin and angiotensin II), hyperkalemia
  Action: iso-osmotic principal cell reabsorption of Na via epithelial Na channel (ENaC) in exchange for K^+ or H^+

HYPONATREMIA

Pathophysiology (*JASN* 2008;19:1076; *NEJM* 2015;372:1349)

- **Excess H_2O relative to Na**, usually due to ↑ **ADH**
- ↑ ADH may be *appropriate* (eg, hypovolemia or hypervolemia with ↓ EAV)
- ↑ ADH may be *inappropriate* (SIADH)
- Rarely, ↓ ADH (appropriately suppressed), but kidneys unable to maintain nl $[Na]_{serum}$

at steady state, solute intake = solute excretion; urine output = solute excretion/U_{osm}

nl dietary solute load ~750 mOsm/d, min U_{osm} = 50 mOsm/L, ∴ UOP can be up to ~15 L

↑ *H_2O intake (1° polydipsia):* ingestion of massive quantities (usually >15 L/d) of free H_2O overwhelms diluting ability of kidney → H_2O retention

↓ solute intake ("tea & toast" & beer potomania*):* ↓↓ daily solute load → insufficient solute to excrete H_2O intake (eg, if only 250 mOsm/d, minimum U_{osm} = 50 mOsm/L → excrete in ~5 L; if H_2O ingestion exceeds this amount → H_2O retention)

Workup (*JASN* 2012;23:1140 & 2017;28:1340; *Crit Care* 2013;17:206; *NEJM* 2015;372:55)

- **History:** (1) acute vs. chronic (>48 h); (2) sx severity; (3) risk for neuro complications (alcoholism, malnourished, cirrhosis, older women on thiazides, hypoxia, hypoK)
- Measure **plasma osmolality**

  Hypotonic (P_{osm} <280) most common scenario; true excess of free H_2O relative to Na

  Isotonic (P_{osm} 280–295): rare lab artifact from hyperlipidemia or hyperproteinemia

  Hypertonic (P_{osm} >295): excess of another effective osmole (eg, glucose, mannitol) that draws H_2O intravascularly; for each 100 mg/dL ↑ glc >100 mg/dL → ↓ [Na] by ~2 mEq/L
- For hypotonic hyponatremia, ✓ **volume status** (JVP, skin turgor, dry axilla, mucous membranes, edema, ascites), effusions, vital signs, orthostatics, BUN/Cr, $FE_{UricAcid}$, U_{Na}
- Measure **U_{osm}**, although useful for dx in limited circumstances, b/c almost always >300

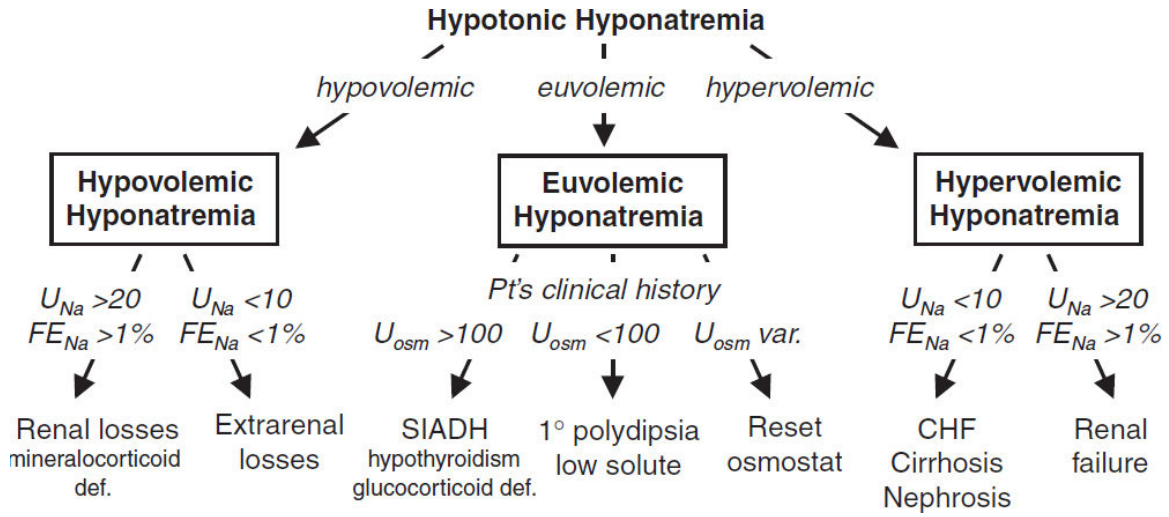
  U_{osm} <100 in ↑ H_2O intake (1° polydipsia) or ↓ solute intake (beer potomania, "tea & toast")

  U_{osm} >300 does not mean SIADH; must determine if ↑ ADH appropriate or inappropriate

  however, U_{osm} can be important when deciding on *treatment* (see below)
- If euvolemic and ↑ U_{osm}, evaluate for glucocorticoid insufficiency and hypothyroidism

• If available, consider $FE_{UricAcid}$ as >12% suggests SIADH (*J Clinc Endo* 2008;93:2991)

Figure 4-4 Approach to hyponatremia



Hypovolemic hypotonic hyponatremia (ie, ↓↓ total body Na, ↓ TBW)

• **Renal losses** (U_{Na} >20 mEq/L, FE_{Na} >1%): diuretics (esp. thiazides, because loop diuretics
↓ tonicity of medullary interstitium, Δ for H_2O absorption, & ∴ urine concentrating ability), salt-wasting nephropathy, cerebral salt wasting, mineralocorticoid deficiency

• **Extrarenal losses** (U_{Na} <10 mEq/L, U_{Cl} <10 mEq/L if alkalemia, FE_{Na} <1%): hemorrhage, GI loss (diarrhea or vomiting), third-spacing (pancreatitis), ↓ PO intake, insensible losses

Euvolemic hypotonic hyponatremia (ie, ↑ TBW relative to total body Na)

• **SIADH** (euvolemia or mild hypervolemia, typically **inapprop U_{osm} >100,** U_{Na} >20 mEq/L)
Malignancy: lung (SCLC), brain, GI, GU, lymphoma, leukemia, thymoma, mesothelioma
Pulmonary: pneumonia, TB, aspergillosis, asthma, COPD, PTX, mechanical ventilation
Intracranial: trauma, stroke, SAH, seizure, infxn, hydrocephalus, Guillain-Barré
Drugs: antipsychotics, antidepress. (SSRI, TCA, MAOi), haloperidol, chemo (vincristine, cisplatin), AVP, MDMA, NSAIDs, opiates, amiodarone (*Am J Kidney Dis* 2008;52:144)

Miscellaneous: pain, nausea, postoperative state

- **Endocrinopathies:** ↑ ADH activity seen in *glucocorticoid deficiency* (co-secretion of ADH & CRH) and *severe hypothyroidism/myxedema coma* (↓ CO/SVR → ADH release & ↓ GFR)
- **Psychogenic polydipsia** (U_{osm} <100, ↓ $FE_{Uric\ Acid}$): usually intake >15 L/d
- **Low solute** (↓ U_{Na}, ↓ U_{osm}) "tea & toast"; beer potomania
- Reset osmostat: chronic malnutrition (↓ intracellular osmoles) or pregnancy (hormonal effects) → ADH physiology reset to regulate a lower $[Na]_{serum}$

Hypervolemic hypotonic hyponatremia (ie, ↑ total body Na, ↑ ↑ TBW)

- ↓ EAV → ↑ RAAS → ↑ aldosterone & ↑ adrenergic tone → ↑↑ ADH (*Am J Med* 2013;126:S1)
- **CHF** (↓ CO & renal venous congestion → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Cirrhosis** (splanchnic arterial vasodilation + ascites → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Nephrotic syndrome** (hypoalbuminemia → edema → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Advanced renal failure** (diminished ability to excrete free H_2O; U_{Na} >20 mEq/L)

Treatment (*NEJM* 2015;372:55; *JASN* 2017;28:1340; *CJASN* 2018;13:641 & 984)

- **Approach:** depends on *volume status*, *acuity* of hyponatremia, and if *symptomatic*
  - Acute sx: *initial* rapid correction of $[Na]_{serum}$ (2 mEq/L/h for the first 2–3 h) until sx resolve
  - Asx or chronic symptomatic: correct $[Na]_{serum}$ at rate of ≤0.5 mEq/L/h
  - Rate ↑ Na *should not exceed 6* (chronic) to *8* (acute) mEq/L/d to avoid central pontine myelinolysis/osmotic demyelination (CPM/ODS: paraplegia, dysarthria, dysphagia)
  - If severe (<120) or neuro sx: consider 3% NaCl. dDAVP 1-2 *μ*g q8h in consultation with nephrology (to prevent rapid overcorrection) (*AJKD* 2013;61:571; *CJASN* 2018; 13:641)
- **Frequent lab draws** and **IVF rate adjustments** are cornerstones of treatment
- **Rapid correction:** can lead to CPM/ODS (esp if chronic or Na <120 mEq/L). Should be emergently reversed w/ dDAVP ± D_5W; partial

neuro recovery possible (*CJASN* 2014;9:229).

- **Effect of IV fluids**: complex as depends not only on $[Na]_{infusate}$ but also UOP and U_{osm}

Scenario	Formula to estimate new $[Na]_{serum}$ after 1 L infusion
If minimal UOP and none of infused Na excreted	$\frac{(\text{current } [Na]_{serum} \times TBW) + [Na]_{infusate}}{TBW + 1}$
If euvolemic (eg, in SIADH) & all infused Na excreted	$\frac{(\text{current } [Na]_{serum} \times TBW) + [Na]_{infusate} - [Na]_{infusate}}{TBW + 1 - \frac{Infusate_{osm}}{U_{osm}}}$

In SIADH "fixed" high U_{osm}. ∴ in SIADH w/ U_{osm} 616, 1 L NS (154 mEq Na or 308 mOsm solute in 1 L H_2O) will be excreted in 0.5 L H_2O → net *gain* 0.5 L H_2O. ∴ NS *worsens* $[Na]_{serum}$ if U_{osm} >$infusate_{osm}$. In contrast, 1 L 3% NaCl (1026 mOsm) would be excreted in ~1.7 L urine → net *loss* 0.7 L H_2O. ∴ 3% saline ↑ $[Na]_{serum}$.

Effect of 1 L infusion in 70-kg male w/ $[Na]_{serum}$ 110 mEq/L & U_{osm} 616 mOsm/kg			
IVF Type	**$[Na]_{content}$**	**No UOP**	**Infused Na excreted**
0.9% NaCl	154 mEq/L	+1.0 mEq/L	-1.3 mEq/L
3% NaCl	513 mEq/L	+9.4 mEq/L	+1.8 mEq/L

- **Hypovolemic hyponatremia:** volume repletion with isotonic 0.9% saline at a **slow rate**. Once volume replete → stimulus for ADH removed (w/ very short ADH $t_{½}$) → kidneys excrete free H_2O → serum Na will correct rapidly (D_5W ± dDAVP if overcorrection)
- **SIADH** (*NEJM* 2007;356:2064; *AJKD* 2020;76:203): **fluid restrict** + treat underlying cause

  hypertonic saline (± loop diuretic; *AJKD* 2020;76:203) if sx or Na fails to ↑ w/ fluid restriction Intermittent bolus of 3% saline (~2 mL/kg q6h) vs. continuous infusion (~0.5 mL/kg/h) similar (*JAMA IM* 2021;181:81) when moderate symptoms. Must recheck serum Na frequently during hypertonic use (at least q2h).

NaCl tabs if chronic and no CHF. Consider urea 0.25–0.5 g/kg/d (*CJASN* 2018;13:1627)

aquaresis: vaptans (vasopressin receptor antag) for refractory SIADH (*NEJM* 2015;372:23)

- **Hypervolemic hyponatremia:** free water restrict (1st line), diurese w/ loop diuretics (avoid thiazides) & ↑ EAV (vasodilators to ↑ CO in CHF, colloid infusion in cirrhosis)

  vaptans sometimes used; however, no mortality benefit, hypoNa recurs after stopping drug, high risk of overcorrection, contraindicated in cirrhosis (*NEJM* 2015;372:2207)

HYPERNATREMIA

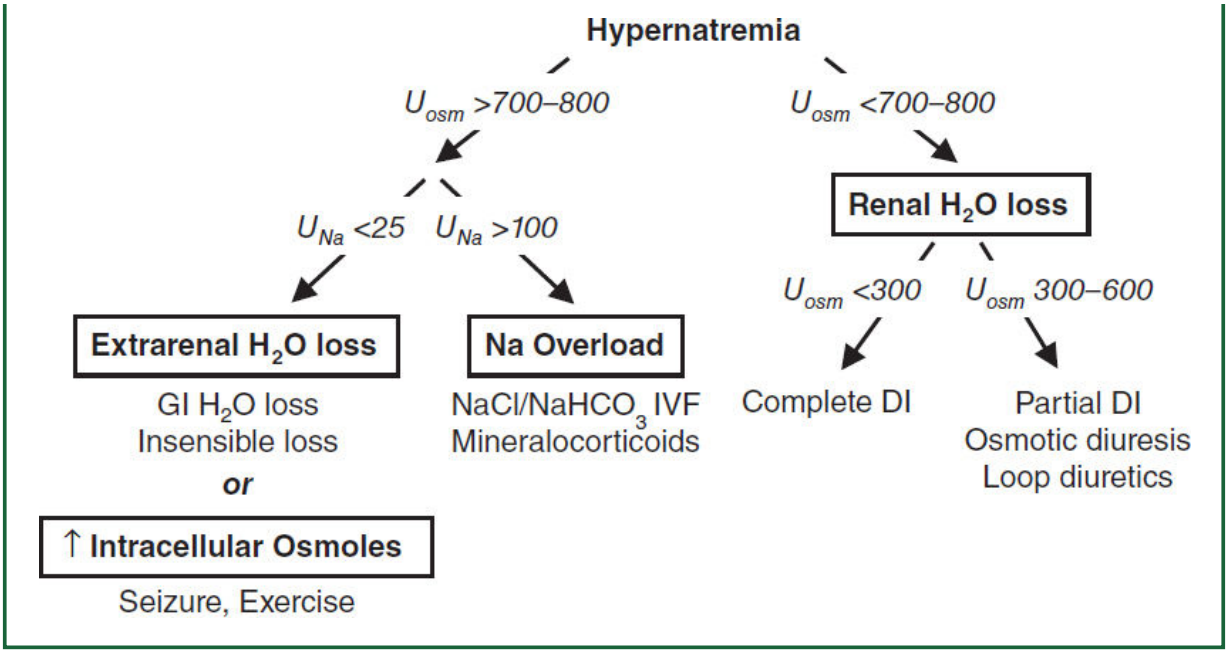
Pathophysiology (*Crit Care* 2013;17:206; *NEJM* 2015;372:55)

- Deficit of water relative to sodium; by definition, all hypernatremic Pts are hypertonic
- Usually **loss of hypotonic fluid** (ie, "dehydration"); occasionally infusion of hypertonic fluid, post-ATN diuresis w/ loss of low or electrolyte-free water (*Am J Neph* 2012;36:97)
- ***And* impaired access to free water** (eg, intubation, Δ MS, elderly): hypernatremia is a powerful thirst stimulus, ∴ usually only develops in Pts w/o access to H_2O or ill

Workup

- ✓ U_{osm}, U_{Na}, volume status (vital signs, orthostatics, JVP, skin turgor, BUN, Cr)

Figure 4-5 Approach to hypernatremia



Extrarenal H_2O loss (U_{osm} >700–800)

- **GI H_2O loss:** vomiting, NGT drainage, osmotic diarrhea, fistula, lactulose, malabsorption
- **Insensible loss:** fever, exercise, ventilation, burns

Renal H_2O loss (U_{osm} <700–800)

- **Diuresis:** osmotic (glucose, mannitol, urea), loop diuretics
- **Diabetes insipidus** (*Nature Reviews Nephrology* 2015;11:576)

  ADH deficiency (central) or resistance (nephrogenic)

  Central: hypothalamic or posterior pituitary disease (congenital, trauma/surgery, infiltrative/IgG4); also idiopathic, hypoxic/ischemic encephalopathy (shock, Sheehan's syndrome), anorexia, sarcoidosis, histiocytosis, drugs: EtOH, phenytoin, snake venom, tumors: craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary

  Nephrogenic (*Annals* 2006;144:186)

  congenital (ADH receptor V2 mutation, aquaporin-2 mutation; *Pediatric Clinics* 2019;66:227)

  drugs: **lithium**, amphotericin, demeclocycline, foscarnet, cidofovir, ifosfamide

  metabolic: **hypercalcemia**, **severe hypokalemia**, protein malnutrition, congenital

  tubulointerstitial: **postobstruction**, **recovery phase of ATN**, PKD, sickle cell, Sjögren's, amyloid, pregnancy (placental

vasopressinase)

DI usually presents as severe polyuria and mild hypernatremia

Other (U_{osm} >700–800)

- **Na overload:** hypertonic saline (eg, resuscitation w/ $NaHCO_3$), mineralocorticoid excess
- **Seizures**, ↑ **exercise:** ↑ intracellular osmoles → H_2O shifts → transient ↑ $[Na]_{serum}$

Treatment (*NEJM* 2015;372:55)

- **Restore access to H_2O** or supply daily requirement of H_2O (≥1 L/d)
- **Replace free H_2O deficit** (also replace concurrent volume deficit if appropriate):

$$\textbf{Free } H_2O \textbf{ deficit (L)} = \frac{[Na]_{serum} - 140}{140} \times TBW$$

TBW = wt (kg) × 0.6 (♂) or 0.5 (♀)
if elderly use 0.5 (♂) or 0.45 (♀)

shortcut: for typical 70-kg man, free H_2O deficit (L) ~$([Na]_{serum} - 140)/3$

$$\Delta\,[Na]_{serum} \text{ Per L infusate} = \frac{[Na]_{serum} - [Na]_{infusate}}{TBW + 1}$$

eg, 1 L D_5W given to 70-kg man w/ [Na] = 160 mEq/L will ↓ $[Na]_{serum}$ by 3.7 mEq

nb, do not forget to correct Na if hyperglycemia also present

- Rate of correction depends on acuity of onset and risk:
  - chronic (>48 hr): ~12 mEq/d appears safe w/o risk of cerebral edema (*CJASN* 2019;14:656)
  - acute (<48 hr): may ↓ Na by 2 mEq/L/h until Na 145
  - hyperacute (min-hrs) & life threatening (ICH, seizure): rapidly infuse D_5W ± emergent HD
- *Estimate:* in 70-kg man, 125 mL/h of free H_2O will ↓ [Na] by ~0.5 mEq/L/h
- ½ NS (77 mEq/L) or ¼ NS (38 mEq/L) provides both volume & free H_2O (500 or 750 mL of free H_2O per L, respectively); can give free H_2O via NGT/OGT
- Formulas provide only estimates; ∴ recheck serum Na frequently
- **DI and osmotic diuresis:** see "Polyuria" section below
- **Na overload:** D_5W + diuretic. Consider HD if life threatening (ICH, hypertonia, seizures).

POLYURIA

Definition and pathophysiology

- **Polyuria** defined as >3 L UOP per day
- Due to an *osmotic* or a *water diuresis;* almost always due to osmotic diuresis in inpatients

Workup

- Perform a timed urine collection (6 h sufficient) and measure U_{osm}
- 24-h osmole excretion rate = 24-h UOP (actual or estimate) × U_{osm}
  >1000 mOsm/d → osmotic diuresis; <800 mOsm/d → water diuresis

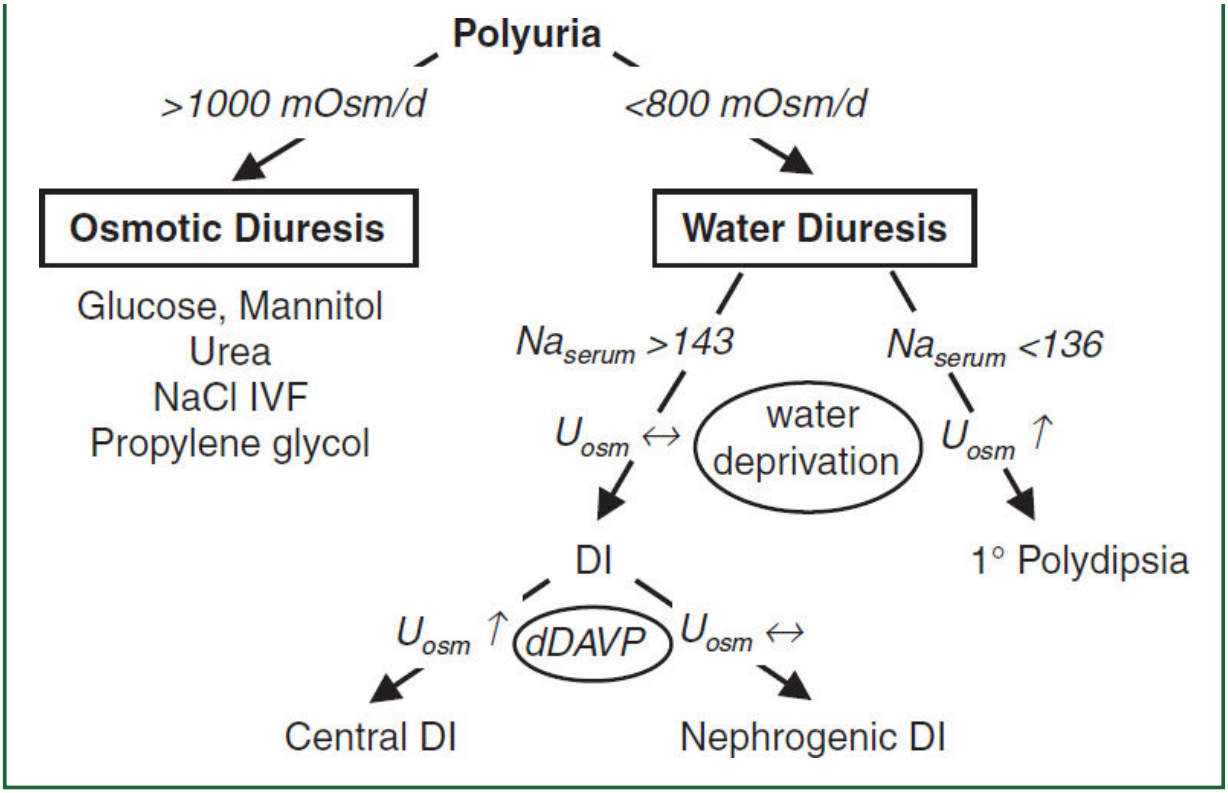
Osmotic diuresis

- Etiologies
  Hyperglycemia (>180 exceeds PCT reabsorption), mannitol, propylene glycol
  Na: NaCl IVF, recovering AKI (eg, post obstruction)
  Urea: ↑ protein feeds, hypercatabolism (burns, steroids), GI bleed, resolving azotemia

Water diuresis

- Etiologies: DI (Na_{serum} >143) or **1° polydipsia** (Na_{serum} <136)
  see "Hypernatremia" above for list of causes of central and nephrogenic DI
- Workup of DI: U_{osm} <300 (complete) or 300–600 (partial)
  water deprivation test (rarely used)
  hypertonic saline-stimulated plasma copeptin >4.9 pmoL/L indicates 1° polydipsia (97% accuracy vs. 77% for water deprivation; *NEJM* 2018;379:428)

Figure 4-6 Approach to polyuria



Treatment

- **1° polydipsia:** treat psychiatric illness, check meds, restrict access to free H_2O
- **Osmotic diuresis:** address underlying cause, replace free H_2O deficit (see "Hypernatremia" for formula to calculate) and ongoing losses
- **DI:**
  - Central DI: desmopressin (dDAVP, 1st line), low Na/protein diet + HCTZ, chlorpropamide
  - Nephrogenic DI: treat underlying cause if possible; Na restriction + HCTZ (mild volume depletion → ↓ delivery of filtrate for free H_2O absorption), consider amiloride for Li- induced DI (*Kid Int* 2009;76:44), indomethacin (*NEJM* 1991;324:850) or trial desmopression
  - Pregnancy-induced DI: due to vasopressinase from placenta, ∴ Rx w/ dDAVP

POTASSIUM HOMEOSTASIS

Overview (*NEJM* 2015;373:60)

- Renal: K excretion regulated at **distal nephron** (CCD) by principal & α-intercalated cells
  - Distal Na delivery & urine flow: Na absorption → lumen electronegative → K secretion
  - Metabolic alkalemia and aldosterone: increase Na absorption and K secretion
  - nb, diurnal urinary K excretion (day >night), ∴ 24-h sample preferred over spot
- Transcellular shifts: most common cause of acute Δ in serum K (98% intracellular)
  - Acid-base disturbance: K^+/H^+ exchange across cell membranes
  - Insulin → stimulates Na-K ATPase → hypokalemia (mitigates postprandial ↑ K)
  - Catecholamines → stimulate Na-K ATPase → hypokalemia; reversed by β-blockers
  - Massive necrosis (eg, tumor lysis, rhabdo, ischemic bowel) → release of intracellular K
  - Hypo- or hyperkalemic periodic paralysis: rare disorders due to channel mutations
- Diet: alone rarely causes ↑ or ↓ K (total body store ~3500 mEq, daily intake ~100 mEq)

HYPOKALEMIA

Transcellular shifts ($U_{K:Cr}$ <13 mEq/g)

- Alkalemia, insulin, catecholamines, β_2-agonists, hypothermia, hypokalemic/thyrotoxic periodic paralysis, acute ↑ hematopoiesis (megaloblastic anemia Rx w/ B_{12}, AML crisis), chloroquine; overdose: Ba/Cs, antipsychotics (risperidone, quetiapine), theophylline

GI potassium losses ($U_{K:Cr}$ <13 mEq/g)

- GI losses *plus* metabolic acidosis: diarrhea, laxative abuse, villous adenoma

• Vomiting & NGT drainage usually manifest as *renal losses* due to 2° hyperaldo & met. alk.

Renal potassium losses ($U_{K:Cr}$ >13 mEq/g)

• Hypotensive or normotensive
  acidosis: DKA, RTA [distal RTAs (type I) >proximal RTAs (type II)]
  alkalosis: diuretics (thiazide >loop), vomiting/NGT drainage (via 2° hyperaldosteronism)
    Bartter's syndrome (loop of Henle dysfxn→ furosemide-like effect; *JASN* 2017;28:2540)
    Gitelman's syndrome (DCT dysfxn→ thiazide-like effect (*KI* 2017;91:24)
  drugs: acetaminophen overdose, PCN, gent., ampho, foscarnet, cisplatin, ifosfamide
  ↓ Mg: less Mg to inhibit principal cell ROMK channel, ∴ ↑ K secretion (*JASN* 2010;21:2109)
• Hypertensive: mineralocorticoid excess
  1° hyperaldosteronism (eg, Conn's syndrome, glucocorticoid-remediable aldosteronism)
  2° hyperaldosteronism (eg, renovascular disease, renin-secreting tumor)
  Nonaldosterone mineralocorticoid (eg, Cushing's, Liddle's [↑ ENaC], exogenous, licorice)

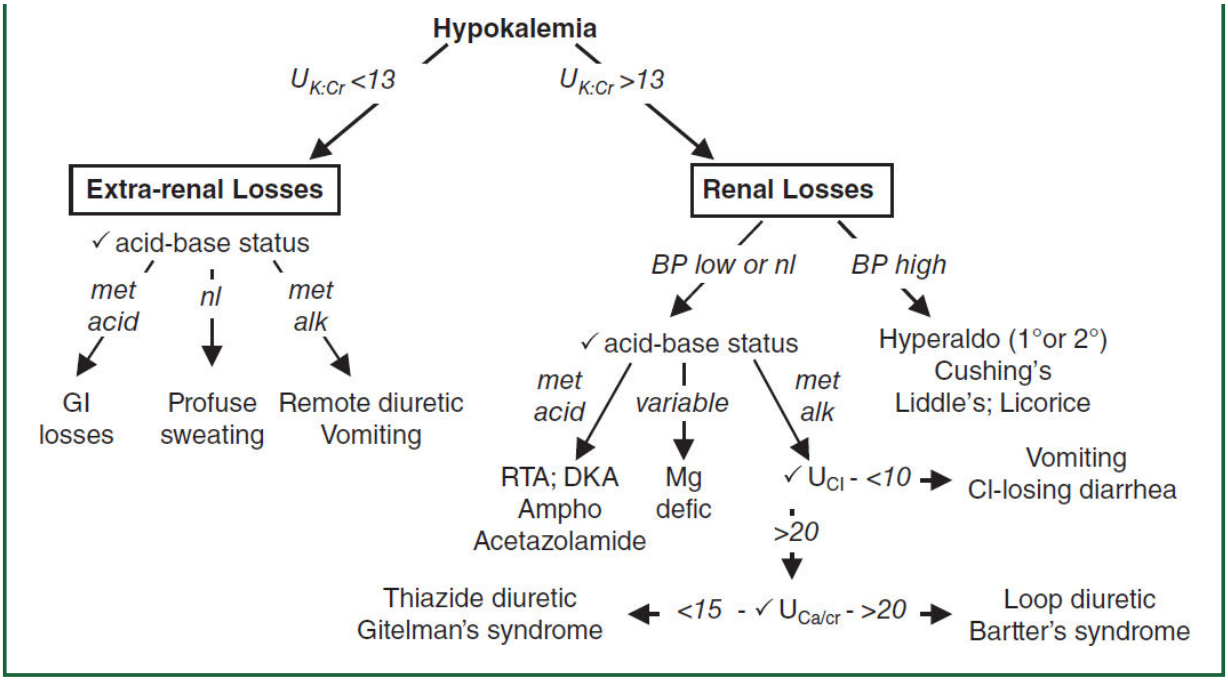
Clinical manifestations

• Nausea, vomiting, ileus, weakness, muscle cramps, rhabdomyolysis, ↓ insulin secretion
• Renal: ammoniagenesis, phosphaturia, hypocitraturia, NaCl & HCO_3 retention, polyuria
• ECG: may see U waves, ↑ QT, flat Tw, ST depression, ventricular ectopy (PVCs, VT, VF)

Workup (*JAMA* 2021;12:1216)

• Identify transcellular shifts & treat. TTKG validity questioned (*Curr Op Nephro* 2011;20:547).
• ✓ **$U_{K:Cr}$**: >13 mEq/g → renal loss; <13 mEq/g → extrarenal loss (*AJKD* 2019;74:682)
• If renal losses, ✓ **BP**, **acid-base**, **U_{Cl}** (U_{Na} unreliable), $U_{Ca/Cr}$, renin, aldosterone, cortisol

Figure 4-7 Approach to hypokalemia



Treatment (*JAMA* 2000;160:2429)

- *If true potassium deficit:* **potassium repletion** (↓ 1 mEq/L ≈ 200 mEq total body loss)
  Dosage: 40 mEq PO q4h, 10 mEq/h (IV), 20 mEq/h (central line), 40 mEq in 1 L IVF
- Replete K^+ to >3 or >4 mEq/L if high-risk (HTN, CHF, arrhythmias, MI, digoxin, cirrhosis)
- Beware of excessive potassium repletion if transcellular shift cause of hypokalemia
- Treat underlying cause (if ↓ vol: avoid dextrose as ↑ insulin → intracellular potassium shifts)
- Consider Rx that ↓ K loss: ACEI/ARB, K^+-sparing diuretics, βB
- Replete Mg if <2 mEq/L: IV Mg-SO_4 1–2 g q2h and oral Mg-oxide (limited by diarrhea).
  Causes of low Mg: GI loss (diarrhea, bypass, pancreatitis, malnutrition, PPI); renal loss (diuretics, nephrotoxic drugs, EtOH, ↑ Ca, 1° wasting syndromes, volume expansion)

HYPERKALEMIA

Transcellular shifts (*BMJ* 2009;339:1019)

- Acidemia, ↓ insulin (DM), cell lysis (tumor, rhabdo, ischemic bowel, hemolysis, transfusions, resorbing hematomas, hyperthermia,

rewarming), hyperkalemic periodic paralysis, ↑ osmolality. Drugs: succinylcholine, aminocaproic acid, digoxin, β-blockers.

Decreased GFR

- Any cause of oliguric or anuric AKI or any cause of end-stage renal disease

Normal GFR but with ↓ renal K excretion

- Normal aldosterone function
  - ↓ EAV (K excretion limited by ↓ **distal Na delivery & urine flow**): CHF, cirrhosis
  - Excessive K intake: in conjunction with impairment in K excretion or transcellular shift
  - Ureterojejunostomy (absorption of urinary K in jejunum)
- **Hypoaldosteronism:** same as etiologies of hypoaldo RTA (type IV)
  - ↓ renin: DM, NSAIDs, chronic interstitial nephritis, HIV, multiple myeloma, Gordon's
  - Normal renin, ↓ aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin, ketoconazole
  - ↓ response to aldosterone
  - Meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors
  - Tubulointerstitial disease: sickle cell, SLE, amyloid, diabetes

Clinical manifestations

- Weakness, nausea, paresthesias, palpitations; Renal: ↓ NH_4^+ secretion → acidosis
- ECG: ST depression, peaked T waves, ↓ QT, ↑ PR interval, ↑ QRS width, loss of P wave, sine wave pattern, PEA/VF (ECG: low sens., cardiac arrest can be first manifestation!)

Workup (*Crit Care Med* 2008;36:3246)

- Rule out pseudohyperkalemia (IVF w/ K, tourniquet, hemolysis, ↑ plt or WBC), rule out transcellular shift

Treatment of Hyperkalemia			
Intervention	**Dose**	**Onset**	**Comment**
Ca gluconate Ca chloride[a]	1–2 amps IV	<3 min	Transient effect (30–60 min) Stabilizes cell membrane

Treatment of Hyperkalemia			
Insulin	reg insulin 5–10 U IV + 1–2 amps $D_{50}W$	15–30 min	Peak 30–60 min, lasts 4–6 h ↓ K 0.5–1.2 mEq/L
Bicarbonate (esp. if acidemic)	1–2 amps IV 150 mEq in 1 L D_5W	15–30 min	Exchange K for H^+ in cells Lasts 5–6 h; ↓ K 0.7 mEq/L
β2 agonists	albuterol 10–20 mg inh. or 0.5 mg IV	30–90 min	Peak 90 min, lasts 2–6 h ↓ K 0.5–1.4 mEq/L (IV >inh)
K-binding resins	SPS[b] 15–60 g PO/PR patiromer 8.4–25.2 g/d PO Na zirconium 5–10 g PO	4–24 hrs hrs-d hrs	Exchange K for cations in gut (Na, Ca, H); ↓ K 0.8–1 mEq/L/d. Edema & HTN w/ Na zirconium.
Diuretics	furosemide ≥40 mg IV	30 min	↓ total body K
Hemodialysis	Most rapid in 1st hr (1 mEq/L)		↓ total body K (*JASN* 2017;28:3441)

[a]CaCl contains more calcium and is typically reserved for codes (↑ risk of tissue necrosis) or via central line

[b]~0.4% intestinal necrosis esp. postop, ileus, SBO/LBO, bowel disease (UC), renal txp (*Clin Nephro* 2016;85:38)

- **Assess GFR**, if normal, then ✓U_K, U_{Na} (<25 mEq/d ↓ distal Na delivery). ✓ $U_{K:Cr}$ (<13 favors ↓ renal K excretion).
- *Rate of onset* important to note when establishing a treatment plan (*Mayo Clinic* 2020;96:744)
- **Stabilize** (initial): 10% CaCl (central) or gluconate (IV). ↑ memb. potential → ↓ excitability
- **Redistribute**: insulin + dextrose (continuous if NPO), HCO_3, β_2-agonists
- **Eliminate**: SPS, patiromer, Na zirconium, diuretics (w/ saline if preserved renal fxn), consider emergent HD in life-threatening situations
- Patient information for diet education: http://www.kidney.org/atoz/content/potassium

KIDNEY DISEASE

ACUTE KIDNEY INJURY (AKI)

Definition (*KDIGO* 2012;2:1)

- **Stages in ICU correspond to** ↑ hospital mortality and LOS (*Crit Care Med* 2009;37:2552)
  - Stage 1: Cr ≥0.3 mg/dL in 2d or ↑ Cr ≥50%, or UOP <0.5 mL/kg/h for ≥6h
  - Stage 2: ↑ Cr 2–3x baseline in 7d or UOP <0.5 mL/kg/h for ≥12h
  - Stage 3: ↑ 3x baseline in 7d, UOP <0.3 mL/kg/h for ≥24h, anuria ≥12h, or Cr >4
- *Cannot* estimate GFR using Cr in setting of AKI or Δ'ing Cr (requires steady state)

Workup (*NEJM* 2014;371:55)

- **H&P:** meds, contrast, or other nephrotoxins; ↓ PO intake, HoTN, infxn/sepsis; trauma, myalgias; BPH/retention. Search for insult 24–48 hr prior ↑ Cr. VS, vol status, rash.
- **Urine evaluation:** output, urinalysis, **sediment**, electrolytes, and osmolality
- **Fractional excretion Na (FE_{Na})** = $(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$; if diuretic, ✓ $FE_{UN}=(U_{UN}/P_{UN})/(U_{Cr}/P_{Cr})$
- Renal U/S or CT: r/o obstruction & cortical atrophy in chronic kidney disease
- Serologies (if indicated): see "Glomerular Disease"
- Renal biopsy (microscopy, IF, and EM): if etiology unclear (esp. if proteinuria/hematuria). Relative contraindic.: SBP>150, ASA/NSAID, anticoag, cirrhosis. DDAVP if GFR <45.

Etiologies and Diagnosis of Acute Kidney Injury (*Ann Inter Med* 2017;9:66)	
Etiologies	**UA, Sediment, Indices**

Etiologies and Diagnosis of Acute Kidney Injury (*Ann Inter Med* 2017;9:66)		
Prerenal	↓ **Effective arterial volume** (*NEJM* 2007;357:797) Hypovolemia, ↓ CO (CHF), ↓ oncotic pressure (cirrhosis, nephrotic), vasodilation (sepsis) Δ **local renal perfusion:** NSAIDs, ACEI/ARB, contrast, calcineurin inhib, HRS, hyperCa **Large vessel:** RAS (bilateral + ACEI), VTE, dissection, abd compart. synd. (renal vs. compress), vasculitis	Bland Transparent hyaline casts FE_{Na} <1%, BUN/Cr >20 FE_{UN} ≤35%
Intrinsic	**Acute tubular necrosis (ATN)** *Severe ischemia, sepsis, CIN* (↓ RBF + toxin) *Toxins* Drugs: vanc, AG, cisplatin, foscarnet, HES (starch), IVIG, pentamidine, amphotericin, tenofovir Pigments: Hb, myoglobin (*NEJM* 2009;361:62) Monoclonal: Ig light chains (*Blood* 2010;116:1397) Crystals: UA, ACV, MTX, indinavir, oral $NaPO_4$	Pigmented granular muddy brown casts ± RBCs & protein from tubular damage FE_{Na} >2%, BUN/Cr <20 (except pigment, CIN) FE_{UN} >50%
	Acute interstitial nephritis (AIN) *Allergic:* β-lactams, sulfa drugs, NSAIDs, PPIs *Infection:* pyelo, viral, legionella, TB, leptospirosis *Infiltrative:* sarcoid, lymphoma, leukemia *Autoimmune:* Sjögren's, TINU, IgG4, SLE, ICIs	WBCs, WBC casts, ± RBCs w/ neg UCx ⊕ urine eos in abx ⊕ lymphs in NSAIDs
	Small-med vessel: chol emboli, PAN, TMAs (TTP, HUS, atypical HUS, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	± RBCs ⊕ urine eos in chol emboli
	Glomerulonephritis (see "Glomerular Disease")	Dysmorphic RBCs, RBC casts

Etiologies and Diagnosis of Acute Kidney Injury (*Ann Inter Med* 2017;9:66)		
Post	**Bladder neck:** BPH, prostate cancer, neurogenic bladder, anticholinergic meds **Ureteral** (bilateral or unilateral in single kidney): malig, LAN, retroperitoneal fibrosis, nephrolithiasis	Bland ± non-dysmorphic RBCs, WBC, crystals

General treatment (*CJASN* 2008;3:962)

- Prerenal: isotonic IVF ≈ alb (*NEJM* 2004;350:22). No clear benefit of balanced crystalloids (eg, LR) over normal saline (*NEJM* 2018;378:829 & 2022;386:815).
- Avoid nephrotoxic insults (meds and contrast); renally dose medications
- Optimize hemodynamics (both MAP & CO) and maintain euvolemia (*NEJM* 2007;357:797)
- *No* benefit to dopamine (*Annals* 2005;142:510), diuretics (*JAMA* 2002;288:2547), or mannitol

Managing complications

- May take 1–3 wk to recover from ATN; anticipate volume overload, ↑ K, ↑ PO_4, acidosis
- Episodes of AKI ↑ risk of CKD progression, even after recovery (*NEJM* 2014;371:58)
- Indications for urgent dialysis (when condition refractory to conventional therapy)
  - **A**cid-base disturbance: refractory acidemia
  - **E**lectrolyte disorder: hyperK; hyperCa, hyperPO_4, tumor lysis syndrome
  - **I**ntoxications (http://www.extrip-workgroup.org/): Poison Control (1-800-222-1222)
    - Indicated for: methanol, ethylene glycol, metformin, Li, valproic acid, salicylates, barbiturates, theophylline, thallium
    - Consider for: carbamazepine, APAP, dig (Rx Digibind), dabigatran (Rx idarucizumab)
  - **O**verload: refractory hypervolemia → hypoxemia (eg, CHF)
  - **U**remia: pericarditis, encephalopathy, bleeding
- In stage 3 AKI, wait until above indication or oliguria >72 hrs (*NEJM* 2016;375:122; *Lancet* 2020;395:1506). If oliguria >72 hrs, further delaying until urgent indication ↑ mortality (*Lancet* 2021;397:1293).

DISEASE-SPECIFIC MANAGEMENT

Acute interstitial nephritis (AIN) (*CJASN* 2017;12:2046 & *JASN* 2020;31:435)

- Commonly drug-induced: β-lactams, sulfa drugs, NSAIDs, PPIs, quinolones, allopurinol
- If suspected, prompt removal of offending drug; ? early steroids w/in 7d of dx
- Rechallenging after suspected ICI-induced AIN may depend on oncology natural history

Cardiorenal syndrome (CRS) (*CJASN* 2017;12:1624)

- Multifactorial pathophys including: 1) ↓ CO, 2) ↑ renal venous congestion, 3) ↑ RAAS
- Bidirectionality: acute CHF → AKI, and oliguric AKI can worsen CHF (*JACC* 2008;52:1527)
- Rx: **IV loop diuretics** (bypass gut edema; dosing below); no diff. between high vs. low dose and bolus vs. gtt (*NEJM* 2011;364:797). No clinical benefit: dopa, nesiritide, ultrafilt.
- Prognosis: 7% ↑ mortality a/w each 10 mL/min ↓ eGFR in ADHF (*JACC* 2006;47:1987)

Contrast-induced acute kidney injury (CIAKI) (*NEJM* 2019;380:2146)

- Risk factors: CKD, DM, CHF, age, hypotension, ↑ contrast volume (*JACC* 2004;44:1393)
- AKI 24–48 h post contrast, peaks 3–5 d, resolves 7–10 d (consider chol emboli if does not)
- Prevention: consider if eGFR <60 (espec. w/ proteinuria), DM, MI, HoTN (*CJASN* 2013;8:1618)
  - **Isotonic IV fluids:** may be helpful if high risk (*Lancet* 2017;389:1312)
    - Outpatients: 3 mL/kg/h × 1 h prior, 1–1.5 mL/kg/h × 6 h after (*JAMA* 2004;291:2328)
    - Inpatients: 1 mL/kg/h × 6–12 h pre, intra, post-procedure (*Lancet* 2014;383:1814)
  - Hold ACEI/ARB (*AJKD* 2012;60:576), NSAIDs, diuretics. Min. contrast & use iso-osmolar.
- Nephrogenic systemic fibrosis: fibrosis of skin, joints, internal organs ~2–4 wk post gado exposure in CKD 4–5 (*JACC* 2009;53:1621). Postgado HD encouraged, though limited data.

Hepatorenal syndrome (HRS; ***see "Cirrhosis";*** *AJKD* 2013;62:1198)

- **Albumin** + *either* IV vasopressors (norepi, terlipressin) *or* octreotide & midodrine

Obstructive diseases

- Dx: renal U/S if undifferentiated or CT abd/pelvic (I^-) if suspect nephrolithiasis

- Rx: Foley if urethra vs. perc. nephrostomy if above ureters (eg, stones), tamsulosin/finasteride
- Watch for post-obstructive diuresis after relieving blockage, replace ½ UOP w/ ½ NS.
  Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly.

Polycystic kidney disease (*NEJM* 2008;359:1477; 2017;377:1988)
- Mostly AD *PKD1/PKD2* mutations → renal cysts. PKD1 (85%) younger-onset ESRD.
- Rx: hydration, low-salt diet; tolvaptan reduces GFR decline. Family genetic screening.

Rhabdomyolysis (*NEJM* 2009;361:62)
- Pathophys: myoglobin-induced oxidant injury, vasoconstriction, myoglobin precipitation & pre-renal (extravasation). Can lead to ↓ Ca, ↑ K, and ↑ PO_4.
- Diagnosis: UA ⊕ for heme but 0 RBCs (ie, myoglobinuria)
- Risk of AKI when CK >20,000. Rhabdo and mortality risk score: *JAMA Int Med* 2013;173:1821.
- Aggressive IVF (tailor IVF to target UOP ~3 mL/kg). If urine pH <6.5, consider $NaHCO_3$ ✓ K & Ca frequently, trend CK. Monitor for compartment syndrome.

Scleroderma renal crisis (*Nature Neph* 2016;12:678)
- 5–20% diffuse cutaneous SSc w/ narrowing glomerular vessels. Sx: renal failure, severe HTN, encephalopathy. Rx: max ACEi for BP control.

COVID-19 associated AKI (*Am J Physiol Renal Physiol* 2021;4:403)
- 17% of inPts. ATN >collapsing FSGS (high-risk *APOL1* genotype). ↑ clotting risk w/ RRT

Thrombotic microangiopathies (TMAs): ***see "Hematology"***

CHRONIC KIDNEY DISEASE (CKD)

Definition and etiologies (*Lancet* 2021;10302:786)
- **GFR** <60 for ≥3 mo *and/or* **kidney damage** (albuminuria, structural abnormality)
- Prevalence 15% in U.S.
- Albuminuria predicts all-cause & CV mortality, CKD progression (*NEJM* 2004;351:1296)

- Cr poor estimate of GFR, use equation (https://www.kidney.org/professionals/kdoqi/gfr_calculator) Cystatin-C–based formula less influenced by race than Cr-based (*NEJM* 2021;385:1737)
- Etiologies: DM (45%), HTN/RAS (27%), glomerular (10%), interstitial (5%), PKD (2%), congenital, drugs, myeloma, repeated insults (eg, Mesoamerican nephropathy)
- Progression to ESRD: kidney failure risk equation (*JAMA* 2016;315:164; kidneyfailurerisk.com)

Stages of CKD (*Kid Int* 2013;3[Suppl]:5)

GFR Stage	GFR mL/min/1.73 m^2	Goals
1 (nl or ↑ GFR)	>90	Dx/Rx of underlying condition & comorbidities, slow progression; cardiovascular risk reduction
2 (mild)	60–89	Estimate progression
3a (mild-mod)	45–59	Evaluate and treat complications
3b (mod-severe)	30–44	Evaluate and treat complications
4 (severe)	15–29	Prepare for renal replacement therapy (RRT)
5 (kidney failure)	<15 or dialysis	Dialysis if uremic/volume overload; Tx

Albuminuria stage based on albuminuria (mg/d) or spot urine alb (mg) to Cr (g) ratio
Stages: A1 = <30 (normal/mild); A2 = 30–300 (moderate); A3 = >300 (severe)

Signs and Symptoms of Uremia (*NEJM* 2018;379:669)

General	Nausea, anorexia, malaise, uremic fetor, metallic taste, hypothermia
Skin	Uremic frost (white crystals in & on skin), pruritus, calciphylaxis
Neurologic	Encephalopathy (Δ MS, ↓ memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
Cardiovascular	Pericarditis, atherosclerosis, HTN, CHF, cardiomyopathy (LVH)
Hematologic	Anemia, bleeding (due to platelet dysfunction and Epo deficiency)
Metabolic	↑ K, ↑ PO_4, acidosis, ↓ Ca, 2° hyperparathyroidism, osteodystrophy

Complications & treatment (*JAMA* 2019;322:1294; *KI* 2021;99:S1)

- **General:** renal referral when GFR <30 or proteinuria, access planning (avoid subclavian lines, preserve an arm by avoiding phlebotomy, BP measurements, IVs)
- **CV risk reduction:** consider usual preventive Rx including statin, βB, etc.
- **Dietary restrictions:** Na (if HTN), K (if oliguric or hyperkalemic), PO_4, mod protein.

- **Diabetes:** strict glc control; ACEI/ARB, SGLT2i and MRA (*NEJM* 2020;383:2219) slow CKD progression (↓ glomerular pressure)
- **SGLT2i:** in proteinuric CKD (min eGFR 25-30) w/ or w/o DM, transient ↓ in eGFR (<5) but then 30-40% ↓ risk of CKD progression & ↓ mortality (*NEJM* 2019;380:2295 & 2020;383:1436)
- **BP control:** goal ideally <120/80, a/w ↓ mortality. ACEI or ARB, not both. For outPts, ✓ Cr & K in 1–2 wk, d/c if Cr ↑ 30% or K >5.4 (after dietary Δ & loop diuretic).
- **Metabolic acidosis:** sodium bicarbonate or sodium citrate if low HCO_3 (*JASN* 2015;26:515)
- **Hyperkalemia:** 2-g K diet, see "Potassium Homeostasis"
- **Anemia:** goal Hb 10–11.5 g/dL, worse outcomes if target higher (*NEJM* 2009;361:2019)
  - epoetin (start 80–120 U/kg SC, divided 3×/wk) or darbepoetin (0.75 mg/kg q 2 wk)
  - iron supplementation to keep transferrin sat >20% (often given IV in HD Pts).
  - HIF inhib. ↑ endogenous EPO production, not yet approved (*NEJM* 2021;385:2313 & 2325).
- **Uremic bleeding:** desmopressin (dDAVP) 0.3 µg/kg IV or 3 µg/kg intranasally
- **2° hyperPTH:** ↑ PO_4, ↑ FGF-23, ↓ calcitriol, & ↓ Ca → ↑ PTH → renal osteodystrophy

CKD stage	3	4	5
Target PTH (pg/mL)	35–70	70–110	150–600

  - Phosphorus binders (*take with meals!*) (*NEJM* 2010;362:1312). Non-Ca–based binders (eg, sevelamer) a/w ↓ mort. compared to Ca-based (*Lancet* 2013;382:1268).
  - If PTH above goal then start vit. D (if 25-(OH)D <30) or 1,25-(OH)D analogue (calcitriol); stop if ↑ Ca (*AJKD* 2009;53:408)
  - Cinacalcet (parathyroid Ca-sensing receptor agonist) if ↑ PTH despite phosphorus binders ± vit. D analogue (*CJASN* 2016;11:161); consider parathyroidectomy
- **Calciphylaxis** (calcific uremic arteriopathy, *NEJM* 2018;378:1704)
  - Pathophys: calcification of media in dermal small- to med-sized blood vessels & SC fat → ischemia and skin necrosis w/ painful lesions (*NEJM* 2007;356:1049)

Risk factors: ESRD, ♀>♂, DM, vit K def, obesity, warfarin, local trauma, thrombophilias

Dx: skin bx, but limitations (*Kidney Int* 2018;94:390); bone scan used in support of dx

Rx: ↓ risk factors, wound care/surgical debridement, manage hyperPTH, d/*c* vit D, Ca, & warfarin (DOAC okay). Pain control, palliative care, ? Na thiosulfate.

Prognosis: 60% 1-y mortality in ESRD Pts (*AJKD* 2015;66:133)

- **Anticoag:** ESRD at ↑ bleed risk; if using DOAC, consider apixiban >rivaroxaban >dabigatran due to protein binding/renal clearance (*JASN* 2017;28:2241)
- **Transplant evaluation**

DIURESIS

General considerations

- ↑ Na & H_2O excretion for treatment of HTN or edema in CHF, renal failure, and cirrhosis
- Daily wt most effective method of documenting successful diuresis

Loop diuretics (*NEJM* 2017;377:1964)

- **Drugs:** furosemide (Lasix), torsemide, bumetanide (Bumex), ethacrynic acid
- **Mech:** inhib NaK2Cl cotransporter in thick ascending limb (ThAL, site of 25% Na reabsorp) → ↓ medullary osmotic gradient & ↓ free H_2O reabsorption via ADH

  Transient venodilation may aid in pulmonary congestion (*NEJM* 1973;288:1087)

  Response is fxn of amt of drug excreted; ∴ ↑ dose needed in renal insufficiency, CHF

  Sigmoidal dose response curve; ∴ ↑ dose until induce diuresis, ↑↑ dose beyond that point yields diminishing returns compared with ↑ frequency of dosing
- **Dosing:** bioavailability PO furosemide ~50%, PO torsemide & bumetanide ~90%

  40 mg IV = 80 mg PO Lasix = 20 mg PO/IV torsemide = 1 mg IV/PO bumetanide

  Dose furosemide bid-qid; qd dosing can yield initial diuresis, but then anti-natriuresis. Cont. vs. bolus IV similar in acute CHF (*NEJM* 2011;364:797). Ethacrynic acid if sulfa allergy.

? ↑ diuresis w/ co-administration of albumin if ↓ serum albumin (*Crit Care Med* 2005;33:1681)

- **Adverse effects:** ↑ Na, ↓ K, ↓ Mg, ↓ Ca, hyperuricemia, ototoxicity, hypersensitivity (sulfa)

Thiazide diuretics (*JASN* 2017;28:3414)

- **Drugs:** hydrochlorothiazide (HCTZ), chlorothiazide (Diuril), metolazone (Zaroxolyn)
- **Mech:** inhib Na-Cl cotransporter in the distal convoluted tubule (DCT); 5% Na reabsorp
  synergistic with loop diuretic, esp. if chronic loop use
  ↓ effect when GFR <30, *except metolazone,* which is still effective in renal insufficiency
- **Dosing:** give 30 min prior to loop diuretic
- **Adverse effects:** ↓ Na, ↓ K, ↓ Mg, ↑ Ca, HLD, pancreatitis, ↑ glc, hypersensitivity

K-sparing diuretics (*NEJM* 2017;377:1964)

- **Drugs:** spironolactone (Aldactone), amiloride, triamterene, eplerenone
- **Mech:** ↓ Na reabsorption (~1%) in collecting duct (amiloride/triamterene inhibit principal cell Na channel [ENaC]; spironolactone/eplerenone inhibit mineralocorticoid receptor).
  Relatively weak natriuretic activity, useful in combination with thiazide or in cirrhosis.
- **Adverse effects:** ↑ K (esp. w/ ACEI), metabolic acidosis, gynecomastia (spironolactone)

Approach to Diuresis (if inadequate diuresis, go to next step)	
Step	**Action**
1	**Loop diuretic PO:** ✓ response at 1–3 h, redose at 2× prior dose if needed
2	**Add thiazide diuretic PO** (potentiates response to loop diuretic)
3	**Loop diuretic IV:** bolus bid–qid ± thiazide (*may start here if inPt*) ↑ dose w/ ↑ Cr; initial effective IV Lasix dose ≈ 30 × Cr (ie, if Cr = 4 → 120 mg IV)
4	**Loop diuretic infusion:** bolus + continuous IV infusion ± thiazide (PO or IV)
5	**RRT:** consider ultrafiltration, CRRT, or HD

Disease state specific regimens

- Renal insufficiency: loop diuretic (↑ dose to achieve effective delivery to ThAL) ± thiazide
- CHF: loop diuretic (↑ frequency over ↑ dose), IV for gut edema + thiazide (watch K & Mg)

- Nephrotic syndrome: urinary albumin binds secreted loop diuretic, use 2–3× normal dose
- Cirrhosis: spironolactone (blocks 2° hyperaldosteronism) + Lasix in 2.5:1 ratio
- Severe metabolic alkalosis: acetazolamide & treat underlying cause

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Renal Replacement and Dialysis

General

- Acute indications: see "AKI"; choices CVVH vs. HD
- Chronic indications: timing of RRT initiation should factor in Pt QoL, uremic sx, risk of development of urgent/acute indications; modalities PD vs. HD (no clear diff in outcomes)
- Outcomes of ESRD: death from CVD (50%), infxn (30%), withdrawal of care (20%)

Modalities			
	HD	**CVVH**	**PD**
Physiology	Diffusion	Convection	Diffusion
Access	AV fistula/graft or CVC	CVC	Peritoneal catheter
Prescription	Duration, volume goal; K, Na, Ca, HCO_3 in bath, anticoag	Volume goal, K & Ca in replacement fluid (HCO_3 vs. citrate)	PD fluid (dextrose, icodextrin), dwell time, # cycles
Complic.	HoTN, arrhythmia, disequilibrium syndrome* if very high BUN, ↑ CO HF	HoTN, ↓ PO_4, ↓ iCa (citrate toxicity in hepatic dysfxn)	Peritonitis, ↑ glc, ↓ albumin, R pleural effusion

*Disequilibrium syndrome: sx cerebral edema due to H_2O shifts after urea removal

Hemodialysis (HD) (*NEJM* 2010;363:1833)

- Solute removal across *semipermeable* membrane, countercurrent blood & dialysate flow
  - Volume removal: Na/H_2O ultrafiltered via transmembrane pressure (TMP) gradient
  - Solutes: Cr, urea, K diffuse from blood → dialysate, HCO_3 from dialysate → blood
  - Solute removal inversely proportional to size ∴ effective removal of K, urea, Cr, not PO_4
- 6× vs. 3×/wk improved HTN, LV mass, QoL, but ↑ vasc issues (*NEJM* 2010;363:2287); w/ 3×/wk HD, ↑ mortality risk during 2-d interval (Sa–Tu or Fri–Mo) (*NEJM* 2011;365:1099)

- Fever w/ catheter: empiric abx (vanc + GNR coverage qHD). GPC >GNR >mixed/fungal. Remove/replace catheter (depends on organism), "lock" abx (*JASN* 2014;25:2927).
- Central vein stenosis: assoc. with longer HD duration, tunneled catheters. HeRO grafts bypass subclavian stenosis with flow into central vein (*J Vasc Access* 2016;17:138).

Vascular Access		
	Advantages	**Disadvantages**
AV fistula	Highest patency Lowest risk of bacteremia Lowest mortality (*JASN* 2013;24:465)	Long maturation time (2–6 mo) Primary nonfunction (20%)
AV graft	Easier to create than AVF Maturation time (2–3 wk)	Poor 1° patency, often requiring thrombectomy or angioplasty
Catheter	Immediate use Use as bridge to AVF/AVG	Highest risk of bacteremia ↓ blood flow → ↓ HD efficiency

Continuous veno-venous hemofiltration (CVVH) (*NEJM* 2012;367:26)

- *Hemofiltration* rather than dialysis. Blood under pressure passes down one side *highly permeable* membrane filtering H_2O and solutes via TMP gradient (convective clearance); filtrate discarded. Replacement fluid infused (solute concentration similar to plasma, except no urea, Cr, PO_4). Fluid balance by adjusting filtrate/replacement fluid.
- Replacement fluid rate determines clearance. Choice of replacement fluid buffer:
  HCO_3 (+ heparin to prevent clotting, although can be run heparin-free)
  citrate: hepatically metabolized to HCO_3, ∴ cannot be given in cirrhosis/liver failure. Provides anticoag w/in machine via Ca chelation. Citrate toxicity: ↓ iCa but nl/ ↑ serum Ca and AG met acidosis.
  Dose adjust for solute and volume removal (*AJKD* 2016;68:645)
- Other CRRT modalities: CVVHD (dialysis), CVVHDF (filtration & dialysis) (*AJKD* 2016;68:645)
- Benefits compared w/ HD: ↓ gross fluid shift (preferred in HoTN), but slower clearance of solutes and toxins

Peritoneal dialysis (PD) (*JAMA* 2017;317:1864)

- Fluid removed via convection using oncotic pressure (eg, dextrose). ↑ concentrations and dwell times removes more fluid (less as glc equilibrates).

- PD fluid: dextrose (1.5%, 2.5%, or 4.25%), buffer (lactate), Na^+, Ca^{2+}, Mg^{2+}
- Infuse 10 min, dwell 90 min–5.5 h, drain 20 min; exchanges done manually or using cycler at night (automated or cont. ambulatory peritoneal dialysis APD, CAPD)
- PD peritonitis: abd pain & cloudy drainage (WBC >100 & >50% PMNs). 60–70% GPC, 15–20% GNR. Rx: abx IV or in PD, catheter removal for certain org (yeast, *Pseudomonas*).
- Sclerosing peritonitis, a rare long-term complication (*NEJM* 2002; 347:737)
- Hyperglycemia: exacerbated by inflammation, long dwell times, and higher [glucose]
- Benefits: lower cost, independence, preservation of residual kidney function. No Δ mortality vs. HD (*AJKD* 2018;71:344).

Kidney transplantation (*Med Clin N Am* 2016;100:435)

- Refer when GFR <20. Contraindic: active malig, infxn, ischemia, noncompl, subst use
- 5-yr survival: living donor 91%; deceased donor 70–84% (*AJKD* 2016;23:281). Donors have minor ↑ risk of ESRD (*Am J Transplant* 2014;14:2434).
- Immunosuppression: calcineurin inhib (tacrolimus>CsA) or CTLA4 inhib (belatacept) (*NEJM* 2016;374:333), antimetabolite (MMF>AZA), prednisone, mTOR inhib (sirolimus) if others contraindicated
- Rejection: Ab (ABMR) or T-cell mediated (TCMR), a/w poor graft survival; BANFF criteria (*Am J Transplant* 2018;18:293). Rx options: ↑ immunosupp., pulse steroids, IVIG, rituximab.
- Late renal dysfxn: usual AKI causes + calcineurin tox, rejection (*NEJM* 2010;363:1451), BK virus, recurrence of 1° disease; usual w/u + immunosupp levels, donor-specific antigen (DSA), BK virus load, U/S, then bx if no other cause (*CJASN* 2008;3:S56; *CJASN* 2011;6:1774)
- ↑ infxn (incl opportunistic such as CMV, JC, BK viruses; *CJASN* 2012;7:2058) & cancer (PTLD)
- ↑ CVD risk due to HTN (calcineurin inhib, RAS), DM & dyslipidemia (immunosupp meds)

GLOMERULAR DISEASE

GLOMERULONEPHRITIS (GN)

Definition (*Lancet* 2016;387:2036; *JASN* 2016;27:1278)

- ↑ glomerular inflammation → endothelial & podocyte injury
- Histology: proliferative (↑ cells), sclerosing (scar), necrotizing (areas cell death). Focal (<50% of glomeruli) to diffuse to crescentic. Segmental (<50% tuft) to global (100%).
- Clinically: hematuria w/ dysmorphic RBCs or RBC casts, ± subnephrotic proteinuria often w/ AKI, HTN, edema
- Progression: acute ≈ days; rapidly progressive (RPGN) ~6 wk; chronic ≈ mos; can be asx

ANCA ⊕ Vasculitis (pauci-immune, minimal staining) ~40–45% of total						
Pathogen: infxn, drug (hydral, allopurinol, contam cocaine) (*CJASN* 2017;12:1680)						
Disease	**Gran**	**Renal**	**Pulm**	**Asthma**	**ANCA Type[a]**	**ANCA ⊕**
Granulomatosis with polyangiitis[b]	⊕	80%	90% (+ ENT)	—	anti-PR3	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO	70%
Eosinophilic gran with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO	50%

[a]Predominant type; can see either type (*NEJM* 2012;367:214); [b]GPA (Wegener's); EGPA (Churg-Strauss)

Anti-GBM Disease (linear staining) <15% of total (*CJASN* 2017;12:1162)			
Disease	**Glomerulonephritis**	**Pulm Hemorrhage**	**Anti-GBM**
Goodpasture's	⊕	⊕	⊕
Anti-GBM disease	⊕	—	⊕

Immune Complex (IC) Disease (granular staining) ~40–45% of total (*CJASN* 2018;13:128)	
Renal-Limited Diseases	**Systemic Diseases**
Infection-Related GN (*Staph* & *Strep;* ↓ C3, ± ASLO)	**SLE** (*CJASN* 2017;12:825) (⊕ ANA, ⊕ anti-dsDNA, ⊕ anti-Sm, ↓ C3, ↓ C4)
Membranoproliferative GN (MPGN) (↓ C3)	**Cryoglobulinemia** (⊕ cryocrit, ⊕ RF, ⊕ HCV, SPEP, ↓ C3, ↓ C4)

Immune Complex (IC) Disease (granular staining) ~40–45% of total (*CJASN* 2018;13:128)	
Fibrillary and immunotactoid GN (normal C3/C4)	**Endocarditis** (fever, ⊕ BCx, valvular disease, ↓ C3)
IgA nephropathy (normal C3, ±↑ IgA) (*NEJM* 2013;368:2402; *CJASN* 2017;12:677)	**Henoch-Schönlein purpura** (IgA nephropathy + syst. vasculitis w/ IgA deposits, nl C3, ±↑ IgA)

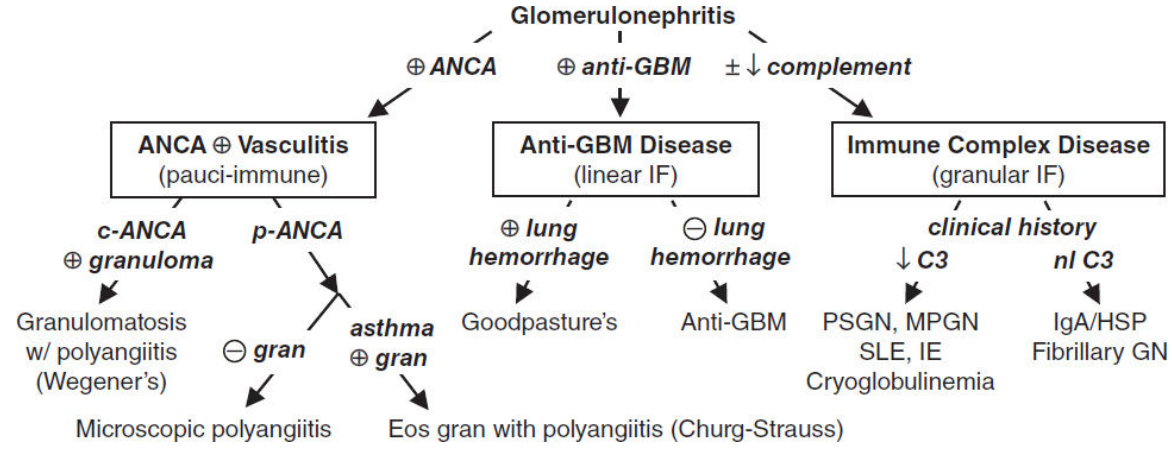
Oncology-related glomerulopathy (*CJASN* 2016;11:1681)

- Associations between malig (solid tumors & heme) and/or their Rx (HSCT & chemo- therapeutics) and GN, nephrotic syndrome, and thrombotic microangiopathies (TMA)
- Most common associations: membranous (solid tumors, HSCT), MCD (Hodgkin's, solid tumors), MPGN (CLL, MM), TMA (HSCT, VEGF, anti-EGFR, CNIs, TKIs, mTOR)
- **Monoclonal glomerulopathy of renal significance:** Ig-mediated kidney disease by nonmalignant B or plasma cells. Workup: SPEP, sFLC, flow cytometry, IFE, BMBx.

Workup (*JAMA* 2017;318:1276)

- *Acute GN/RPGN ± lung hemorrhage is an emergency* → requires early Dx and Rx
- UA + sediment (dysmorphic RBCs) ✓ ANCA, anti-GBM, C3/C4, SPEP, serum FLC
- Depending on hx: ANA, anti-dsDNA/Sm, RF, Hep B&C, HIV, ASLO, BCx, cryocrit, skin bx
- Consider GN mimics: thrombotic microangiopathies (qv), myeloma, AIN, cholesterol emboli
- Renal biopsy with immunofluorescence (IF) + electron microscopy (EM)

Figure 4-8 Approach to glomerulonephritis based on immunofluorescence pattern



Treatment (*AJKD* 2020;75:124 & 2020;76:265)

- If acute GN/RPGN suspected, give 500–1000 mg methylpred. IV qd × 3d *ASAP* while awaiting bx results.
- SLE nephritis: induction w/ steroids + cyclophosphamide (CYC) or MMF (*CJASN* 2017;12:825)
- ANCA ⊕ or anti-GBM: pulse steroids + CYC (or rituximab). Plasma exchange if ⊕ anti-GBM. Controversial in ANCA ⊕ only, even w/ GN or pulm hemor. (*NEJM* 2020;382:622).
- See "Vasculitis" for further disease-specific Rx details (eg, eculizumab for atypical HUS)

Asymptomatic Glomerular Hematuria

Definition and etiologies

- Hematuria ± proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular more common; see "Hematuria")
- Ddx: any cause of GN (esp. IgA); also consider Alport's (X-linked, deafness, renal failure), thin basement membrane nephropathy (autosomal dominant, benign; *JASN* 2013;23:364)

IgA nephropathy (*CJASN* 2017;12:677; *AJKD* 2021;78:429)

- Most common cause of GN; ♂ pred; peak incidence 20–30s; can also be post-infectious
- Wide range of clinical presentations: asx hematuria (30–40%), gross hematuria ~1–3 d after URI (10–15%), chronic GN (10%), nephrotic syndrome (5%), RPGN (<5%)
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: ↑Cr, HTN, proteinuria a/w poor prog. (*AJKD* 2012;59:865). 20–40% ESRD w/in 20 y.
- Rx: ACEI/ARB; if persistent proteinuria (> 1g/d), clinical trial enrollment or shared decision for steroids, consider SGLT2i (*NEJM* 2020;383:1436); ± cytotoxic Rx for GN; ? fish oil

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Nephrotic Syndrome

Definition (*JASN* 2014;25:2393)

- Podocyte injury (effacement) → loss of proteins (albumin, ATIII, Ig)
- Clinically: proteinuria >3.5 g/d, albumin <3 g/dL, edema, ↑ chol., VTE (25%), infection

Primary glomerular diseases (grouped by pathology)

- **Focal segmental glomerulosclerosis** (40%; *CJASN* 2017;12:502). Primary: permeability factor. Secondary: *adaptive* (hyperfiltration, sickle cell, obesity, anabolic steroids, OSA, ↑ protein, vesico-ureteral reflux); *meds/toxins* (IFN, bisphosphonates, NSAIDs, heroin), *viral* (COVID-19, HIV) or genetic (*ApoL1* mutation in AA; *JASN* 2015;26:1443).
- **Membranous nephropathy** (30%; *CJASN* 2017;12:938, *JASN* 2021;32:268): Primary: Ab to PLA2R [70%], THSD7A [5%], other (EXT1-2, NELL1, Sema3B). Secondary: *infxn* (HBV, HCV, HIV, syphilis); *autoimmune* (eg, SLE); *carcinomas*; *drugs* (NSAIDs, penicillamine).
- **Minimal change disease** (20%, more common in children; *CJASN* 2017;12:332) allergies, NSAIDs, ampicillin, Hodgkin's disease, SLE, DM, MG, celiac disease
- **Membranoproliferative GN** (5%, *mixed* nephrotic/nephritic features; *CJASN* 2014;9:600)
  Immune complex mediated: infection (esp. HCV ± cryos, IE, HBV, "shunt" nephritis, other chronic infxns), SLE, cryos, Sjögren's, lymphomas, dysproteinemia, idiopathic
  Complement mediated (rare); dense deposit disease (DDD), C3GN
- **Fibrillary-immunotactoid glomerulopathy** (1%; *JASN* 2008;19:34)
- **Mesangial proliferative GN** (? atypical forms of MCD/FSGS, 5%) IgM, C1q nephropathy

Systemic diseases with secondary glomerular involvement

- **Diabetes mellitus** (*CJASN* 2017;12:2032): nodular glomerulosclerosis (Kimmelstiel-Wilson lesion); glomerular hyperfiltration → microalbuminuria → dipstick ⊕ → nephrotic range (10–15 y). Proliferative retinopathy seen in 90% of type 1 and 60% of type 2.
- **Amyloidosis:** AL or light-chain amyloid or AA amyloid secondary to inflammation
- **SLE** (*CJASN* 2017;12:825): typically membranous nephropathy (WHO class V)
- **Cryoglobulinemia** (*AJKD* 2016;67): a/w HCV, monoclonal gammopathy. Typically MPGN.

Workup (*BMJ* 2008;336:1185)

- U/A + sediment: usually benign; ± oval fat bodies ("Maltese crosses"; *NEJM* 2007;357:806)
- Measure proteinuria: 24-h urine or spot urine protein/Cr ratio (not accurate in AKI), renal bx

- 2° causes: ↑ Hb_{A1C} + retinop. → DM; ✓ ANA, anti-dsDNA, tox screen, C3/C4, SPEP/light chains, fat pad bx, cryocrit, HBV/HCV, HIV, RPR, APLA2R Ab, age-approp. CA screen

Treatment (*NEJM* 2013;368:10)

- General: protein suppl.; diuretics for edema; treat hyperlipidemia, Na restriction (<2 g/d)
- **ACEI** or **ARB:** ↓ proteinuria → slow nonimmunologic progression of renal disease
- 1° glomerular: steroids ± rituximab or cytotoxic therapy (*CJASN* 2014;9:1386; *NEJM* 2019;381:36)
- Secondary causes: treat underlying disease
- Watch for malnutrition (protein loss), consider anticoag if albumin <2.5 in membranous (*KI* 2014;85:1412), infection (esp. encapsulated organisms b/c loss of Ig)

URINALYSIS

Urine Dipstick	
Metric	**Significance and Uses**
Specific gravity	Estimate U_{osm}: each 0.001 above 1 ≈ 30 osm (SG 1.010 → U_{osm} ≈ 300) SG and U_{osm} useful in evaluating AKI, dysnatremias, polyuria Heavy substances (glucose, contrast) ↑ SG more than U_{osm}
pH	Range: 4.5–8.5; useful in evaluation of stones, RTAs, infection (urease UTI)
Protein	Detects albuminuria (>300 mg/d); see "Proteinuria." False ⊖: dilute urine
Blood	See "Hematuria"; ⊕ from RBCs, free Hgb, or free myoglobin (eg, rhabdo) False ⊕: semen, dilute urine (→ osmotic cell lysis), ↑ pH, vaginal blood False ⊖: vit C
WBC	Suggests inflammation (UTI, interstitial nephritis, GN)
Ketones	Detects acetoacetate (ie, ketoacidosis) but *not* β-hydroxybutyrate
Leuk est	Lysed PMNs. Se 80% for UTI. FN: proteinuria, glycosuria FP: ↓ pH or SG
Nitrite	Suggests presence of nitrate reductase ⊕ bacteria (most enteric GNRs)
Bilirubin	↑ in biliary or hepatic disease
Glucose	⊕ in hyperglycemia (>180 mg/dL), pregnancy, Fanconi's syndrome, SGLT2i

Urine Sediment (microscopic examination) (*Am J Kidney Dis* 2008;51:1052)	
Method: Centrifuge fresh sample (prox. port if Foley) × 3–5 min at 1500–3000 rpm; pour off supernatant in one motion; resuspend pellet by agitating base of tube; pour suspension onto slide w/ coverslip; view under "high dry" power; phase contrast for RBC morphology	
Cells	RBCs: assess amount & morphology (many dysmorphic → glomerular) WBCs: PMNs (UTI) vs. eosinophils (AIN; may require special stain) Epithelial cells: tubular (ATN), transitional (bladder or ureters), squamous
Casts *(see urinalysis photo inserts in appendix)*	*Proteins molded in lumen of renal tubule ± entrapped cellular elements RBC → GN* WBC → AIN, pyelonephritis, GN Granular ("muddy brown"): degenerating cellular casts → ATN Tubular cell → ATN Hyaline: Tamm-Horsfall protein (nonspecific) Waxy and broad → advanced chronic kidney disease
Crystals *(see urinalysis photo inserts in appendix)*	Calcium oxalate monohydrate: spindle, oval, or dumbbell shaped Calcium oxalate dihydrate: envelope shaped or octahedral Uric acid: variable shape; polychromatic under polarized light Cystine: hexagon shaped Struvite: coffin-lid shaped; seen in chronic UTI with urea-splitting organisms Drugs: sulfa, protease inhibitors: "shocks of wheat"; acyclovir: fine needles

PROTEINURIA

Etiologies of Proteinuria		
Category	**Description**	**Etiologies**
Glomerular (can be >3.5 g/d)	Disruption of filtration barrier → lose albumin	Glomerulonephritis Nephrotic syndrome
Tubulointerstitial (usually <1–2 g/d)	↓ reabsorption of freely filtered proteins → lose globulins	ATN; AIN Fanconi's syndrome
Overflow	↑ production of freely filtered proteins	Multiple myeloma Myoglobinuria
Isolated	By def'n: asx, normal renal fxn, sed, & imaging, no h/o renal disease	Functional (fever, exercise, CHF) Orthostatic (only when upright) Idiopathic (transient or persistent)

- **Urine dipstick**
  - 1+ ≈30 mg/dL, 2+ ≈100 mg/dL, 3+ ≈300 mg/dL, 4+ >2 g/dL; interpretation depends on SG; eg, 3+ in very concentrated urine might not indicate heavy proteinuria
  - Insensitive for microalbuminuria and myeloma light chains (Bence-Jones protein)
- **Spot urine:** protein (mg/dL)/creatinine (mg/dL) ≈ g/d of proteinuria (*NEJM* 1983;309:1543) unlike urine dipstick, will accurately measure myeloma light chains
  - reliable surrogate for 24-hr urine, esp. 1st morning void (*JASN* 2009;20:436); inaccurate if AKI depends on Cr production, ∴ underestimates if muscular, overestimates if cachectic
- **Moderate albuminuria** (30–300 mg/d *or* mg/L *or* mg/g Cr): early sign of glomerular vascular disease; marker for ↑ risk of CV adverse outcomes (*KI* 2013;3:19)
- Orthostatic proteinuria: typically in adolescents; ~90% of young ♂ with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously

HEMATURIA

Etiologies of Hematuria	
Extrarenal (far more common)	**Intrarenal**

Etiologies of Hematuria	
Nephrolithiasis Neoplasm: transitional cell, prostate Infxn: cystitis, urethritis, prostatitis Foley trauma BPH Schistosoma haematobium	Nephrolithiasis or crystalluria Neoplasm Trauma/exercise Vascular: renal infarcts, renal v. thromb., sickle cell Glomerular: IgA, thin BM, others PKD (*NEJM* 2008;359:1477)

- Wide, overlapping ages for various etiologies, but general guide for common causes:
  <20 y: GN, UTI, congenital; 20–60 y: UTI, nephrolithiasis, cancer
  >60 y ♂: prostatitis, cancer, UTI; >60 y ♀: UTI, cancer

Workup (*NEJM* 2021;385:153)

- **Urine dipstick:** ⊕ if ≥3 RBCs; ⊕ dipstick and ⊖ sediment → myo- or hemoglobinuria
- **Urine sediment:** dysmorphic RBCs or RBC casts → GN → consider renal bx
- If suggestive sx, r/o UTI or nephrolithiasis
- Low cancer risk: repeat U/A in 4–6 wks; if still ⊕ → cystoscopy + imaging
- Intermediate risk (eg, ♂ 40–59 yrs or ♀ 50–59 yrs or 10–30 pack-yrs): cystoscopy + U/S
- High risk (eg, age ≥60 or >30 pack-yrs): CT urography (Se 96%, Sp 98%) + cystoscopy
- Rx: if obstruction: bladder irrigation and 3-way Foley on CBI

NEPHROLITHIASIS

Types of stones and risk factors (*Nat Rev Dis Prim* 2016;2:16008)

- **Calcium** (Ca oxalate >Ca phosphate): **70–90% of kidney stones** (*NEJM* 2010;363:954)
  - Urine findings: ↑ Ca, ↑ oxalate (Ca-ox only), ↑ pH (Ca-phos only), ↓ citrate, ↓ volume
  - 2° hypercalciuria: 1° hyperparathyroidism, distal RTA, sarcoid, Li use
  - 2° hyperoxaluria: Crohn's, ileal disease w/ intact colon, gastric bypass, pancreatic insuffic.
  - Diet: ↑ animal protein, ↑ sucrose, ↑ Na, ↓ K, ↓ fluid, ↓ fruits/vegetables, ↑ vit. C, ↓ Ca
- **Uric acid:** 5–10% of kidney stones, radiolucent on plain film
  - Urine findings: ↑ uric acid, ↓ pH (eg, from chronic diarrhea)
- **Magnesium ammonium phosphate** ("struvite" or "triple phosphate")
  - Chronic upper UTI w/ urea-splitting organisms (eg, *Proteus, Klebs*) → ↑ urine NH_3, pH >7
- **Cystine:** inherited defects of tubular amino acid reabsorption

Clinical manifestations

- Hematuria (absence does not exclude diagnosis), flank pain, N/V, dysuria, frequency
- Ureteral obstruction (stones >5 mm unlikely to pass spont.) → AKI if solitary kidney
- UTI: ↑ risk of infection proximal to stone; urinalysis of distal urine may be normal

Workup

- **Non-contrast CT** 97% Se, 96% Sp (ureteral dilation w/o stone suggests recent passage); U/S (Se 57%, Sp 98%) may serve as initial test in stable patient (*NEJM* 2014;371:1100)
- Strain urine for stone to analyze; U/A & UCx; electrolytes, BUN/Cr, Ca, PO_4, PTH
- 24-h urine × 2 (>6 wk after acute setting) for Ca, PO_4, oxalate, citrate, Na, Cr, pH, K, vol.

Acute treatment (*JAMA* 2020;323:1961)

- Analgesia (narcotics ± NSAIDs; combination superior, *Ann Emerg Med* 2006;48:173), ensure adequate fluid repletion, antibiotics if UTI
- α-blocker >CCB to pass stone if ≤10 mm (*Cochrane;* 2014:CD008509, *Lancet* 2006;368:1171)
- Indications for **immediate urologic eval and/or hosp:** obstruction (esp. solitary or transplant kidney), urosepsis, intractable pain or vomiting, significant AKI
- Urologic Rx: lithotripsy (*NEJM* 2012:367:50), ureteroscopic removal, lap/perc nephrolithotomy

Chronic treatment (*CJASN* 2016;11:1305 & 2017;12:1699)

- Increase fluid intake (>2 L/d) for goal UOP 2 L/d (*J Nephrol* 2016;29:211)
- Calcium stones: 24-h urine identifies **specific urinary risk factors to treat**
  - Diet: ↓ Na and meat (*NEJM* 2002;346:77), ↓ oxalate foods & sucrose/fructose
  - Meds: thiazides (↓ urine Ca), K-citrate if low urine citrate, allopurinol if high urine uric acid
  - Avoid low dietary Ca as ↑ oxalate absorp (*NEJM* 2002;346:77), unclear role of Ca suppl.
- Uric acid: fluid intake, urine alkalinization (K-citrate) to pH 6.5–7, allopurinol
- Magnesium ammonium phosphate (struvite): antibiotics for UTI; urologic intervention; acetohydroxamic acid; urease inhibitor reserved for experienced clinician, poorly tolerated
- Cystine: fluid, urine alkaliniz (K-citrate) to 7–8, d-penicillamine, tiopronin (*KI* 2006;69:1041)

ANEMIA

↓ in RBC mass: Hct <41% or Hb <13.5 g/dL (men); Hct <36% or Hb <12 g/dL (women)

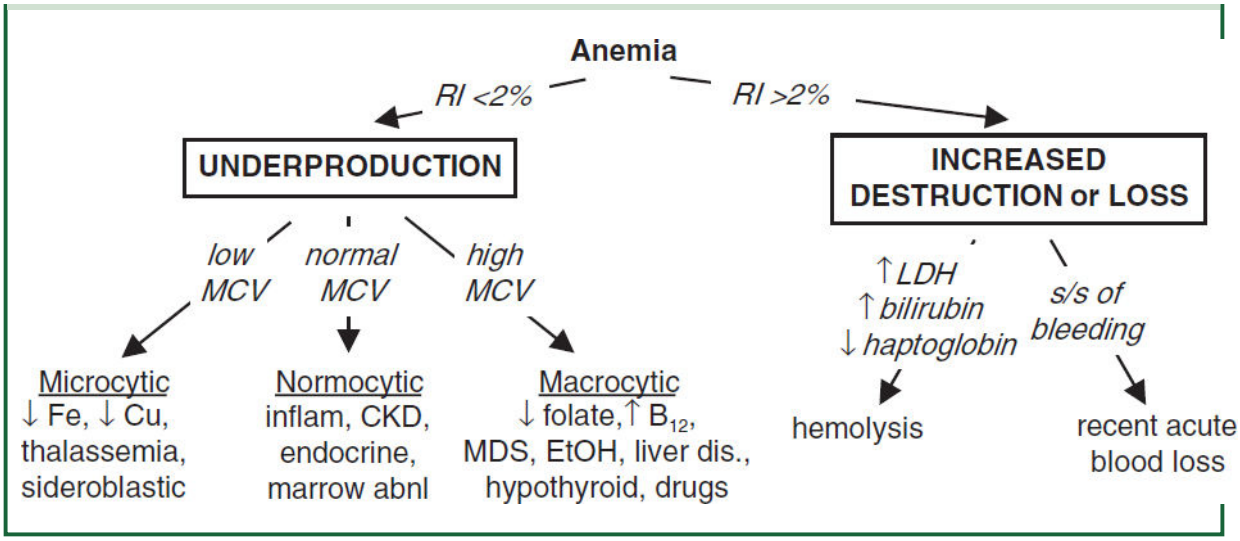
Clinical manifestations

- Symptoms: ↓ O_2 delivery → fatigue, exertional dyspnea, angina (if CAD)
- Signs: pallor (mucous membranes, palmar creases), tachycardia, orthostatic hypotension
- Other findings: **jaundice** (hemolysis), **splenomegaly** (thalassemia, neoplasm, chronic hemolysis), **petechiae/purpura** (bleeding disorder), **glossitis** (iron, folate, vitamin B_{12} defic.), **koilonychia** (iron defic.), **neurologic abnormalities** (B_{12} defic.)

Diagnostic evaluation

- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including **pica**), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- **Reticulocyte index** (RI) = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor maturation factors for a given Hct: 45% = 1, 35% = 1.5, 25% = 2, 20% = 2.5 RI >2% → adequate marrow response; RI <2% → hypoproliferation
- **Peripheral smear:** select area where roughly ⅓ RBCs touch each other; ✓ RBC size, shape, inclusions (see "Appendix" & "Peripheral Smear"), WBC morphology, plt count
- Additional labs as indicated: hemolysis labs (if RI >2%, see below), iron/TIBC, ferritin, folate, B_{12}, LFTs, BUN, & Cr, TFTs, Hb electrophoresis, enzyme/gene mutation screens
- **Bone marrow (BM) aspirate and biopsy (bx)** with cytogenetics as indicated

Figure 5-1 Approach to anemia and common causes



MICROCYTIC ANEMIAS

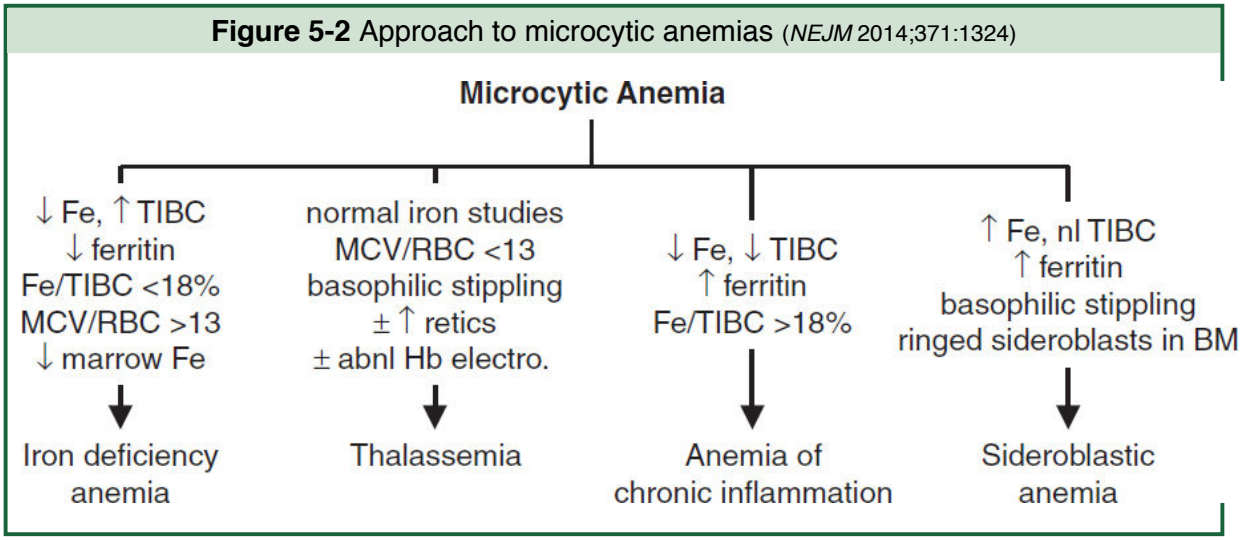


Figure 5-2 Approach to microcytic anemias (*NEJM* 2014;371:1324)

Iron deficiency (*Lancet* 2021;397:233)

- ↓ marrow iron & depleted body iron stores → ↓ heme synthesis → microcytosis → anemia
- Special clinical manifestations: angular cheilosis, atrophic glossitis, pica (consumption of nonnutritive substances such as ice, clay), koilonychia (nail spooning)
  Plummer-Vinson syndrome (iron deficiency anemia, esophageal web & atrophic glossitis)
- Etiologies: **chronic bleeding** (GI—incl. cancer, menstrual, parasites, NSAIDs, etc.), ↓ **supply** (malnutrition; ↓ absorp. due to celiac

sprue, Crohn's, ↑ gastric pH, subtotal gastrectomy), ↑ **demand** (preg; *Blood* 2017;129:940). Iron-refractory iron-defic. anemia (IRIDA; rare genetic disorder due to hepcidin dysregulation; *Nat Genet* 2008;40:569).

- Diagnosis (eval ideally before Rx): ↓ **Fe**, ↑ **TIBC**, ↓ **ferritin** (esp. <15), ↓ **transferrin sat** (Fe/TIBC; esp. <15%), ↑ soluble transferrin receptor; ↑ plt. Unless hx c/w other etiology, *initiate workup for GIB*, incl. *H. pylori* serology. ? Celiac labs (**anti-TTG**, anti-endomysial IgA Abs). Cytogenetics & molecular testing as indicated (eg, MDS, leukemia).
- Treatment: oral Fe TID (~6 wks to correct anemia; ~6 mo to replete Fe stores; nb, oral Fe does not give ⊕ Hemoccult). With severe anemia, persistent losses, prior to Epo Rx, or while inpatient, use *IV iron* (Fe-sucrose, -gluconate, -dextran).

Thalassemias (*Lancet* 2018;391:155)

- ↓ synthesis of α- or β-globin chains of Hb → ≠ subunits → destruction of RBCs and erythroid precursors; ∴ anemia from hemolysis *and* ineffective erythropoiesis
- **α-thalassemia** (*NEJM* 2014;371:1908): deletions in α-globin gene complex (nl 4 α genes), seen w/ Southeast Asian, Mediterranean, African, Middle East ancestry
  - 3 α → silent carrier; 2 α → α-thal minor = mild anemia, α-thal-1 (--/αα, milder) or
  - α-thal-2 (-α/-α); 1 α → HbH (β_4) disease = severe anemia, hemolysis, and splenomegaly
  - 0 α genes → Hb Barts (γ_4) = intrauterine hypoxia and hydrops fetalis
- β**-thalassemia:** mutations in β-globin gene → absent or ↓ gene product seen w/ Mediterranean (espec. Greek or Italian), African, or Asian ancestry
  - 1 mutated β gene → thal minor (or trait) = mild anemia (no transfusions)
  - 2 mutated β genes → thal intermedia (occasional transfusions) or thal major (= Cooley's anemia; transfusion dependent) depending on severity of mutations
- Special clinical manifestations: chipmunk facies, pathologic fractures, hepatosplenomegaly (due to extramedullary hematopoiesis), high-

output CHF, bilirubin gallstones, Fe overload
- Dx: MCV <70, **normal Fe, ferritin**, **MCV/RBC count <13** [Mentzer Index, 60% Se, 98% Sp; (*Ann Hem* 2007;86:486)], ± ↑ retics, basophilic stippling; **Hb electrophoresis:** ↑ HbA_2 ($\alpha_2\delta_2$) in β-thal; *normal* pattern in α-thal trait, ∴ PCR or supravital stain for dx
- Treatment: folate; transfusions + Fe chelator [either deferoxamine (IV) or deferasirox (PO)]; ? splenectomy if ≥50% ↑ in transfusions; gene therapy in development (*NEJM* 2018;378:1479); luspatercept (↓ SMAD signaling) in β-thal major (*NEJM* 2020;382:1219)

Anemia of chronic inflammation (see below)

Sideroblastic anemia
- Defective heme biosynthesis within RBC precursors
- Etiologies: **hereditary/X-linked** (*ALAS2* mutations), **idiopathic**, **MDS-RARS**, **reversible** (alcohol, lead, isoniazid, chloramphenicol, copper deficiency, hypothermia)
- Special clinical manifestations: hepatosplenomegaly, iron overload syndromes
- Dx: social, work, & TB hx; can be micro-, normo-, or macrocytic; variable populations of hypochromic RBCs; ↑ Fe, nl TIBC, ↑ ferritin, basophilic stippling, RBC **Pappenheimer bodies** (Fe-containing inclusions), **ring sideroblasts** (w/ iron-laden mitochondria) in BM
- Treatment: treat reversible causes; trial of pyridoxine, supportive transfusions for severe anemia with chelation therapy; high-dose pyridoxine for some hereditary cases

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NORMOCYTIC ANEMIAS

Anemia of chronic inflammation (ACI; *NEJM* 2012;366:4)
- ↓ RBC production due to impaired iron utilization and functional iron deficiency from ↑ **hepcidin;** cytokines (IL-6, TNF-α) cause ↓ Epo responsiveness/production
- Etiologies: autoimmune disorders, chronic infection, inflammation, HIV, malignancy
- Dx: ↓ **Fe**, ↓ **TIBC (usually normal or low transferrin sat)**, ± ↑ **ferritin;** usually normochromic, normocytic (~70% of cases) but

can be microcytic if prolonged
- Coexisting iron deficiency common. Dx clues include ↓ serum ferritin levels, absence of iron staining on BM bx, ⊕ response to a trial of oral iron and/or ↑ soluble transferrin receptor/ferritin index (*Am J Clin Pathol* 2012;138:642).
- Treatment: treat underlying disease ± iron and/or erythropoiesis-stimulating agent (ESA; eg, Epo). Iron if ferritin <100 or Fe/TIBC <20%. Consider ESA if Epo <500. Avoid ESA in cancer if treatment goal is cure (*Lancet* 2009;373:1532). Transfuse PRBCs only if symptomatic & insufficient time to wait for response to Epo or underlying disease Rx.

Anemias of other chronic disorders
- Anemia of CKD: ↓ Epo; treat w/ Epo & iron (see "Chronic Kidney Disease")
- Endocrine deficiencies: hypometabolism and ↓ O_2 demand with thyroid, pituitary, adrenal, or parathyroid disease → ↓ Epo; can be normocytic or macrocytic

Sideroblastic anemia (see above)

Pure red cell aplasia
- Destructive antibodies or lymphocytes → ineffective erythropoiesis
- Associated with thymoma, CLL, parvovirus infection, autoimmunity, drugs
- Diagnostic studies: **lack of erythroid precursors on BM bx**, other lines normal
- Treatment: thymectomy if thymus enlarged; IVIg if parvovirus and immunosuppressed (*Clin Infect Dis* 2013;56:968); immunosuppression/chemoRx if CLL or idiopathic; supportive care w/ PRBC transfusions; ? erythropoietin receptor agonist if due to antierythropoietin Ab (*NEJM* 2009;361:1848); consider hematopoietic cell transplantation.

MACROCYTIC ANEMIAS

includes megaloblastic and nonmegaloblastic causes

Megaloblastic anemia

- **Impaired DNA synthesis** → cytoplasm matures faster than nucleus → ineffective erythropoiesis and macrocytosis; due to **folate** or **B_{12} deficiency;** also in **MDS**
- ✓ **folate** and **vitamin B_{12};** ↑ LDH & indirect bilirubin (due to ineffective erythropoiesis)
- Smear: **neutrophil hypersegmentation, macro-ovalocytes**, anisocytosis, poikilocytosis

Folate deficiency

- Folate present in leafy green vegetables and fruit; total body stores sufficient for **2–3 mo**
- Etiologies: **malnutrition** (alcoholics, anorectics, elderly), ↓ absorption (sprue), impaired metabolism (methotrexate, pyrimethamine, trimethoprim; *NEJM* 2015;373:1649), ↑ requirement (chronic hemolytic anemia, pregnancy, malignancy, dialysis)
- Diagnosis: ↓ folate; ↓ RBC folate, ↑ homocyst. but nl methylmalonic acid (unlike B_{12} defic.)
- Treatment: folate 1–5 mg PO qd for 1–4 mo or until complete hematologic recovery; *critical to r/o B_{12} deficiency first (see below)*

Vitamin B_{12} deficiency (*NEJM* 2013;368:149)

- B_{12} present only in foods of animal origin; total body stores sufficient for **2–3 y**
- Binds to **intrinsic factor** (IF) secreted by gastric parietal cells; absorbed in terminal ileum
- Etiologies: malnutrition (alcoholics, vegans), **pernicious anemia** (PA, autoimmune disease against gastric parietal cells, a/w polyglandular endocrine insufficiency and ↑ risk of gastric carcinoma), other causes of ↓ absorption (gastrectomy, sprue, Crohn's disease), ↑ competition (intestinal bacterial overgrowth, fish tapeworm)
- Clinical manifestations: **neurologic** changes (**subacute combined degeneration**) affecting peripheral nerves, posterior & lateral columns of the spinal cord and cortex → numbness, paresthesias, ↓ vibratory & positional sense, ataxia, dementia, mood
- Dx: ↓ B_{12} (even low nl); ↑ homocysteine & methylmalonic acid; anti-IF Ab; ↑ gastrin in PA

- Treatment: 1 mg B_{12} IM qd × 7 d → q wk × 4–8 wk → q month for life
  - neurologic abnormalities are reversible if treated w/in 6 mos
  - folate can reverse *hematologic* abnormalities of B_{12} deficiency but not *neurologic* changes (and can "steal" B_{12} stores → worsening of neuro complications)
  - oral supplementation (2 mg qd) appears feasible as well (*Cochrane Rev* CD004655) even w/o IF

Nonmegaloblastic macrocytic anemias

- **Liver disease:** often macrocytic, may see target cells, or spur cell anemia w/ hemolysis
- **Alcoholism:** BM suppression & macrocytosis independent of folate/B_{12} defic. or cirrhosis
- **Other causes:** reticulocytosis; hypothyroid; MDS; meds impairing DNA synth (zidovudine, 5-FU, hydroxyurea, Ara-C); hereditary orotic aciduria; Lesch-Nyhan syndrome

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PANCYTOPENIA

Etiologies

- Hypocellular bone marrow (nl cellularity ~100 – age): **aplastic anemia**, hypoplastic MDS
- Cellular bone marrow: **MDS**, aleukemic leukemia, PNH, severe megaloblastic anemia
- Myelophthesis (marrow replacement, PMF); systemic dis. (hypersplen, sepsis, EtOH/toxin)

Clinical manifestations

- Anemia → fatigue; neutropenia → recurrent infections; thrombocytopenia → mucosal bleeding & easy bruisability

Aplastic anemia (stem cell failure) (*NEJM* 2015;373:35)

- Epidemiology: 2–5 cases/10^6/y; biphasic (major peak in adolescents, 2nd peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ hypocellularity, usually nl cytogenetics
- Etiologies: **idiopathic** (½ – ⅔ of cases)
  - **Stem cell destruction: radiation, chemotherapy, chemicals** (eg, benzene)

Med rxn (eg, chloramphenicol, NSAIDs, sulfa drugs, gold, carbamazepine, antithyroid)
Viruses (HHV-6, HIV, EBV, parvovirus B19); **post-viral hepatic failure** (not Hep A/B/C)
Immune disorders (SLE, GVHD post-HSCT, thymoma)
PNH (see below); Fanconi's anemia (congenital disorder w/ pancytopenia, macrocytic anemia, ↑ risk of MDS, AML, & SCC of head & neck, and multiple physical anomalies)
Shortened telomeres: seen w/ telomerase (*TERT, TERC*) mut. (10% of aplastic anemia), dyskeratosis congenita/DKC1 mut; a/w IPF, cirrhosis (*NEJM* 2009;361:2353)
Somatic mutations: PNH clones in ~50% of aplastic anemia (*Haematologica* 2010;95:1075)

- Treatment and prognosis
  Immunosuppression (CsA/tacrolimus, ATG): 70–80% respond, with 80–90% 5-y survival in responders (96% vs. 76% w/ horse vs. rabbit ATG; *NEJM* 2011;365:430); 15–20% 10-y incidence of clonal disorders (mostly MDS, AML, PNH)
  TPO mimetics (eg, eltrombopag): use 1st-line w/ immunosuppression (*NEJM* 2022;386:11)
  Supportive care: transfusions, abx, possible utility of G-CSF & Epo (if Epo <500)
  Allogeneic HSCT: for *young* Pts → ~80% long-term survival and significantly ↓ risk of malignant evolution, but has risk of transplant-related morbidity & mortality; if possible, avoid transfusions (risk of alloimmunization) pretransplant

Myelodysplastic syndromes (MDS) (qv)

Paroxysmal nocturnal hemoglobinuria (PNH) (*Blood* 2009;113:6522)

- Acquired clonal stem cell disorder = inactivating somatic mutation of *PIG-A* gene → deficiency of GPI-anchor for CD55 & CD59 (inhib of complement) → complement-mediated RBC lysis, plt aggregation, & hypercoagulability
- Clinical: intravascular **hemolytic anemia**, **hypercoagulability** (venous >arterial; esp. intraabdominal, cerebral), smooth muscle dystonias, **deficient hematopoiesis** (cytopenias); a/w aplastic anemia, MDS and evolution to AML

- Dx: **flow cytometry** (↓ CD55 & CD59) on RBCs and granulocytes; urine hemosiderosis
- Treatment: supportive care (iron, folate, transfusions); consider anticoagulation.
  Allogeneic HSCT for hypoplasia or severe thrombosis.
  Pegcetacoplan (binds C3, prevents complement cascade activation) superior to eculizumab (Ab inactivates terminal complement C5s) in ↓ hemolysis & stabilizing Hb levels (*NEJM* 2021;384:1028). Eculizumab effective in pregnancy (*NEJM* 2015;373:1032); must have meningococcal vaccination.

Myelophthisic anemia (see also "Primary Myelofibrosis")

- Infiltration of bone marrow by cancer (commonly metastatic solid tumors), leukemia, infection, fibrosis (primary myelofibrosis), granulomas, lysosomal storage disorders

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HEMOLYTIC ANEMIAS

Causes of Hemolytic Anemia by Mechanism (*Lancet* 2000;355:1169 & 1260)

Cause	Mechanism	Examples	Mode
Intrinsic	Enzyme deficiency	*G6PD* deficiency	**Hereditary**
	Hemoglobinopathies	Sickle cell anemia, thalassemia	
	Membrane abnormalities	Hereditary spherocytosis	
		PNH, spur cell anemia in liver disease	**Acquired**
Extrinsic	Immune-mediated	Autoimmune; drug-induced, tx rxn	
	Traumatic	MAHA; prostheses (valves, TIPS)	
	Direct infections, toxins	Malaria, babesiosis; snake & spider venoms; Wilson's; hypotonic infusions	
	Entrapment	Hypersplenism	

Diagnostic evaluation

- ↑ retic count (RI >2%), ↑ LDH, ↓ hapto (83% Se, 96% Sp), ↑ indirect bili, ✓ vit C & Cu
- Autoimmune hemolysis: Coombs' test = direct antiglobulin test (DAT) → ⊕ if agglutination occurs when antisera against Ig or C3 are applied to patient RBCs

- Location of hemolysis (many conditions can include components of both)
  Intravascular: RBC destruction in vessels (shear by mech valve, DIC, toxins); assoc. w/ hemoglobinemia, hemoglobinuria, hemosiderinuria, ↑↑ LDH, ↓ haptoglobin.
  Extravascular: more common cause. Mϕ clear damaged/opsonized RBC; splenomegaly (reticuloendothelial expansion in spleen, liver, BM, LNs); ↑ LDH ↓ hapto
- Family h/o anemia; personal or family h/o cholelithiasis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (*Lancet* 2008;371:64)

- X-linked defect of metabolism (*G6PD* mutations) w/ ↑ susceptibility to oxidative damage
- Most common in ♂ of African or Mediterranean descent (malaria-endemic areas)
- Hemolysis precipitated by **drugs** (sulfonamides, dapsone, nitrofurantoin, rasburicase, primaquine, doxorubicin, methylene blue), **infxn**, **DKA**, **foods** (favism, *NEJM* 2018;378:60)
- Diagnosis: smear may show RBC **Heinz bodies** (oxidized Hb) that result in **bite cells** once removed by spleen; ↓ G6PD levels (*may be normal after acute hemolysis* because older RBCs have already lysed and young RBCs may still have near-normal levels)

Sickle cell anemia (*NEJM* 2017;376:1561 & *Lancet* 2017;390:311)

- Recessive β-globin mutation → structurally abnl hemoglobin (HbS). ~8% African Americans heterozygotes ("sickle trait"; usually w/o sx); ~1/400 homozygotes (sickle cell disease).
- ↓ O_2 → HbS polymerizes → RBC sickles, ↓ RBC deformability → **hemolysis** & **microvascular occlusion** due to endothelial activ. & PMN adhesion (*Blood* 2013;122:3892)
- **Anemia:** chronic hemolysis ± acute aplastic (parvo. B19) or splenic sequestration crises
- **Vaso-occlusion & infarction:** acute chest syndrome & stroke (high mortality), pulmonary HTN, painful crises, splenic sequestration, renal papillary necrosis, avascular necrosis, dactylitis (hand–foot syndrome), priapism

- **Infection:** splenic infarction → overwhelming infection by **encapsulated organisms;** infarcted bone → **osteomyelitis** (*Salmonella*, *Staph. aureus*), can be life threatening
- Diagnosis: sickle-shaped RBCs and Howell-Jolly bodies on smear; Hb electrophoresis
- Treatment: hydroxyurea, folic acid; voxelotor (Hgb S polymerization inhibitor) ↓ hemolysis & ↑ Hgb (*NEJM* 2019;381:509)
- Vaccines: pneumo, meningo, H flu, HBV
- Pain & vaso-occlusive crises: analgesia (consider PCA; ask Pt what worked prev.), IVF, transfusion only if sx & *Hgb below Pt's baseline* (often low) given alloimmunization & Fe accumulation (need chelation); Ppx w/ crizanlizumab (anti-P-selectin; *NEJM* 2017;376:429)
- Acute chest (fever, ↑ WBC, pulm. infilt., r/o other causes): O_2, abx, IVF, exchange txfusion
- TIA/stroke: often exchange transfusion (goal Hgb 10) ± thrombolytics
- Gene therapy in development (*NEJM* 2021;384:205)

Hereditary spherocytosis (HS) (*Lancet* 2008;372:1411)

- Defect in cytoskeleton of RBC membrane (ankyrin, α- and β-spectrin, band 3, & pallidin)
- Most common in N. European populations (1/5000 births); ⊕ FHx (75% of Pts)
- Anemia, jaundice (mostly neonates), splenomegaly, pigmented gallstones
- Diagnosis: spherocytes on smear, ⊕ osmotic fragility test (~80% Se), ↓ eosin-5-maleimide (EMA) binding (93% Se; 99% Sp; *Haemat* 2012;97:516), acidified glycerol lysis test (Se 95%)
- Treatment: folate, transfusions, splenectomy for moderate and severe HS (balance w/ ↑ risk of future thrombosis and infection; *J Thromb Haemost* 2008;6:1289)

Paroxysmal nocturnal hemoglobinuria (see above)

Autoimmune hemolytic anemia (AIHA)

- Acquired, antibody-mediated RBC destruction
- **Warm AIHA: IgG** Abs opsonize RBCs *at body temp* → removal by spleen
  Etiologies: idiopathic, lymphoproliferative (CLL, NHL), autoimmune (SLE), drugs, HIV, babesiosis (*NEJM* 2017;376:939)

- **Cold AIHA: IgM** Ab binds to RBCs *at temp <37°C* → **complement fixation** → intravascular hemolysis and acrocyanosis on exposure to cold
  Etiologies: idiopathic, lymphoprolif. disorders (eg, Waldenström's; monoclonal), ***Mycoplasma pneumoniae*** infxn and infectious mononucleosis (polyclonal)
- Diagnosis: spherocytes on smear, ⊕ **Coombs';** ✓ cold agglutinin titer, splenomegaly
- Treatment (*Blood* 2017;129:2971): treat underlying disease
  Warm AIHA: corticosteroids ± splenectomy, IVIg, cytotoxic agents, rituximab
  Cold AIHA: avoid cold; steroids ineffective; rituximab (*Blood* 2004;103:2925); complement inhibitors (sutimlimab) approved for cold agglutinin disease (*NEJM* 2021;384:1323)

Drug-induced hemolytic anemia

- Acquired, Ab-drug mediated destruction vs. direct drug effect. Abx: ceph., sulfa drugs, rifampin, ribavirin. CV: methyldopa, procainamide, quinidine, thiazides. TCAs, phenothiazines, NSAIDs, sulfonylureas, MTX, 5-FU, rasburicase (G6PD defic.)
- Diagnosis: Coombs' usually negative, ↑ LDH; Treatment: discontinue offending agent

Microangiopathic hemolytic anemia (*MAHA; NEJM* 2014;371:654)

- Intra-arteriolar fibrin damages RBCs → acquired intravascular hemolysis
- Etiologies: **hemolytic-uremic syndrome** (**HUS**), **thrombotic thrombocytopenic purpura** (**TTP**), **disseminated intravascular coagulation** (**DIC**), malignancy, malignant HTN, eclampsia/HELLP, mech. cardiac valves, infected vascular prostheses
- Diagnosis: **schistocytes** ± ↓ plts ± ↑ PT in DIC, ↑ Cr in HUS, ↑ LFTs in HELLP
- Rx: see "DIC" section in "Coagulopathies" and "TTP/HUS" sections in "Platelet Disorders"

Hypersplenism

- Stasis/trapping in spleen → Mϕ attack/remodel RBCs → spherocytosis → hemolysis

Causes of Splenomegaly	
Etiology	**Comments***
RES hyperplasia	Hemolytic anemia, sickle cell disease, **thalassemia major**
Immune hyperplasia	Infxn [HIV, EBV, CMV, TB, **malaria**, **kala azar** ("black water fever" from visceral leishmaniasis), ***Mycobacterium avium*** complex], autoimmune disorders (SLE, RA w/ Felty's syndrome), sarcoidosis, serum sickness
Congestion	Cirrhosis, CHF, portal/splenic vein thrombosis, **schistosomiasis**
Infiltration (nonmalignant)	Lysosomal storage disorders (**Gaucher's**, Niemann-Pick), glycogen storage diseases, histiocytosis X, splenic cysts
Neoplasm	**MPN (CML, PMF, PV, ET), CMML, leukemia, lymphoma (NHL, HL, hairy cell leukemia, CLL, PLL, WM),** T-LGL, myeloma, amyloid

RES = reticuloendothelial system; *__boldface__ = causes of massive splenomegaly.

DISORDERS OF HEMOSTASIS

Clinical Characteristics of Bleeding Disorders		
Feature	**Platelet/Vascular Defect**	**Coagulation Defect**
Site	Skin, mucous membranes	Deep in soft tissues (muscles, joints)
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas
Bleeding	After minor cuts: yes After surgery: immediate, mild	After minor cuts: unusual After surgery: delayed, severe

Figure 5-3 Approach to abnormal hemostasis (*NEJM* 2014;370:847)

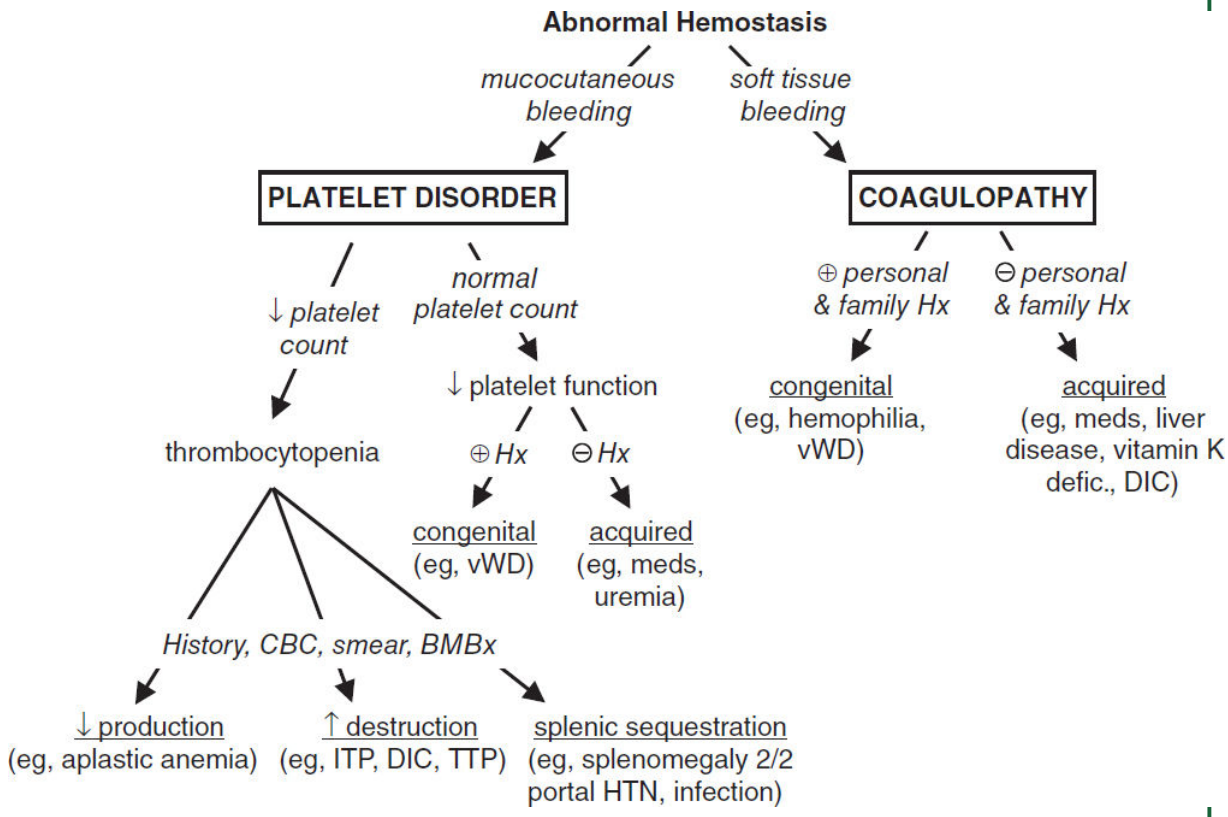
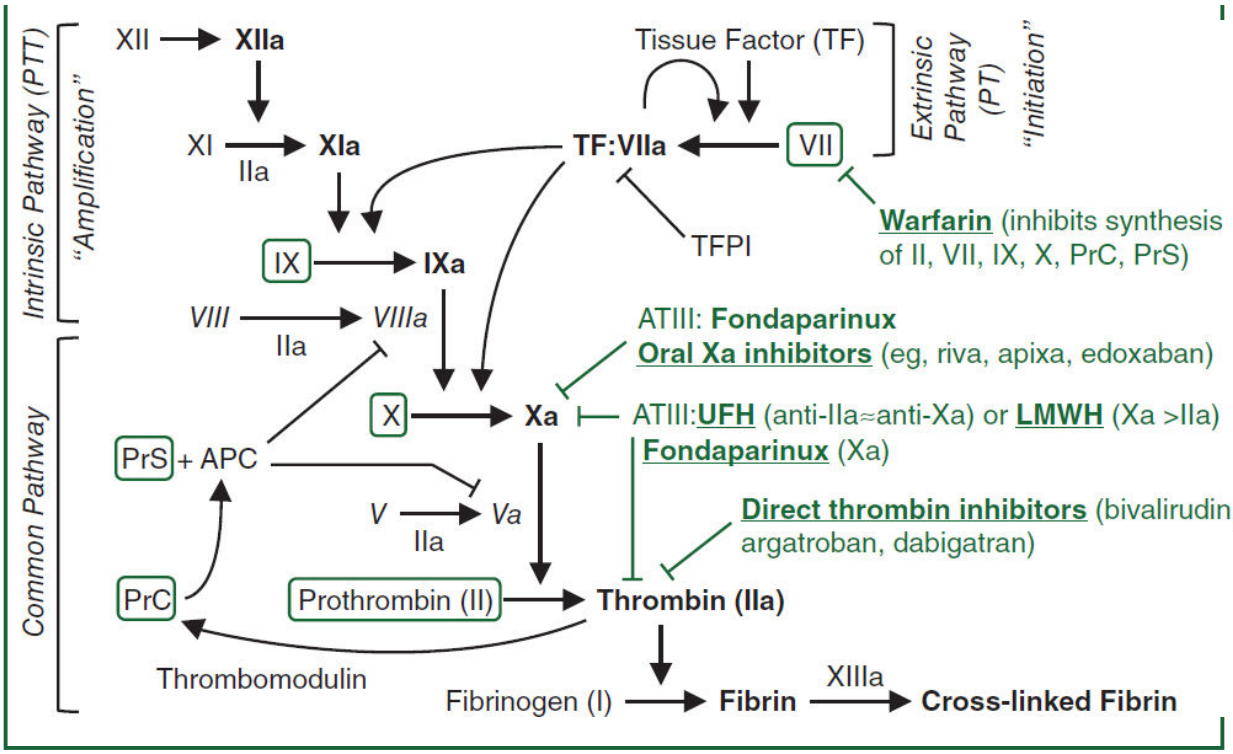


Figure 5-4 Coagulation cascade and sites of action for anticoagulants (*NEJM* 2008;359:938)



See "Coagulopathies" for reversal agents for anticoagulants. APC, activated protein C; AT, antithrombin; PrC, protein C; PrS, protein S; TF, tissue factor; TFPI, tissue factor pathway inhib.

Purpura (***nonblanching*** purple/red lesions due to extravasation of RBCs into dermis)

- **Nonpalpable** (macular; ≤3 mm in diameter = petechiae; >3 mm = ecchymoses)
  platelet disorder: thrombocytopenia, defect in platelet fxn
  thromboemboli: DIC, TTP, cholesterol or fat emboli, other thrombotic microangiopathies
  trauma or vascular fragility: amyloidosis, Ehlers-Danlos, scurvy
- **Palpable** (papular); **vasculitis:** leukocytoclastic, HSP, PAN, RMSF;
  infectious emboli: meningococcemia, bacterial endocarditis
- ***Purpura fulminans*** (aka retiform purpura): **purpura** + **hypotension** + **DIC;** typically due to infxn/sepsis, protein C or S deficiency or APS (see section on DIC)

PLATELET DISORDERS

THROMBOCYTOPENIA (Plt count <150,000/µL)

Thrombocytopenia and Risk of Bleeding	
Platelet Count (cells/µL)	**Risk**
50,000–100,000	Risk with major trauma; can proceed with general surgery
<50,000	Risk with minor trauma or surgery
<20,000	Risk of *spontaneous* bleeding (less so with ITP)
<10,000	Risk of severe, life-threatening bleeding

Etiologies

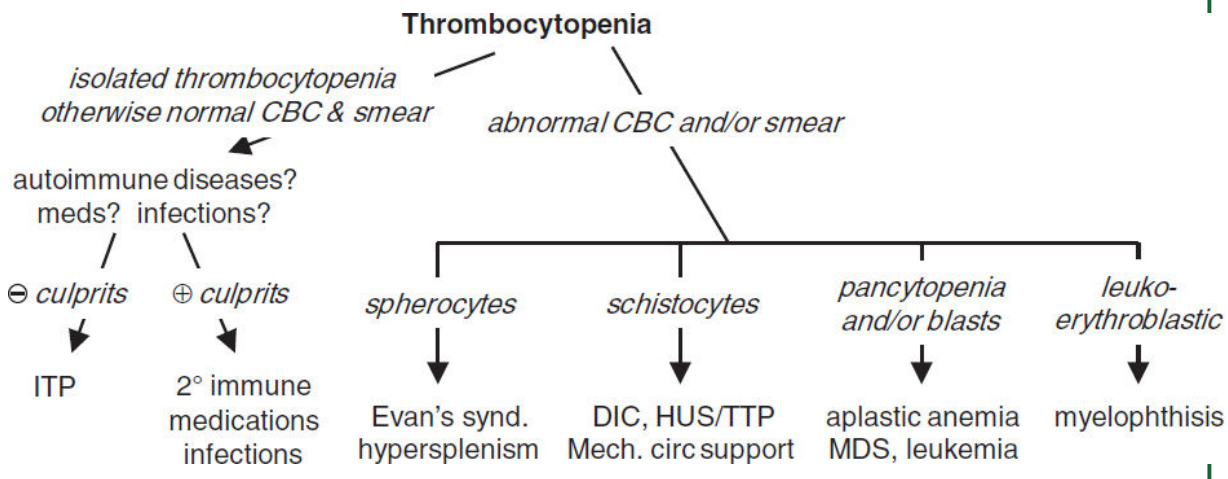
- **↓ production**
  - **Hypocellular bone marrow:** aplastic anemia (qv), rarely MDS, drugs (eg, thiazides, antibiotics, chemotherapy), alcohol, cirrhosis, viral infection
  - **Hypercellular bone marrow:** MDS, leukemia, severe megaloblastic anemia
  - **Marrow replacement:** myelofibrosis, hematologic and solid malignancies, granulomas
- **↑ destruction**
  - **Immune-mediated** (distinguish primary from secondary; *Blood* 2009;113:2386)
    - 1° (idiopathic): immune thrombocytopenic purpura (**ITP**, see below)
    - 2°: infxn (**HIV**, **HCV**, HSV), collagen vascular dis. (**SLE**), APS, lymphoprolif. (**CLL**, lymphoma), drugs (*many*, including **heparin**, abciximab, quinidine, sulfonamides, vanco), alloimmune (posttransfusion), vaccine-induced
  - **Non–immune-mediated: MAHA** (DIC, HUS, TTP), ticlopidine/clopidogrel, vasculitis, preeclampsia/HELLP, cardiopulm bypass, CVVH, IABP, cavernous hemangioma, viral
- **Abnormal distribution or pooling:** splenic sequestration, dilutional, hypothermia

- **Critical illness**: multifactorial (*Hematology Am Soc Hematol Educ Program* 2017;1:660)
- **Unknown:** ehrlichiosis/anaplasmosis, babesiosis, RMSF

Diagnostic evaluation

- H&P: meds, infxns, underlying conditions, splenomegaly, lymph nodes, **bleeding hx**
- **CBC with differential:** isolated thrombocytopenia *vs.* multilineage involvement
- **Peripheral smear** (r/o pseudothrombocytopenia due to platelet clumping)
  - ↑ destruction → look for large plts, ↑ MPV, **schistocytes** (see "Peripheral Smear" inserts)
  - ↓ production → rarely limited to platelets → look for **blasts**, hypersegmented PMNs, leukoerythroblastic Δs; can see inclusion bodies (anaplasma), parasites (*Babesia*)

Figure 5-5 Approach to thrombocytopenia



- Additional laboratory evaluations as indicated (eg, viral titers, flow cytometry, ANA, APLA)
  - if anemia: ✓ reticulocyte count, LDH, haptoglobin, bilirubin to detect hemolysis
  - if hemolytic anemia: ✓ PT, PTT, fibrinogen, D-dimer, Coombs, ANA
  - BM bx for unexplained thrombocytopenia, esp. if associated with splenomegaly

Primary immune thrombocytopenic purpura (ITP) (*Blood* 2010;115:168)

- Isolated thrombocytopenia due to immune plt *destruction* (auto-Ab to plts) & ↓ *production* (auto-Ab to megakaryocytes) without precipitant
- Clinical manifestations: insidious onset of mucocutaneous bleeding; ♀:♂ = 3:1
- *Diagnosis of exclusion (r/o 2° ITP);* no robust clinical or lab parameters, but typically:
  CBC: isolated ↓ plt (<100,000/μL); 10% have ITP + AIHA = Evans syndrome
  Peripheral smear: large platelets (not specific), r/o pseudothrombocytopenia
  BM bx: ↑ megakaryocytes, nl cellularity. Consider if other CBC or smear abnl or diagnostic uncertainty (*Blood* 2011;117:4910).
  ✓ HBSAg & anti-HBc prior to rituximab (and before IVIg, which could alter results)
- Treatment: rarely indicated if plt >50,000/μL unless bleeding, trauma/surgery, anticoag.

Treatment of Primary ITP in Adults		
Approach	**Treatment**	**Notes**
First-line or upfront therapy	**Steroids:** prednisone 0.5–2 mg/kg/d PO tapered ~4 wk, or dexamethasone 40 mg PO × 4 d	↓ Mϕ FcR & ↓ anti-plt Ab 70–90% have initial response ~20% sustained remission
	IVIg (1 g/kg/d IV × 2–3 d) *Consider if need rapid ↑ in plt in 24–48 hrs; lasts 2–6 wks*	Blocks Mϕ FcR, ↓ anti-plt Ab Interferes w/ Mϕ uptake Ab-coated plts; 80% have initial response
	Anti-Rh(D) Ig: alternative to IVIg if RBC Rh(D) ⊕; 50–75 mcg/kg/d	Ab-coated RBCs overwhelm Mϕ FcR Avoid if h/o hemolysis; *not often used*
Second-line or maint. therapy	**Romiplostim**, **el/avatrombopag**	TPO-R agonists → ↑ plt prod
	Rituximab (anti-CD20) ± dex	anti–B-cell Ab
	Splenectomy* *(less common)*	~65% long-term remission
	AZA, CYC, MMF	Immunosuppressants
	Danazol: 600 mg/d	Androgen (hirsutism) ↓ plt clearance
Chronic/ refractory	**Romiplostim** or **eltrombopag**	Allows splenectomy to be deferred
	Fostamatinib: 75–150 mg BID	Spleen tyrosine kinase (SYK) inhibitor

Treatment of Primary ITP in Adults		
	Vinca alkaloids	Good initial response, less durable
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1 g/d IV × 3 d	See above
	IVIg	See above
	Platelet transfusion	Given w/ IVIg or anti-Rh(D)

*Post-splenectomy vaccinations needed. (*Blood Adv* 2019;3:3829; *Eur J Haem* 2018;100:304)

Secondary immune thrombocytopenic purpura (2° ITP)

- Diagnosis: viral serologies (HIV, HCV, HBV, EBV), *H. pylori* Ab, ANA, pregnancy test, APLA, TSH, parvovirus, & CMV PCR. *Anti-plt Ab tests often sent but less useful.*

Heparin-Induced Thrombocytopenias (*Chest* 2012;141:e495S; *NEJM* 2015;373:252)		
Feature	**Type I** (not clin. signif)	**Type II** (clinically significant HIT)
Mechanism	Direct effect of heparin (non-immune)	Immune (Ab)-mediated IgG against plt factor 4—heparin complex
Incidence	10–20%	1–3% with UFH, 0–0.8% LMWH
Onset	After 1–4 d of heparin therapy	After 4–10 d, but can occur in <24 h if prior exposure w/in 100 d (persistent Ab). Postop highest risk. Can occur after heparin d/c.
Platelet nadir	>100,000/μL	~60,000/μL, ↓ >50%
Sequelae	None	Thrombotic events **(HITT)** in 30–50%
Management	Can continue heparin and observe	**Discontinue heparin** Alternative anticoagulation

- Treat underlying etiology
- Pathophysiology (type II): Ab binds heparin-PF4 → immune complex binds to plt → **plt activation**, further PF4 release → plt aggregates removed from circulation → **thrombocytopenia;** procoagulants released by plts and tissue factor released by endothelial cells damaged by HIT Abs → **prothrombotic state**
- Diagnosis *(need clinical + pathologic)*
  Clinical: plt <100k *or* ↓ 50% from baseline; or **venous** (DVT/PE) or **arterial** (limb ischemia, CVA, MI) thrombosis (4:1 ratio); skin necrosis; ? ↑ heparin resistance

Pathologic: ⊕ HIT Ab using PF4-heparin ELISA (≥90% Se, IgG-specific ELISA Sp 94%), may confirm w/ functional plt assay (serotonin-release) (>95% Se/Sp)

Clinical context important: HIT Ab (esp. IgM ELISA) may be ⊕ in 10–20% of Pts on UFH/LMWH (*Am J Hem* 1996;52:90), up to 50% of cardiac bypass Pts (*Circ* 1997;95:1242)

Pretest prob w/ **"4 T's" criteria** (*Blood* 2012;120:4160): ≤3 points → 99% NPV, investigate other causes; 4–5 points 22% PPV & 6–8 points 64% PPV, ✓ lab test & replace UFH

Evaluation of Suspected HIT ("4T's")			
Factor	**2 Points**	**1 Point**	**0 Points**
Thrombo-cytopenia	↓ >50% *and* nadir ≥20k	↓ 30–50% *or* nadir 10–19k	↓ <30% *or* nadir <10k
Timing	5–10 d *or* ≤1 d if heparin w/in 30 d	? 5–10 d (but not clear), >10 d *or* ≤1 d if hep w/in 30–100 d	≤4 d w/o recent hep
Thrombosis	New thromb, skin necrosis, acute rxn after IV UFH	Prog/recurrent thromb, suspect thromb or non-nec skin lesion	None
Other cause	None apparent	Possible	Definite

- Treatment of HIT (type II) (*NEJM* 2015;373:252; *Blood Adv* 2018;2:3360)
  - **Discontinue heparin** *(incl. flushes, LMWH Ppx, heparin lines).* Avoid plts (anecdotal link w/ thrombosis); if given warfarin, give vit K to reverse, prevent warfarin skin necrosis.
  - **Nonheparin anticoag** (argatroban, bivalirudin; *NEJM* 2013;368:737) *regardless of thrombosis;* start warfarin when plt >150k, overlap ≥5 d or DOAC (*Blood* 2017;130:1104)
  - ⊕ thrombosis (HITT): anticoagulate for ≥3–6 mo
  - ⊖ thrombosis (HIT): screen for DVT; unclear duration of subsequent anticoag (until plt count recovers, often ~2–3 mo if no clot); *25–50% thrombosis rate w/in 30 d*
- H/o HIT: if PF4 Ab ⊖ or SRA ⊖ (typically >100 d after dx) → may consider re-exposure to UFH (eg, for surgery); HIT recurrence low but can be seen (*Blood* 2014;123:2485)

Thrombotic microangiopathies (TMA; *NEJM* 2014;371:654; *Lancet* 2017;390:681)

- Endothelial injury → plt aggreg. & microvasc. thrombosis → ↓ plt & RBC hemolysis (MAHA)
- Dx: unexplained **thrombocytopenia** (typically <20k) + **MAHA** → *sufficient for dx* ⊕ **schistocytes** (>2–3/hpf), ⊖ Coombs, normal PT/PTT & fibrinogen ↑↑ LDH (tissue ischemia + hemolysis), ↑ indirect bili., ↓↓ haptoglobin, ↑ Cr (esp. in HUS)
  Biopsy: arterioles filled with platelet hyaline thrombi
  Ddx: DIC, vasculitis, malignant hypertension, preeclampsia/HELLP syndrome
- **Thrombotic thrombocytopenic purpura (TTP)**
  Pathophys: ↓↓ ADAMTS13 protease activity (hereditary [Upshaw Schulman Syn.] or autoAb) → vWF multimers persist on endothelial surface → plt adhesion/aggregation → thrombosis
  Clinical: **pentad** (all 5 in only ~5%) = ↓ plts + MAHA (100%) ± Δ MS (65%) ± renal failure (50%, late feature) ± fever (25%)
  PLASMIC score to discriminate TTP from other TMAs (*Lancet Haematol.* 2017;4:157)
  Rx: **urgent plasma exchange** ± glucocorticoids; FFP if delay to plasma exchange, caplacizumab (*NEJM* 2019;380:335), rituximab for 2° prevention (*Blood Adv.* 2017;1:1159),
  plt transfusions contraindic. → ↑ microvascular thromb (*J Thromb Haemost.* 2020;18:2496)
- **Hemolytic-uremic syndrome (HUS)**
  Pathophys: (1) Shiga toxin damages renal endothelial cells → intrarenal thrombi; *or* (2) complement dysregulation (hereditary or acquired), so-called "atypical HUS"
  Clinical: **triad** = thrombocytopenia + MAHA + renal failure (bloody diarrhea if Shiga)
  Rx: supportive care; eculizumab (*J Nephrol* 2017;30:127); plasma exchange if CNS sx
- **Drug-induced TMA** (clinically similar to TTP; *Blood* 2017;129:2857)
  Immune-mediated (Ab reacts w/ plts & endothelial cells): eg, quinine, gemcitabine?
  Direct toxicity mediated: eg, gemcitabine, mitomycin, tacrolimus, CsA, bevacizumab

Disseminated intravascular coagulation (DIC): see "Coagulopathies"

DISORDERS OF PLATELET FUNCTION

Mechanisms and Etiologies of Platelet Function Abnormalities		
Function	**Inherited**	**Acquired**
Adhesion	Bernard-Soulier; vWD	Uremia; acquired vWD
Aggregation	Afibrinogenemia Glanzmann's thrombasthenia	$P2Y_{12}$ inhibitors, GP IIb/IIIa inhibitors Dysproteinemias (myeloma)
Granule release	Chediak-Higashi syndrome Hermansky-Pudlak syndrome	Drugs (ASA, NSAIDs); liver disease; MPN; cardiopulmonary bypass

Tests of platelet function

- Platelet aggregation tests: measure aggregation in response to agonists (eg, ADP)

von Willebrand's disease (vWD) (*NEJM* 2016;375:2067)

- von Willebrand's factor (vWF) function = platelet glue & plasma carrier of factor VIII
- vWD most common inherited bleeding disorder; ~85% (type 1) have partial quantitative vWF defic., ~15% (type 2) qualitative defic., <1% (type 3) total/near-total absence of vWF
- Acquired vWD: a/w many disorders (malig, MPN w/ ↑ plt count; autoimmune; hypo-thyroidism; drugs) and caused by different mechanisms (anti-vWF Abs, ↑ clearance, ↓ synthesis); Heyde's syndrome = vWF destruction by severe AS, a/w GI AVMs/bleed
- Diagnosis: ↓ **vWF:Ag**, ↓ **vWF activity** (measured by ristocetin cofactor assay), ↓ **factor VIII**, ± ↑ PTT, ± ↓ platelets; confirm with **vWF multimer analysis**
- Clinical condition, factor VIII levels and ristocetin cofactor assay useful to guide Rx decision
- Rx: **desmopressin** (dDAVP, IV/IN; tachyphylaxis) → ↑ endothelial cell release of vWF; efficacy depends on type (avoid in type 2), ∴ ✓ response before use w/ bleeding or procedures; **vWF replacement:** cryo, vWF-rich factor VIII concentrates, recomb. vWF

Uremic bleeding

- Uremia → platelet dysfunction including ↓ aggregation, impaired adhesiveness

- Treatment: **dDAVP**, cryoprecipitate, correct anemia (improves plt aggregation and adhesion by increasing plt interactions with endothelium), consider holding anti-plt agents

COAGULOPATHIES

Screening Test Abnormalities in Inherited and Acquired Coagulopathies				
PT	**PTT**	**Factors**	**Inherited**	**Acquired**
↑	↔	VII	FVII defic.	**Vit. K defic.; liver dis.;** factor inhib.
↔	↑	VIII or IX	Hemophilias, vWD	**Antiphospholipid Ab;** factor inhib.
↑	↑	I, II, V, or X	Fbgn, FII or FV defic.	**DIC; liver dis.;** factor inhib.

Further coagulation tests (*JAMA* 2016;316:2146)

- Mixing study: useful if ↑ PT or PTT; mix Pt's plasma 1:1 w/ normal plasma and retest
  PT/PTT normalizes → factor **deficiency;** PT/PTT remains elevated → factor **inhibitor**
- Coagulation factor levels: useful if mixing study suggests factor deficiency
  DIC → all factors consumed; ∴ ↓ factors V and VIII
  Liver disease → ↓ all factors *except* VIII; ∴↓ factor V, normal factor VIII
  Vitamin K deficiency → ↓ factors II, VII, IX, X (and protein C, S); ∴ normal V and VIII
- **DIC screen:** ↓ fibrinogen (consumed), fibrin degradation products (FDPs, ⊕ from intense fibrinolysis), ↑ D-dimer (more specific FDP test that detects degradation of X-linked fibrin)

Hemophilias (*Lancet* 2016;388:187)

- X-linked recessive **factor VIII** (hemophilia A) or **factor IX** (hemophilia B) **deficiency**
- Classification: mild (5–25% normal factor activity), moderate (1–5%), or severe (<1%)
- Clinical manifestations: hematomas, hemarthroses, bruising, bleeding (mucosal, GI, GU)
- Diagnosis: ↑ PTT (normalizes w/mixing study), normal PT & vWF, ↓ factor VIII or IX
- Prophylaxis indicated if <1% activity of factor VIII or IX

- Rx: purified/recomb. factor VIII or IX; desmopressin (mild disease); anti-fibrinolytics (aminocaproic acid; tranexamic acid); cryo (FVIII); emicizumab (bridges factor IX and X), effective for hemophilia A w/ and w/o inhibitors (*NEJM* 2017;377:809 & 2018;379:811)

Coagulation factor inhibitors (anti-factor antibodies; anti-factor VIII most common)

- Etiologies: hemophilia; postpartum; lymphoproliferative & autoimmune disorders; cancers
- Diagnosis: ↑ PTT (does *not* normalize w/ mixing study); Bethesda assay quantitates titer
- Rx: if high titer → **recomb. factor VIIa**, porcine factor concentrates, activated prothrombin complex; for others → high-purity human factor, plasmapheresis, immunosuppression

Disseminated intravascular coagulation (DIC) (*NEJM* 2014;370:847)

- Etiologies: trauma, shock, infection, malignancy (esp. APL), obstetric complications
- Pathogenesis: *massive* activation of coagulation that overwhelms control mechanisms
  - **Thrombosis** in microvasculature → ischemia + microangiopathic hemolytic anemia
  - Acute consumption of coagulation factors and platelets → **bleeding**
  - Chronic DIC → able to compensate by ↑ factors and platelets → **thrombosis**
- Diagnosis: ↑ PT, ↑ PTT, ↓ **fibrinogen** (may be *nl* b/c acute phase), ⊕ **FDP/D-dimer**, ↓ plts, ⊕ schistos, ↑ LDH, ↓ hapto; *chronic* DIC: ⊕ FDP/D-dimer, variable plts, other labs nl
- Treatment: Rx underlying process; support w/ **FFP**, **cryo** (goal fbgn >100 mg/dL) & **plts**

Vitamin K deficiency

- Etiologies: malnutrition, ↓ absorption (antibiotic suppression of vitamin K-producing intestinal flora or malabsorption), liver disease (↓ stores), warfarin

Properties and Antidotes for Anticoagulants & Fibrinolytics (*Circ* 2016;134:248)

Properties and Antidotes for Anticoagulants & Fibrinolytics (*Circ* 2016;134:248)			
Anticoag.	**$t_{1/2}$**	**Labs**	**Rx for O/D w/ Serious Bleeding** (+ d/c anticoag)
UFH	60–90′, RES	↑ PTT	**Protamine** IV 1 mg/100 U UFH (max 50 mg). For infusions, dose to reverse 2× UFH given per h.
LMWH	2–7°, K	anti-Xa*	Protamine reverses ~60%. 1 mg per 1 mg enox.
Bivalirudin	25′, K	↑ PTT	Dialysis
Argatroban	45′, L	↑ PTT	? Dialysis
Warfarin	36°, L	↑ PT	*No bleeding:* vit K 2.5 mg PO if INR >9, o/w no e/o clinical benefit (*Blood Adv* 2019;3:789) *Bleeding:* **vit. K** 10 mg IV + either 4F-PCC (KCentra, 25, 35, or 50 U/kg for INR 2–4, 4–6, or >6) or **FFP** 2–4 U IV q6–8h (slower, more volume)
Fibrinolytic	20′, LK	↓ fbgn	**Cryo**, **FFP**, ± tranexamic or aminocaproic acid
Rivaroxaban Apixaban Edoxaban	8–12°, K >L	↑ PT* anti-Xa*	Andexanet alfa (factor Xa decoy receptor): 800 mg bolus (30 mg/min) → 8 mg/min infusion (½ of above if taking ½ dose DOAC or ≥8 hrs since last dose; *NEJM* 2019;380:1326); 4F-PCC if andexanet not available
Dabigatran	~12°, K	↑ PTT*	Idarucizumab: mAb binds drug (*NEJM* 2017;377:431)

*Routine monitoring not performed. Mode of excretion: K, kidney; L, liver; RES, reticuloendothelial system. 4F-PCC: prothrombin complex concentrate (FII, VII, IX, X; Protein C & S). Anti-fibrinolytics: tranexamic, aminocaproic acid.

HYPERCOAGULABLE STATES

Suspect in Pts with venous or arterial thrombosis at young age or unusual locations, recurrent thromboses or pregnancy loss, or ⊕ FHx

Inherited Hypercoagulable States			
Risk Factor	**Prevalence**	**VTE***	**Comments**
Factor V Leiden	3–7%	2.65	Activated protein C (APC) resistance
Prothrombin mutation	2%	1.45	G20210A → ↑ prothrombin level
Hyperhomocysteinemia	5–10%	_	Inherited or acquired (vitamin defic., hypothyroid, renal insufficiency)
Protein C deficiency	0.02–0.05%	2.8	Warfarin-induced skin necrosis risk
Protein S deficiency	0.01–1%	2.8	
Antithrombin III def.	0.04%	2.8	May be heparin resistant

*Relative risk of **recurrent** VTE compared to patient w/o respective thrombophilia (*JAMA* 2009;301:2472)

Vascular Beds Affected by Inherited and Acquired Hypercoagulable States		
	Venous	**Venous and Arterial**
Inher.	**Factor V Leiden** Prothrombin mutation ↓ protein C, S or AT III	Hyperhomocysteinemia (inherited or acquired) Dysfibrinogenemia
Acquired	Stasis: immobilization, surgery, CHF Malignancy Hormonal: OCPs, HRT, tamoxifen, pregnancy Nephrotic syndrome	Platelet defects: myeloproliferative disorders, HIT, PNH (although venous >arterial) Hyperviscosity: polycythemia vera, Waldenström's -macroglobulinemia, sickle cell, acute leukemia Vessel wall defects: vasculitis, trauma, foreign bodies Others: **antiphospholipid syndrome,** IBD

Diagnostic evaluation (not routinely required for initial VTE; *NEJM* 2017;377:1177)

- APC resistance screen; prothrombin PCR test; functional assays for proteins C and S, ATIII; homocysteine level; factor VIII levels;

anticardiolipin and lupus anticoagulant Ab. Also consider nephrotic syndrome, PNH (esp. if mesenteric thrombus).
- Consider *JAK2* mutation testing if suspect MPN or splanchnic thrombosis
- Proteins C & S and ATIII levels unreliable during acute thrombosis and anticoagulation ∴ levels best assessed ≥2 wk after completing anticoagulation course
- Age-appropriate malignancy screening (occult cancer in ~4% of initial unprovoked VTE; no benefit of routine abd/pelvis CT; *NEJM* 2015;373:697)

Treatment
- Asx w/ inherited risk factor: consider prophylactic anticoag. if develops acquired risk factor
- Thrombosis w/ inherited risk factor: see "Venous Thromboembolism"

Antiphospholipid syndrome (APS) (*NEJM* 2018;398:2010)
- Definition: dx requires ≥1 clinical & ≥1 laboratory criteria
  - Clinical: **thrombosis** (any) or **complication of pregnancy** (≥3 spont. abortions before 10 wk or ≥1 fetal loss after 10 wk or premature birth before 34 wk)
  - Laboratory: ⊕ lupus anticoagulant (LA), or ⊕ **moderate–high titer** anticardiolipin (ACL), or ⊕ β_2-glycoprotein-I (β_2-GP-I) Ab, on ≥2 occasions, at least 12 wk apart
- Features: **DVT/PE/CVA**, **recurrent fetal loss**, ↓ plts, hemolytic anemia, livedo reticularis
- "**Catastrophic APS**": ≥3 organ systems in <1 wk w/ ⊕ APLA & tissue microthrombi; 44% mortality (*Arth Rheum* 2006;54:2568); Rx w/ plasmapheresis, rituximab
- **Antiphospholipid antibodies (APLA)**
  - ✓ *if: SLE, age <40 y & arterial thromb, recurrent venous thromb, spontaneous abortion*
  - ACL: Ab against cardiolipin, a mitochondrial phospholipid; IgG more specific than IgM
  - LA: Ab that prolongs phospholipid-dependent coagulation reactions; ∴ ↑ **PTT** that does *not* correct with mixing study but does correct with excess phospholipids or platelets; PT not affected b/c the reaction contains much more phospholipid

β_2-GP-I: Ab against β_2-glycoprotein-I, IgG or IgM (uncertain role of Abs in pathogenesis)

False ⊕ VDRL nontreponemal test for syphilis (cardiolipin is part of Ag complex)

Risk of thromboembolic phenomena may increase with titer of APLs

- Etiologies: primary (idiopathic) or secondary due to **autoimmune syndromes** (eg, SLE), **malignancy**, **infections**, drug reactions
- Treatment: UFH/LMWH → warfarin (lifelong for most Pts)

Rivaroxaban inferior to warfarin in triple positive (⊕ ACL, LA, & β_2-GP) (*Blood* 2018;132:1365)

Initial *venous thrombosis:* INR 2–3 (*NEJM* 2003;349:1133; *J Thromb Haemost* 2005;3:848)

Initial *arterial thrombosis:* typically INR 2–3 + ASA 81 mg/d

Recurrent thrombosis on warfarin: consider INR 3–4 vs. LMWH or fondaparinux

DISORDERS OF LEUKOCYTES

Neutrophilia (>7500–10,000/μL)	
Infection	Usually bacterial; ± toxic granulations, Döhle bodies
Inflammation	Burn, tissue necrosis, MI, PE, collagen vascular disease
Drugs and toxins	Corticosteroids, β-agonists, lithium, G-CSF; cigarette smoking
Stress	Release of endogenous glucocorticoids and catecholamines
Marrow stimulation	Hemolytic anemia, immune thrombocytopenia
Asplenia	Surgical, acquired (sickle cell), congenital (dextrocardia)
Neoplasm	Can be 1° (MPN) or paraneoplastic (eg, carcinomas of lung, GI)
Leukemoid reaction	>50,000/μL + left shift, not due to leukemia; unlike CML, ↑ LAP

Neutropenia (<1000/μL)	
Congenital	Myelokathexis, Shwachman-Diamond-Oski, Chédiak-Higashi, retic dysgen., WHIM syndrome, cyclic neutropenia, monoMAC syndrome (↓ monos, NKs)
Infection	Viral (CMV, EBV, HIV); bacterial (*Brucella*, *Rickettsia*, TB); malaria
Nutritional	Vitamin B_{12} or copper deficiency
Drugs and toxins	Chemotherapeutics, clozapine, methimazole, TMP-SMX, NSAIDs, sulfasalazine, phenytoin (*Am J Hem* 2009;84:428), alcohol
Neoplasm	MDS, leukemia (AML, ALL, hairy cell, LGL, others)

Monocytosis (>500/μL)	
Infection	Usually TB, SBE, *Listeria*, *Brucella*, *Rickettsia*, fungi, parasites, syphilis
Inflammation	IBD, sarcoidosis, collagen vascular diseases
Stress	MI, splenectomy, exercise (*Cytokine* 2013;61:364)
Neoplasm	Hodgkin lymphoma, leukemias, MPNs, carcinomas

Eosinophilia (>500/μL)	
Infection	Usually parasitic (helminths)
Allergic	Drugs; asthma, hay fever, eczema; ABPA
Collagen vasc dis.	RA, EGPA (Churg-Strauss), eosinophilic fasciitis, PAN
Endocrine	Adrenal insufficiency

Eosinophilia (>500/μL)	
Neoplasm	HL, CML, mycosis fungoides, carcinomas, systemic mastocytosis
Atheroembolic dis.	Cholesterol emboli syndrome
Hypereosinophilic syndrome	Multiorgan involvement incl. heart & CNS, a/w FIP1L1-PDGFRA fusion (*NEJM* 2003;348:1201); often steroid resistant

Basophilia (>200/μL)	
Neoplasm	MPN, CML, AML, Hodgkin lymph.
Infection	TB, smallpox, parasites
Alteration in BM or reticuloendothelial compartment	Hemolytic anemia, splenectomy
Inflammation or allergy	IBD, chronic airway inflammation

Lymphocytosis (>4000–5000/μL)	
Infection	Usually viral; "atypical lymphocytes" with mononucleosis syndromes Other: pertussis, toxoplasmosis
Hypersensitivity	Drug-induced, serum sickness
Autoimmune	Rheumatoid arthritis (large granular lymphocytes), malignant thymoma
Neoplasm	Leukemia (eg, CLL, hairy cell, LGL), lymphoma (eg, mantle cell, folic.)

Lymphadenopathy	
Viral	HIV, EBV, CMV, HSV, VZV, hepatitis, measles, rubella
Bacterial	Generalized (brucellosis, leptospirosis, TB, atypical mycobacteria, syphilis) Localized (streptococci, staphylococci, cat-scratch disease, tularemia)
Fungal/parasitic	Histo, coccidio, paracoccidioidomycosis, toxoplasmosis
Immunologic	Collagen vascular disease, drugs (eg, phenytoin), serum sickness, histiocytosis X, Castleman's and Kawasaki disease
Neoplasm	Lymphoma, leukemia, amyloidosis, metastatic carcinoma
Other	Sarcoidosis; lipid storage diseases
Factors that favor biopsy	Pt >40 y, >2 cm, location (supraclavicular always abnl), duration >1 mo Consistency (hard *vs.* rubbery *vs.* soft) & tenderness are not reliable Exicisional biopsy preferred over fine needle aspiration (FNA)

TRANSFUSION THERAPY

Blood Products and Indications (*Lancet* 2013;381:1845)	
Packed red blood cells (PRBCs)	For acute blood loss or to ↑ O_2-carrying capacity if end organ ischemia. 1 U PRBC → ↑ Hb by ~1 g/dL. Hb goal >7 g/dL adequate for UGIB & critically ill (*NEJM* 2013;368:11 & 2014;371:1381), ≥8 in acute MI and peri-cardiac surgery (*NEJM* 2018;379;1224; *JAMA* 2021;325:552).
Platelets (plts) (*Annals Int Med* 2015;162:205)	For plts <10k (*NEJM* 2010;362:600) due to chemo/abx. If <20k or if <50k w/ active bleeding. Variable pre-procedure.100k for neurosurgery. 1 U → ↑ plt ~30–60k. Single donor plt apheresis ↓ alloimmunization. *Contraindic:* TTP/HUS, HELLP, HIT. *Refractory* if ↑ <5k 30–60′ post-plts. Suggests consumption such as ITP, DIC, or alloimmunization → trial ABO-matched plts & give more. If still refractory ✓ panel reactive Abs to assess utility of HLA-matched plts.
Fresh frozen plasma (FFP)	Contains all coagulation factors. For bleeding due to defic. of multiple coag factors (eg, DIC, TTP/HUS, liver disease, dilution). Nb, reverse warfarin w/ Kcentra = 4 factor PCC (*JACC* 2020;76:594).
Cryoprecipitate	Enriched for fibrinogen, vWF, VIII, and XIII. 1st line for fibrinogen <100 mg/dL. For bleeding in vWD factor XIII deficiency, use if other products not available.
Irradiated	Prevents donor T-cell engraftment and risk of transfusion-assoc. GVHD (HSCT, heme malignancy, congenital immunodeficiency).
CMV-negative	From CMV-negative donors. For CMV-seronegative pregnant women, transplant candidates/recipients, SCID, AIDS Pts.
Leuko- reduced	WBCs cause HLA alloimmunization & fever (cytokines) and carry CMV. For chronically transfused Pts, potential Tx recip., h/o febrile nonhemolytic transfusion rxn, cases in which CMV-neg products desired but unavailable.
IV immune globulin (IVIg)	Polyvalent IgG from >1000 donors. For postexposure prophylaxis (eg, HAV), certain autoimmune disorders (eg, ITP, Guillain-Barré, MG, CIDP), congenital or acquired hypogammaglobulinemia (CVID, CLL).
Therapeutic apheresis	Removes plasma large molec wt subst. (eg, cryoglobulinemia, Goodpasture's, Guillain-Barré, hyperviscosity syndrome), or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis) from plasma. TTP: replace ADAMTS13. RBC exchange for SCD acute chest or stroke.

Blood Products and Indications (*Lancet* 2013;381:1845)			
Massive transfusion	Large-vol. PRBC → ↓ Ca, ↑ K, ↓ plt, ↑ coags; initial ratio of 1 PRBC: 1 plt:1 FFP accepted but controversial, follow labs (*JAMA Surg* 2017;152:574).		
Transfusion Complications (*NEJM* 2017;377:1261)			
Noninfectious	**Risk (per unit)**	**Infectious**	**Risk (per unit)**
Febrile	1:100	CMV	Common
Allergic	1:100	Hepatitis B	1:220,000
Delayed hemolytic	1:50–75,000	Hepatitis C	1:1,600,000
Acute hemolytic	1:200,000	HIV	1:1,800,000
Febr. non-hemolytic	1:200	Bacteria (PRBCs)	1:500,000
TRALI	1:5000	Bacteria (platelets)	1:12,000

Transfusion reactions

- Reason why blood products (unless massive txfusion) run 1 at a time. For all rxns (except minor allergic): **stop txfusion;** send remaining blood product + fresh blood draw to blood bank.
- **Acute hemolytic:** fever, HoTN, flank pain, AKI w/in 24 h. Due to ABO incompatibility → preformed Abs vs. donor RBCs. Rx: IVF, ↑ UOP w/ diuretics, mannitol, or dopamine.
- **Delayed hemolytic:** generally less severe than acute hemolytic; 5–7 d after transfusion, but can be severe → hyperhemolysis. Due to undetected allo-Abs vs. minor antigens → anamnestic response. Rx usually not required; dx important for future transfusion.
- **Febrile nonhemolytic:** fever, rigors 0–6 h post transfusion. Due to Abs vs. donor WBCs and cytokines in blood product. Rx: acetaminophen ± meperidine; r/o infection, hemolysis.
- **Allergic:** urticaria; rarely, **anaphylaxis** due to rxn to txfused proteins, especially in IgA-deficient Pts w/ anti-IgA Abs (use washed products). Rx: urticaria → diphenhydramine; anaphylaxis → epinephrine ± steroids. Washed products ↓ rxns in chronic txfusions.
- **Transfusion-associated circulatory overload** (TACO): ↑ volume → pulm. edema, ↑ BP. Rx: slow transfusion rate, diuretics, O_2, ± nitrates, ± positive pressure ventilation.
- **Transfusion-related acute lung injury** (TRALI): non-cardiogenic pulm. edema due to donor allo-Abs (from multiparous ♀ plasma) binding recipient WBCs, which then aggregate in pulmonary

vasculature and release mediators causing ↑ capillary permeability. Rx: see “ARDS.” No longer seen in US as plasma only from ♁ donors.

MYELODYSPLASTIC SYNDROMES (MDS)

Myeloid neoplasm overview (*Blood* 2016;127:2391)

- Categories based on clinical features, morphology, immunophenotyping, and genetics

WHO 2016 Classification of Myeloid Neoplasms & Acute Leukemia	
Acute myeloid leukemia	Clonal myeloid stem cell (SC) disorder w/ ≥20% blasts
Myelodysplastic syndromes	Dysplastic clonal myeloid SC disorder → cytopenias; <20% blasts, risk of leukemic transformation
Myeloproliferative neoplasms	Nondysplastic multipotent myeloid SC clonal expansion
MDS/MPN neoplasms	Features of MDS & MPN (eg, CMML, atypical CML)
Myeloid/lymphoid malig. w/ eos & rearrangements of *PDGFR* or *FGFR*1 or w/ *PCM*1-*JAK2*	May be responsive to TKI therapy (eg, imatinib) for *PDGFR* rearrangement
Mastocytosis	Clonal mast cell disorder, assoc w/ *KIT* mutations
Myeloid neoplasms w/ germ line predisposition	MDS, MDS/MPN, acute leukemias in background of predisposing germline mutations (eg, *DDX41*)

Myelodysplastic syndromes (MDS) overview (*Lancet* 2014;383:2239)

- Acquired clonal stem cell disorder → ineffective hematopoiesis → **cytopenias**, **dysmorphic blood cells and precursors**, variable risk of **leukemic transformation**
- Epidemiology: 20–30,000 cases/y; median age ~70 y; male predominance (1.8×)
- **Idiopathic** or 2° to chemo w/ **alkylating agents;** ↑ risk w/ radiation, benzene
- Clinical manifestations: **anemia** (85%), neutropenia (50%), thrombocytopenia (40–65%)
- Diagnosis: dysplasia (usually multilineage) in peripheral smear (oval macrocytes, **pseudo-Pelger-Huët anomaly**) and bone marrow (≥10% dysplasia with blasts ± RS)

- Both **cytogenetic** [eg, del(5q), mono 7, del(7q), trisomy 8, del(20q)] and **molecular** abnl (***TP53***, *EZH2*, *ETV6*, *RUNX1*, *ASXL1*, *SF3B1*, *DNMT3A*) may carry prognostic signif
- Prior to dx MDS: exclude AML (≥20% blasts) and CMML (monos >1 × 10^9/L); r/o 2° BM Δs (defic. of B_{12}, folate, copper); viral infxn (eg, HIV); EtOH; lead, arsenic exposures

WHO 2016 Classification Systems for MDS (*Blood* 2016;127:2391)

Classification	WHO 2008	Features
MDS w/ single lineage dysplasia (MDS-SLD)	RCUD (RA/RN/RT)	1 dysplastic lineage, 1–2 cytopenias, <15% RS*, <5% BM/ <1% PB blasts, no Auer rods
MDS w/ multilineage dysplasia (MDS-MLD)	RCMD	2–3 dysplastic lineages, 1–3 cytopenias, <15% RS*, <5% BM/ <1% PB blasts, no Auer rods
MDS w/ ring sideroblast (MDS-RS)	RARS	≥15% RS or ≥5% RS if *SF3B*1 mut. is present, <5% BM/<1% PB blasts, no Auer rods
MDS w/ isolated del(5q)	Del(5q)	Del(5q) alone or w/ 1 abnl except –7 or del(7q)
MDS w/ excess blasts (MDS-EB)	RAEB-1 RAEB-2	EB-1: 5–9% BM/2–4% PB blasts, no Auer rods EB-2: 10–19% BM/5–19% PB blasts or Auer rods
MDS, unclassifiable (MDS-U)	MDS-U	w/ 1% PB blasts, single lineage dysplasia & pancytopenia, or defining cytogenetic alteration

Certain cytogenetics [eg, t(15;17), t(8;21), inv16, t(16;16), or *MLL* rearrangement] classified as AML, regardless of BM blast count. BM, bone marrow; PB, peripheral blood; RS, ring sideroblast. * <5% RS if *SF3B*1 mutation.

- Rx (*Am J Hematol* 2012;87:692): intensity based on IPSS-R (qv), age, performance status (PS)
  - Poor PS, any risk → supportive care (transfusions, G-CSF, Epo, TPO-mimetic, abx prn)
  - Very low/low risk (IPSS-R) → ESA if Epo <500; lenalidomide (esp. for 5q synd.; *Blood* 2011;118:3765); luspatercept (MDS-RS). TPO-mimetic agents, transfusions.
  - Interm/high risk (IPSS-R) → **allogeneic HSCT** if medically fit, **DNA methyltransferase inh** azacitadine or decitabine (*Lancet Oncol* 2009;10:223) or oral decitabine/cedazuridine

Hypoplastic MDS (rare) → consider **immunosuppression** (CsA, ATG), HSCT

- Prognosis: mutations in *TP53*, *ASXL1, EZH2, RUNX1, ETV6* (*NEJM* 2011; 364:2496) ↓ survival

Revised International Prognostic Scoring System (IPSS-R) (*Blood* 2012;120:2454)							
Variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very good	-	Good	-	Intermed	Poor	Very poor
BM blasts (%)	≤2	-	>2 to <5	-	5–10	>10	-
Hb (g/dL)	≥10	-	8 to <10	<8	-	-	-
Plt (k)	≥100	50 to <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

Total score	**≤1.5**	**>1.5 to 3**	**>3 to 4.5**	**>4.5 to 6**	**>6**
Category	Very low	Low	Intermed	High	Very high
Median survival (y)	8.8	5.3	3.0	1.6	0.8

MYELOPROLIFERATIVE NEOPLASMS (MPN)

General (*NEJM* 2017;376:2168)

- Results from clonal expansion of multipotent hematopoietic stem cell
- Categories of MPN: **polycythemia vera** (PV); **essential thrombocythemia** (ET); **primary myelofibrosis** (PMF); chronic myelogenous leukemia (CML; *BCR-ABL1* ⊕); atypical CML (aCML); chronic neutrophilic leukemia (CNL); systemic mastocytosis; chronic eosinophilic leukemia; MPN-NOS/unclassifiable
- MDS/MPN neoplasms: proliferative and dysplastic features
- Mutations useful as clonal markers & dx tools:
  - Gain of fxn mutations in ***JAK2*** V617F (Janus kinase) frequently present (PV ~95%, ET ~50%, PMF ~50%; *NEJM* 2005;352:1779)
  - ***BCR-ABL1*** fusion in **all** cases of CML; ***SETBP1*** in aCML
  - ***CALR*** exon 9 mutation, type I and II (most MPNs w/o *JAK2* or *MPL* mutation, including ~25% of ET, ~35% of myelofibrosis Pts; *NEJM* 2013;369:2379 & 2391)
  - Type I has better prognosis.
  - ***MPL***, ***TET2, & ASXL1*** mutation w/ lower frequency
  - ***CSF3R*** mutation present in ~60% of CNL; ***KIT*** D816V in 90% of systemic mastocytosis

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POLYCYTHEMIA VERA (PV)

Definition

- ↑ in RBC mass ± ↑ granulocytes and platelets in the absence of physiologic stimulus

Etiologies of erythrocytosis (absolute ↑ RBC)

- Acquired 1°: PV (usually *JAK2*+) or other MPN
- Germline 1°: Chuvash (hypoxia-sensing disorder due to *VHL* mutation), *EGLN* mutations

- Secondary: **carboxyhemoglobinemia; hypoxia** (OSA, COPD**); inappropriate erythropoietin** (renal, hepatic); Cushing's syndrome
- Mimics: *relative* ↑ RBC (↓ plasma) due to dehydration; "stress" erythrocytosis (Gaisböck's syndrome)

Clinical manifestations (common between PV and ET)

- Symptoms (often termed "vasomotor")
  - **Hyperviscosity** (erythrocytosis): headache, dizziness, tinnitus, blurred vision
  - **Thrombosis** (hyperviscosity, thrombocytosis): ↑ **risk of DVT**, **MI**, **stroke**; transient visual disturbances (amaurosis, ocular migraine); Budd-Chiari syndrome; erythromelalgia = intense burning, pain and erythema of extremities due to microvascular ischemia
  - **Bleeding** (abnormal platelet function): easy bruising, epistaxis, GI bleeding
  - ↑ histamine from basophils → **pruritus**, peptic ulcers; ↑ uric acid (cell turnover) → gout
- Signs: **plethora**, **splenomegaly**, hypertension, engorged retinal veins

Diagnostic evaluation

- Men: Hb >16.5 g/dL or Hct >49%, women: Hb >16 g/dL or Hct >48%
- ± ↑ WBC, platelets, basophils; ↑ uric acid, leukocyte alkaline phosphatase, vit B_{12}
- Peripheral smear → no morphologic abnormalities
- ✓ Epo to rule out secondary causes of erythrocytosis; **if Epo ↓, PV more likely** If Epo ↑, then ✓ SaO_2 or PaO_2, carboxyhemoglobin, BM exam
- BM bx → hypercellularity for age, trilineage growth, pleomorphic mature megakaryocytes
- ***JAK2* V617F** mutation in ~95% of PV; other Pts typically harbor *JAK2* exon 12 mutations

Treatment for *JAK2* + PV

- **Phlebotomy** to goal Hct <45% (*NEJM* 2013;368:22), consider <42% in women
- **Low-dose ASA** in all Pts (*NEJM* 2004;350:114)

- **Hydroxyurea** if high risk of thrombosis (age ≥60, prior thrombosis) or if inadequate Hct by phlebotomy alone
- PEG IFNα preferred in younger Pts and pregnancy (*Lancet Haematol* 2017;4:e165)
- Ruxolitinib (JAK1/2 inhibitor) if refractory to or intolerant of hydroxyurea (*NEJM* 2015;372:426)
- Supportive: allopurinol (gout), H_2-blockers/antihistamines (pruritus). Avoid iron supp.
- Data for optimal mgmt of other types of PV (secondary, germline, etc.) currently lacking

Prognosis
- Median survival w/ Rx ~13.5 y (*Blood* 2014;124:2507); ↑ age, WBC, additional acquired somatic mutations → worse prognosis (*Haematol* 2013;160:251)
- Post-PV myelofibrosis (spent phase) occurs in 10–20% of cases, usually after 10 y
- Risk of transformation into acute leukemia (<2–5% lifetime)

ESSENTIAL THROMBOCYTHEMIA (ET)

Definition
- Sustained ↑ in platelets (>450,000/μL) ± ↑ RBC and granulocytes

Etiologies of thrombocytosis
- 1° = ET or other MPN; myelodysplastic syndromes (5q-syndrome); RARS-T
- 2° = **reactive thrombocytosis:** inflammation (RA, IBD, vasculitis), infection, trauma, acute bleed, iron deficiency, postsplenectomy, neoplasms (eg, Hodgkin lymphoma)
- Of patients with plt >1,000,000/μL, <1 in 6 will have ET

Clinical manifestations (also see "Polycythemia Vera")
- Thrombosis with erythromelalgia (risk of thrombosis highest in Pts with leukocytosis), bleeding (acquired vWD), pruritus; mild splenomegaly; migraine, TIA; early fetal loss

Diagnostic evaluation
- Peripheral smear: large hypogranular platelets

- BM bx: megakaryocytic hyperplasia; ⊖ Phil chr; rarely minor reticulin fibrosis; nl Fe; if atypical megakaryoctyes or ↑ reticulin, consider pre-PMF (Rx same as ET, but ↑ risk MF)
- Mutations: ***JAK2* V617F** in ~50%; ***CALR*** in ~45%; ***MPL*** in 5–10%; triple negative <5%
- Patients should not meet WHO criteria for diagnosis of CML, PV, PMF, or MDS
- Check vWF in pts w/ plt>1,000,000 and hold ASA (vide infra) if acquired vWD

Treatment of ET (*Blood Cancer J* 2015;5:e369)

Risk	Age	h/o Thrombosis	*JAK2*	ASA 81 mg qd	Cytoreduction
Very low	<60	N	⊖	Consider if CV risk factors	No
Low			⊕	⊕	No
Intermed	≥60	N	⊖	⊕	±
Very high	≥60	N	⊕	⊕ (hold if lab evid. of acquired vWD)	**Hydroxyurea**, IFNα if young or pregnant
	Any	Y	Any		

Prognosis

- Low-risk Pts have overall survival ≈ control population
- Risk of transformation into acute leukemia <2–3% lifetime; risk of progression to MF ~10%

PRIMARY MYELOFIBROSIS (PMF)

Definition

- Clonal myeloproliferation with reactive marrow fibrosis & extramedullary hematopoiesis
- Prefibrotic stage (pre-PMF): megakaryocyte prolif, grade 1 reticulin fibrosis, ↑ BM cellularity. Compared w/ ET, pre-PMF has ↑ thrombosis, ↑ progression, ↓ survival (*Blood* 2012;120:569).

Etiologies of myelofibrosis

- 1° myelofibrosis (PMF): myeloproliferative neoplasm
- 2° myelofibrosis: post-PV/ET myelofibrosis, other hematologic (CML, AML, ALL, MDS) and solid cancers (breast, prostate), autoimmune (eg, SLE), toxin (benzene), radiation, granulomas (TB, fungal, sarcoid), deposition diseases (eg, Gaucher's)

Clinical manifestations (*BJH* 2012;158:453)

- Ineffective erythropoiesis → anemia; extramedullary hematopoiesis → **massive splenomegaly** (abdominal pain, early satiety) ± hepatomegaly
- Tumor bulk and ↑ cell turnover → fatigue, weight loss, fever, sweats

Diagnostic evaluation (*Blood* 2010;115:1703 & 2016;127:2391)

- Anemia with variable WBC and platelet counts
- Peripheral smear → "**leukoerythroblastic**" (**teardrop cells**, nucleated RBCs, immature WBCs); large abnormal platelets
- BM aspirate → "dry" tap; BM bx → **severe fibrosis**, replacement by reticulin & collagen
- ***JAK2* V617F** in 45–50%; ***CALR*** mut in 45–50%, ***MPL*** mut in 7–10%, triple neg in 1–2%
- No *BCR-ABL* translocation; Pts should not meet criteria for PV or MDS
- DIPSS score for prognosis. High-risk factors: age >65, WBC >25k, Hgb <10, peripheral blasts >1%, symptoms, complex cytogenetics, absence of *CALR* type 1.

Treatment (*Am J Hematol* 2021;96:145)

- In absence of adverse prognostic factors (eg, anemia or sx) → no treatment
- Allogeneic HSCT only potential cure → consider in young Pts w/ high-risk disease
- Supportive care: **transfusions;** ESA if Epo <500 (risk ↑ splenomegaly); consider androgens vs. immunomodulatory agents (eg, lenalidomide) + prednisone; hydroxyurea; ? splenectomy if refractory to transfusions, failed chemoRx, painful splenomegaly
- JAK inh: ruxolitinib (JAK1/2) ↓ sx, ↓ splenomegaly, ↑ survival; preferred (*NEJM* 2012;366:787 & 799); fedratinib (JAK2; *JAMA Oncol* 2015;1:643); pacritinib & momelotinib under study
- Median survival ~6 y (*JCO* 2012;30:2981); transformation into AML occurs at a rate of ~8%/y

LEUKEMIA

ACUTE LEUKEMIA

Definition

- Clonal proliferation of hematopoietic progenitor with failed differentiation into mature elements → ↑ blasts in bone marrow and periphery → ↓ RBCs, platelets, and neutrophils

Epidemiology and risk factors

- Acute myelogenous (AML): ~20k cases/y in U.S.; median age 68 y
- Acute lymphocytic (ALL): ~6k cases/y in U.S.; median age 15 y but 2nd peak in older adults
- Risk factors: **radiation**, **chemo** (alkylating agents, topo II inhib), benzene, smoking, ? rising from acquired somatic mutations and clonal hematopoiesis (*NEJM* 2014;371:2477)
- Secondary to acquired hematopoietic dis.: MDS, MPN (esp. CML), aplastic anemia, PNH
- Inherited: Down's, Klinefelter's, Fanconi's anemia, Bloom synd., ataxia telangiectasia, germline mut. in *TP53* (Li-Fraumeni syndrome)*, DDX41, RUNX1*, *CEBPa,* & *GATA2*

Clinical manifestations

- Cytopenias → **fatigue** (anemia), **infection** (neutropenia), **bleeding** (thrombocytopenia)
- **Leukostasis** (more in AML): blast >50k, ↓ S_aO_2, HA, blurry vision, confusion, TIA/CVA
- **Tumor lysis syndrome** (TLS) from rapid turnover of cells
- **Disseminated intravascular coagulation** (**DIC**; especially with APL)
- Other: leukemic infiltration of skin, gingiva (esp. with monocytic subtypes); chloroma (myeloid sarcoma): extramedullary tumor of leukemic cells, any location; anterior mediastinal mass and SVC syndrome (T-ALL/LBL); hepatosplenomegaly (ALL and monocytic

leukemias); CNS (~10% of ALL; also in monocytic >myeloid leukemias): cranial neuropathies, HA

Diagnostic evaluation (*Blood* 2009;114:937)

- **Peripheral smear:** thrombocytopenia, **blasts** (seen in >95%; ⊕ Auer Rods in AML)
- **Bone marrow:** >20% blasts; mostly hypercellular; test for cytogenetics and flow cytometry for immunophenotype (AML/ALL)
- **Cytogenetic anomalies**: eg, in AML, t(15;17), t(8;21), inv(16) or t(16;16), complex; in ALL, Ph-chromosome [t(9;22)], hyper or hypodiploid, complex
- Molecular mutations in AML: esp *FLT3* (ITD and TKD), *TP53, NPM1;* ALL*: BCR-ABL1*
- Evaluate for complications: TLS (↑ uric acid, ↑ LDH, ↑ K, ↑ PO_4, ↓ Ca), DIC (PT, PTT, fibrinogen, D-dimer, haptoglobin, bilirubin), check for G6PD (prior to giving rasburicase)
- LP (w/ **co-admin of intrathecal chemotherapy** to avoid seeding CSF w/ circulating blasts) for all Pts w/ ALL (CNS is sanctuary site) and for Pts w/ AML w/ CNS sx
- TTE before use of anthracyclines
- **HLA typing** of Pt, siblings >parents/children for potential allogeneic HSCT candidates

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Acute Myelogenous Leukemia (AML)

Classification (WHO; *Blood* 2016;127:2391)

- Features used to confirm myeloid lineage and subclassify AML to guide treatment: morphology: **blasts**, ⊕ **granules**, ± **Auer rods** (eosinophilic needle-like inclusions)
- Immunophenotype: precursor: CD34, CD45, HLA-DR; myeloid: CD13, CD33, CD117; monocyte: CD11b, CD64, CD14, CD15
- Histochem.: myeloperoxidase (myeloid), non-specific esterase, and lysozyme (monocytic)
- Prognosis: *age*, prior *antecedent MPN/MDS* and *genetics* (cytogenetics + molecular mutation status) are key independent risk factors of poor prognosis

ENL 2017 Genetic Risk Classification (*Blood* 2017;129:424)

ENL 2017 Genetic Risk Classification (*Blood* 2017;129:424)	
Risk Category	**Genetic Abnormality**
Favorable	*APL*: t(15;17); *PML-RARa;* t(8;21): *RUNX*1-*RUNX*1*T*1; inv(16): *CBFB-MYH*1; mutated *NPM*1 *w/o FLT3-ITD or w/ FLT3-ITD^{low*}*; biallelic mutation in *CEBPA*
Intermediate	*FLT3-ITD*^{low*}; mutated *NPM*1 & *FLT3-ITD*^{high*}; t(9;11): *MLL-MLLT3*; cytogenetic abnl not classified as favorable or adverse, including normal karyotype w/o mutations in *FLT3-ITD* & *NPM*1
Adverse	-5 or del(5q); -7; -17/abn(17p); complex or monosomal karyotype; t(6;9): *DEK-NUP214*; t(9;22) *BCR-ABL*1; inv(3): *GATA2-MECOM*; wildtype *NPM*1 & *FLT-ITD^{high*}*; mutated *TP53, RUNX*1*, ASXL*1
* low/high: *FLT3-ITD* variant allele frequency (VAF); reflects burden of mut. leukemic cells	

Upfront treatment

- **Induction chemo** "7+3": 7d cont. infusion cytarabine (Ara-C) + 3d bolus anthracycline (daunorubicin or idarubicin)
- Ability to tolerate 7+3 regimen key determinant in subsequent Rx received (vide infra)
- Obtain BM bx 14–21 days after start of induction chemo to assess response
- Regimens for ***fit*** (generally age <75 y)
  - ***FLT3*-ITD/TKD** mutation: 7+3+midostaurin (early generation FLT3 inhib; *NEJM* 2017;377:454)
  - **Core-binding factor** ⊕: t(8;21) or inv(16): 7+3 ± gemtuzumab ozogamicin (mAb targ. CD33)
  - 2° AML or w/ MDS-related changes: CPX-351 (liposomal Ara-C & daunorubicin)
  - Other: age <60 y: 7+3 (high-dose daunorubicin 90 mg/m^2); >60 y: dauno 60 mg/m^2
- Regimens for ***unfit*** (may include age ≥75 y or < 75y w/ ECOG ≥3 or severe cardiac or pulmonary comorbidity; *Leukemia* 2013;27:997)
  - Azacitadine + venetoclax (Bcl2 inhibitor) (*NEJM* 2020;383:617)
  - *IDH1/2* mutation: ivosidenib or enasedinib

Consolidation therapy

- If c*omplete remission* (CR) = ANC >10^3, plt >100, no RBC Rx, <5% BM blasts; **CR ≠ cure**
- Favorable risk: high-dose cytarabine (HiDAC); Intermediate/Poor risk: Allo-HSCT
- Consider maintenance azacitadine if cannot complete curative intent Rx (*NEJM* 2020;383:2526)

Refractory/relapsed disease

- *Repeating mutation analysis* key b/c clonal evolution common and may affect Rx
- *FLT3*-ITD/TKD mutation: gilteritinib (potent FLT3 inhibitor)
- *IDH1* mutation: ivosidenib; *IDH2* mutation: enasidenib (small-molecule inhib of IDH1 or 2)
- Chemo: MEC (mitoxantrone, etoposide, Ara-C); FLAG-Ida (fludarabine, Ara-C, G-CSF, & idarubicin); CLAM (clofarabine, Ara-C, mitoxantrone), gemtuzumab

Prognosis

- CR achieved in 70–80% of Pts <60 y and in 40–50% of Pts >60 y
- Overall survival variable, depends on prognostic factors: ranges from <10% of older Pts w/ poor-risk tumor genetics to >65% of younger Pts w/ favorable prognostic factors

Acute promyelocytic leukemia (APL) (*Blood* 2009;113:1875)

- Rare, ~8% of AML in U.S.; >90% cure rates
- Atypical promyelocytes (large, granular cells; bilobed nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: **t(15;17); *PML-RARA*** (>95% of cases)
- **Medical emergency** with **DIC** and **bleeding** common
- Remarkable responses to **all-*trans*-retinoic acid (ATRA)** & **arsenic trioxide (ATO)** which induce differentiation of leukemic blasts. ∴ ***early initiation of ATRA if APL suspected***
- Non-high-risk APL: ATRA + ATO (induction + 4 cycles consolidation) → CR ~100%; event-free survival 97% and overall survival 99% at 2 y (*NEJM* 2013;362:111)
- High-risk APL: WBC >10k at diagnosis. No clear consensus. In general, chemo (anthracycline or gemtuzumab ozogamicin) added to ATRA + ATO induction and consolidation.

- Differentiation syndrome (ATRA): ~25% of Pts; fever, pulm. infiltrates, SOB, edema, HoTN, AKI; tx w/ dexamethasone 10 mg bid, supportive care (eg, diuresis) (*Blood* 2008;113:775)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL; *Lancet* 2020;395:1146)

Classification

- Lymphoblastic neoplasms may present as acute leukemia (ALL) w/ >**20% BM blasts** or as lymphoblastic lymphoma (LBL, more common in T-cell) w/ mass lesion w/ <20% BM blast
- Morphology: **no granules** (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL, MPO ⊖
- Immunophenotype
  Precursor: CD34, TdT
  B: CD19; variable CD10, CD22, CD79a
  T: CD1a, CD2, cytoplasmic CD3, CD5, CD7

Treatment

- **Induction chemo**
  Ph ⊕ t(9;22) (seen in ~25% of B-ALL): tyrosine kinase inhibitor + chemo/steroids
  Ph ⊖: Adolescents & young adults (<40 y): pedi-like regimen typically w/ PEG-asparaginase. Adults (40–60 y): multiagent chemo incl. anthracycline, vincristine, steroids, cyclophosphamide (CYC). Older (>60 y): reduced-intensity chemo.
- **CNS prophylaxis:** intrathecal MTX/cytarabine ± cranial irradiation *or* systemic MTX
- **Post-remission therapy** (choice depends on risk of recurrence)
  1) Average risk: consolidation/intensification chemo (~7 mo) → maintenance (~2–3 y)
  2) High risk: high-dose chemo w/ allo-HSCT considered for Pts in CR1. High-risk disease includes: Ph ⊕; Ph-like (based on gene expression); MLL translocation t(4;11); complex karyotype; hypodiploid (<44 chromosomes); early T-cell phenotype (ETP; lacks CD1a, CD8, $CD5^{weak}$, myeloid markers); minimal residual

disease (MRD) = morphologic remission but flow cytometry or molec. markers of tumor still detectable.

- **Relapse/refractory:** salvage therapy (*below*), then allogeneic HSCT if able

  B cell: blinatumomab (CD19 BiTE-bispecific T-cell engager; *NEJM* 2017;376:836), inotuzumab (CD22 Ab drug conjugate; *NEJM* 2016;375:740); tisagenlecleucel and brexucabtagene autoleucel (CD19 CAR-T, *NEJM* 2018;378:449; *Lancet* 2021;398:491), TKI+chemo/steroids (Ph ⊕t(9;22) only)

  T cell: nelarabine ± cyclophosphamide and etoposide

  Both B & T cell: chemo including high dose cytarabine regimens; clofarabine

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CHRONIC MYELOGENOUS LEUKEMIA (CML; *Lancet* 2021;398:1914)

Definition (*Blood* 2009;114:937)

- **Myeloproliferative neoplasm** with clonal overproduction of hematopoietic myeloid stem cells that can differentiate
- **Philadelphia chromosome** (Ph) = t(9;22) → ***BCR-ABL1*** fusion → ↑ Abl kinase activity

  BCR-ABL1 required for diagnosis (make via karyotyping or FISH; PCR)

Epidemiology and risk factors

- ~6600 new cases/y in U.S.; median age ~64 at presentation; ~15% of adult leukemias
- ↑ risk with irradiation; no clear relation to cytotoxic drugs

Disease classification & manifestations (WHO; *NCCN* v 2.2022)

- **Chronic phase (CP):** <10% blasts (peripheral or bone marrow). Risk stratification based on Sokal (*Blood* 1984;63:789) or Euro scores *(J Clin Pathol* 2001;54:491).
- **Accelerated phase (AP):** 10–19% blasts, ≥20% basos, plts <100k, clonal evolution (karyotype changes) not seen at dx
- **Blastic phase (BP):** ≥20% blasts (peripheral or marrow) and/or extramedullary leukemia
- Most Pts asx or may have mild constitutional s/s related to splenomegaly.

- Worsening constitutional sx, bone pain, rapid ↑ in spleen size herald disease progression

Diagnostic evaluation

- **Peripheral smear: leukocytosis**, left-shifted with *all stages of myeloid maturation;* thrombocytosis, **basophilia**
- **Bone marrow w/ karyotype:** hypercellular, ↑myeloid:erythroid ratio, micromegakaryocytes

Treatment (*Lancet* 2015;385:1447; *Hematol Oncol Clin North Am* 2017;31:577)

- **Tyrosine kinase inhibitors (TKI)** inhibit abl kinase activity.
  - 1st gen: imatinib, 1st TKI against *BCR-ABL1* (*NEJM* 2017;376:917)
  - 2nd gen: nilotinib, dasatinib, bosutinib. ↑ response but ↑ toxicity. No survival difference.
  - 3rd gen: ponatinib; a/w ↓ risk of disease progress, preferred for int-high risk, but ↑ toxicity
  - Imatinib, dasatinib, nilotinib, & bosutinib approved for 1st line Rx. Nilotinib, dasatinib, bosutinib, ponatinib, & asciminib approved for resistant disease; only ponatinib & asciminib effective on T315I mutation (*NEJM* 2012;367:2075, *Blood* 2021;138:2031).
  - STAMP (allosteric inhibitor): asciminib (*NEJM* 2019;381:2315); after ≥2 prior TKIs
  - Resistance: due to ↑ *BCR-ABL1* expression, often 2/2 *ABL* kinase mutation or amplification
  - Side effects: N/V, diarrhea, muscle cramps, cytopenias, ↓ PO_4, ↑ QT, rarely CHF; dasatinib: pericardial & pleural effusions and pulm. HTN; nilotinib: ↑ bili & lipase, CV toxicity; ponatinib: pancreatitis and arterial vascular events (cerebral, cardiac, & PAD)
- TKI discontinuation: consider if complete molecular response (>4.5 log reduction in *BCR-ABL1* transcript) for >2 y. Up to 50% of Pts remain off TKI at 2 y (ie, no molec. recurrence). Success proportional to duration of CMR and risk score at presentation.
- Consider allogeneic HSCT for AP and BP.
- CML in pregnancy: hydroxyurea & all TKIs contraind. If Rx needed, IFN (only option).

Milestones of Therapy

Milestones of Therapy	
Definition	**Optimal Time**
*BCR-ABL*1 ratio <10% IS = 1-log reduction by QT- PCR	3 mo
*BCR-ABL*1 ratio <1% IS = 2-log reduction by QT-PCR (CCyR)	6 mo
*BCR-ABL*1 ratio <0.1% IS = 3-log reduction by QT-PCR (MMR)	12 mo
*BCR-ABL*1 ratio: Pt *BCR-ABL*1 mRNA: *ABL* mRNA in peripheral blood. International Scale (IS) standardizes across labs by normalizing to *BCR-ABL*1:*ABL*1 ratio in a cohort of unRx'd patients.	

Prognosis (*NEJM* 2017;376:917)

- Chronic phase CML Rx'd w/ imatinib: 89% 5-y overall survival, 95% survival free of CML-related deaths, 7% progression to blast phase at 5 y (*NEJM* 2006;355:2408). Pts in CCyR (~equal to QT-PCR if 1% IS) have normal life expectancy. QT-PCR >4-log ↓ can consider TKI discontinuation trial (*Lancet Onc* 2018;19:747).

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

see "Small Lymphocytic Lymphoma"

LYMPHOMA AND CLL

Definition

- Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
- Generally characterized as **Hodgkin lymphoma** (HL) or **non-Hodgkin lymphoma** (NHL)

Clinical manifestations

- Lymphadenopathy (usually nontender)
  - **HL:** superficial (usually **cervical/supraclavicular**) ± mediastinal LAN; **nodal** disease with **orderly**, **anatomic spread** to adjacent nodes
  - **NHL:** diffuse; **nodal and/or extranodal** disease with **noncontiguous spread;** symptoms reflect involved sites (abdominal fullness, bone pain)
- Constitutional ("B") symptoms: **fever** (>38°), drenching **sweats**, ↓ **weight** (>10% in 6 mo)
  - **HL:** periodic, recurrent "Pel-Ebstein" fever; 10–15% have pruritus; ~35% "B" symptoms
  - **NHL:** "B" symptoms vary between subtypes, ~15–50%

Diagnostic and staging evaluation

- Physical exam: lymph nodes, liver/spleen size, Waldeyer's ring, testes (~1% of NHL), skin
- Pathology: **excisional lymph node bx** (*not FNA* b/c need surrounding architecture) with immunophenotyping and cytogenetics (**Reed-Sternberg** (RS) **cells in HL)**; **BM** bx if cytopenias; CLL by peripheral flow in patients w/ peripheral disease; LP if CNS involvement clinically suspected
- Lab tests: CBC, BUN/Cr, LFTs, ESR, LDH, UA, Ca, alb; ✓ HBV & HCV (and must ✓ HBsAg & anti-HBc if planning rituximab Rx due to risk of HBV reactivation); HIV
- Imaging: **PET-CT** to assess disease burden and guide biopsy/therapy, especially in HL, DLBCL. Head CT/MRI *only* if

neurologic symptoms.

Ann Arbor Staging System with Cotswolds Modifications	
Stage	**Features**
I	Single lymph node (LN) region
II	≥2 LN regions on the same side of the diaphragm
III	LN regions on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs
Modifiers: A = no symptoms; B = fever, night sweats or weight loss; X = "bulky" mediastinal disease or mass >10 cm; E = single contiguous extranodal site; H = hepatic; S = splenic	

HODGKIN LYMPHOMA (HL) (*Am J Hematol* 2018;93:704; *Lancet* 2021;398:1518)

Epidemiology and risk factors

- ~9,000 cases/y; bimodal distribution (15–35 & >50 y); ↑ ♂; role of EBV in subsets of HL, esp. immunocompromised patients (eg, HIV)

Pathology

- Affected nodes show RS cells (<1%) in background of non-neoplastic inflammatory cells
- Classic RS cells: bilobed nucleus & prominent nucleoli with surrounding clear space ("owl's eyes"). RS cells are **clonal B-cells:** CD15+, CD30+, CD20– (rarely +).

WHO Histologic Classification of Classical HL		
Nodular sclerosis	60–80%	Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I or II at dx
Mixed cellularity	15–30%	Pleomorphic; older age; male predominance; ≥50% stage III or IV at presentation; intermediate prognosis
Lymphocyte rich	5%	Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis
Lymphocyte depleted	<1%	Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis

- **Nonclassical HL** (5%): nodular lymphocyte predominant (NLP); involves peripheral LN

80% present in stages I–II, Rx w/ RT vs. chemoRT w/ 4-yr PFS 88% and OS 96% (*JCO* 2008;26:434); consider rituximab because most NLP RS cells are CD20+

Stages III–IV treated with combination chemo (see below)

Treatment (*NCCN Guidelines* v5.2021)

- **Stages I–II**: PET adapted **ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine) ± RT Favorable: ABVD × 2–4 cycles ± RT (if PET ⊖ after 2 cycles reduce chemo or RT)

  Unfavorable (>50 y, bulky mediastinum, "B" sx, ESR >50, >3 nodal sites): ABVD × 4–6 + RT (stop at 4 cycles if PET ⊖ after 2 cycles)
- **Stages III–IV: ABVD** × 6 cycles (can omit B if PET ⊖ after 2 cycles; *NEJM* 2016;374:2419); brentuximab (anti-CD30) may replace bleo but more toxic (*NEJM* 2018;378:331); add RT for select Pts as consolidation
- Refractory/relapsed disease: salvage chemo + auto HSCT ± RT

  brentuximab vedotin post-ASCT yields some long-term remissions (*Blood* 2016;128:1562)

  PD1/PDL1 blockade (pembrolizumab or nivolumab) (*NEJM* 2015;372:311, *JCO* 2017;35:19)
- Late treatment effects include ↑ risk for:

  Second cancers: ~4.6× risk for up to 40 y (*NEJM* 2015;373:2499)

  breast (if RT), ∴ annual screening at age 40 or 8–10 y post RT; *leukemia/MDS; NHL*

  Cardiac disease (if RT or anthracycline), ? role of echo/stress at 10 y (controversial)

  Pulmonary toxicity (if bleomycin); **Hypothyroidism** (if RT), ∴ annual TSH (if neck RT)
- **International Prognostic Score** (IPS; *JCO* 2012;30:3383) risk factors: albumin <4 g/dL, Hb <10.5 g/dL, male gender, age >45 y, stage IV, WBC ≥15 k/μL, lymphocytes <600/μL or <8% of diff. 5-yr PFS 62–88% based on # of risk factors.

Non-Hodgkin Lymphoma (NHL)

Epidemiology and risk factors

- 79 types of NHL, ~70,000 new cases/y; median age dx 65 y; ⇕♂ predom; 85% B-cell origin

- Associated conditions: immunodeficiency (eg, HIV, posttransplant); autoimmune disorders (eg, Sjögren's, RA, SLE); infection (eg, EBV, HTLV-I, *H. pylori*)
- Burkitt lymphoma: (1) endemic or African (jaw mass, 80–90% EBV-related); (2) sporadic or American (20% EBV-related); (3) HIV-related

WHO Classification of Lymphoid Malignancies (*Blood* 2016;127:2375)		
Type	**Examples**	**Associated Abnormalities**
Mature B cell → *aggressiveness*	Burkitt's lymphoma	*8q24, c-MYC*
	Diffuse large B-cell lymphoma (DLBCL)	*BCL2, MYC, MLL2, CREBBP, etc.*
	Mantle cell	*t(*11;14*) BCL*1*-IgH* → cyclin D1
	Marginal zone lymphoma (nodal, extranodal, splenic)	*AP*1*2-MALT*1 *& BCL*-1*0-Ig enh*
	Hairy cell leukemia (⊕ TRAP)	*BRAF V600E*
	Follicular lymphoma	*IGH-BCL2, MLL2, CREBBP*
	CLL/small lymphocytic lymphoma	*IGHV, TP53, ATM, SF3B*1*, etc.*
Mature T cell & NK cell	Peripheral T-cell lymphoma	*TET2 and DNMT3A*
	Mycosis fungoides (cutaneous lymphoma)/ Sézary syndrome (+ LAN)	Some *ALK*1 ⊕
	Anaplastic large-cell lymphoma	
	Angioimmunoblastic T-cell lymphoma	

Treatment (*Lancet* 2017;390:298)

- Treatment and prognosis determined by histopathologic classification rather than stage
- Rituximab (anti-CD20; *NEJM* 2012;366:2008) if CD20+
- **Indolent:** generally no cure (except allo HSCT), goal sx mgmt (bulky dis, cytopenia, "B" sx)
  - Follicular Lymphoma Int'l Prog. Index (FLIPI; *Blood* 2004;104:1258): risk factors = age >60, stage III/IV, Hb <12 g/dL, >4 nodal areas, LDH >nl. 5-yr OS 52–90% based on score.
  - Initial: RT if localized, rituximab + chemo (bendamustine, CVP, fludarabine), ibrutinib.
    - Obinutuzumab (anti-CD20) + chemo w/ obin maint ↑ PFS but ↑ tox (*NEJM* 2017;377:1331).

Maintenance: rituximab in indolent, aggressive, and relapsed disease (*Lancet* 2011;377:42)

Hairy cell: cladribine; oral BRAF inhibitor if relapsed/refractory (*NEJM* 2015;373:1733)

Gastric MALT: ✓ *H. pylori*; can cure by treating *H. pylori* if ⊕; RT for relapsed/refractory

- **Aggressive:** goal is cure (*Am J Hematol* 2019;94:604), treatment depends on subtype

  International Prognostic Index (IPI; *Blood* 2007;109:1857): risk factors = age >60 y, stage III/IV, ≥2 extranodal sites, PS ≥2, LDH >nl. 4-yr OS 55–94% based on score.

  R-CHOP (rituximab, cyclophosphamide, doxorubicin = hydroxydaunorubicin, vincristine = Oncovin, prednisone) (*NEJM* 2002;346:235 & 2008;359:613) DLBCL 10-y PFS = 45%; overall survival = 55% (*Blood* 2010;116:2040)

  + **Radiation** for localized or bulky disease

  Consider **CNS prophylaxis** w/ intrathecal vs. systemic high-dose MTX if paranasal sinus, testicular, breast, periorbital, paravertebral, or bone marrow involved; also w/ ≥2 extranodal sites + ↑ LDH. Controversial (*Blood* 2021;139:413).

  Refractory/relapsed disease: salvage chemo; high-dose chemo + auto-HSCT (*JCO* 2001;19:406); allo-HSCT if beyond 2nd relapse (*JCO* 2011;29:1342)

  CAR-T (qv): axicabtagene (*NEJM* 2017;377:2531), tisagenlecleucel (*NEJM* 2019;380:45), lisocabtagene (*Lancet* 2020;396:839), brexucabtagene (mantle cell; *NEJM* 2020; 382:1331)

  Mantle cell: ibrutinib for relapsed/refractory disease (*Lancet* 2016;387:770)

- **Highly aggressive**

  Burkitt: dose-adjusted EPOCH-R (*NEJM* 2013;369:1915) or CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, high-dose cytarabine rituximab) (*Blood* 2008;112:2248)

  All Pts receive CNS & tumor lysis syndrome prophylaxis

  Rituximab ↑ event-free survival (*Lancet* 2016;387:2402)

  High-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 and/or BCL6: "double-/triple-hit", assoc. w/ poor prognosis. Often use DA-R-EPOCH.

HIV-associated NHL (*Blood* 2006;107:13)

- HIV ⊕ imparts 60–100× relative risk
- NHL is an AIDS-defining malignancy along with Kaposi's, cervical CA, anal CA
- Concurrent HAART & chemotherapy likely provide survival benefit
- DLBCL & immunoblastic lymphoma (67%): CD4 <100, EBV-associated. Burkitt lymphoma (20%): can occur with CD4 >200. Generally, treat as immunocompetent, but avoid rituximab if CD4 <50 (due to increased risk of death from infection).
- Primary CNS lymphoma (16%): CD4 <50, EBV-assoc. (also seen in Pts w/o HIV). Rx w/ high-dose MTX-based regimen + steroid ± temozolomide ± RT, consider auto HSCT.

Small Lymphocytic Lymphoma (SLL) or Chronic Lymphocytic Leukemia (CLL)

Definition (*NEJM* 2005;352:804; *Blood* 2008;111:5446)

- Monoclonal, functionally incompetent mature B lymphocytes; CLL & SLL = same disease
- CLL: >5000/μL malignant cells; SLL: <5000/μL malignant cells + LAN ± splenomegaly
- Monoclonal B lymphocytosis: resembles but does not meet CLL criteria, observe

Epidemiology and risk factors

- ~15,000 new cases/y; median age at dx is 71 y; most common adult leukemia

Clinical manifestations

- **Often asx** & identified by lymphocytosis on CBC; 10–20% p/w "B symptoms"
- **Lymphadenopathy** (80%) and **hepatosplenomegaly** (50%)
- **Autoimmune hemolytic anemia** (AIHA) (~10%) or **thrombocytopenia** (ITP) (~1–2%)
- Hypogammaglobulinemia ± neutropenia → ↑ susceptibility to **infections**
- Bone marrow failure in ~13%; monoclonal gammopathy in ~5%
- Aggressive **Richter's transformation** in ~5% into high-grade lymphoma (poor prognosis)

Diagnostic evaluation

- **CBC w/ diff**: **B-cell count**
- **Peripheral smear: lymphocytosis** (predominantly mature-appearing small cells) "**smudge**" cells from damage to abnl lymphs from shear stress of making blood smear
- **Flow cytometry: clonality** with dim surface Ig; CD5+, CD19+, CD20+, CD23+
- Bone marrow (not req for dx): normo- or hypercellular; ≥30% small B lymphocytes
- **Genetics:** del 11q22-23 & del(17p) unfavorable; trisomy 12 neutral; del 13q14 and mut *IGHV* favorable. Nine significantly mutated genes, including *TP53, NOTCH1*, *MYD88*, and *SF3B1.* Key role for spliceosome mutations (*NEJM* 2011;365:2497; *JCI* 2012;122:3432).

CLL Staging & Prognosis

Rai System		Median Survival	Binet System	
Stage	Description		Description	Stage
0	Lymphocytosis *only*	>10 y	<3 node areas	A
I	⊕ lymphadenopathy	7–10 y	>3 node areas	B
II	⊕ hepatosplenomegaly			
III	⊕ anemia (not AIHA)	1–2 y	Anemia or thrombocytopenia	C
IV	⊕ thrombocytopenia (not ITP)			

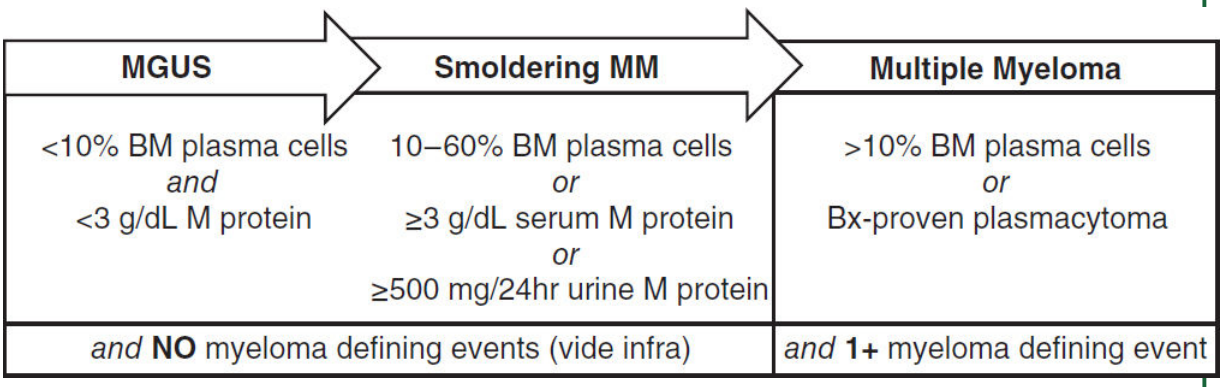
Treatment (*NEJM* 2020;383:460)

- Observation unless "active disease": Rai stage III/IV, Binet stage C, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections
- **First-line:** w/o del(17p)/TP53 use acalabrutinib or ibrutinib (BTK inhibitors) or venetoclax + rituximab; with del(17p)/TP53 use acalabrutinib or venetoclax ± obinutuzumab; ibrutinib + venetoclax w 88% w/ CR but ↑ tox (*NEJM* 2019;380:2095)
- Second-line & beyond: in general, choose Rx w/ mechanism different from 1st line Rx. BTK inhibitors (eg, zanubrutinib), venetoclax, chemo including fludarabine, chlorambucil, or bendamustine + rituximab. Consider allo-HSCT in relapse.
- HSCT is the only curative Rx. Rx choice balances patient/disease characteristics and goals of care. Different rates of complete remission, time to progression, and toxicities.

- Rx for complications: PCP, HSV, VZV Ppx; AIHA/ITP → steroids; recurrent infxns → IVIg

PLASMA CELL DYSCRASIAS

Figure 5-6 Spectrum of nonmalignant to malignant clonal plasma cell disorders



Monoclonal Gammopathy of Uncertain Significance (MGUS) (*NEJM* 2018;378:241)

- ✓ CBC, Ca, Cr, SPEP, serum free light chains, UPEP w/ immunofixation (to exclude MM)
- Close observation: repeat SPEP in 6 mo, then yearly thereafter if stable
- ~1%/y or ~25% lifetime risk → MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum free light chain ratio & M protein ≥1.5 g/dL: ↑ risk of progression to MM

Smoldering Multiple Myeloma

- Need whole-body MRI or PET-CT to rule out occult bone lesions
- Risk of prog. 10%/y, depends on [M protein], subtype, FLC ratio. No defined role for Rx yet though trials ongoing (*NEJM* 2013;369:438; *Blood* 2019;134:781; *JCO* 2020;38:1126).

MULTIPLE MYELOMA (MM)

Definition and epidemiology (*Lancet* 2021;397:410)

- Malignant neoplasm of **plasma cells** producing a monoclonal Ig = "**M protein**"
- ~27,000 new cases/y; median age at diagnosis 69 y; more common in African Americans

Clinical manifestations (CRAB criteria and other less common features)

- Hyper**C**alcemia due to ↑ osteoclast activity
- **R**enal disease: multiple mechanisms include toxic effect of filtered light chains → *renal failure* (cast nephropathy) or *type II RTA;* amyloidosis or light chain deposition disease → *nephrotic syndrome;* hypercalcemia, urate nephropathy, type I cryoglobulinemia
- **A**nemia (normocytic) due to bone marrow involvement; rarely, may see AIHA
- Lytic **B**one lesions due to ↑ osteoclast activity → pathologic fx
- Recurrent infxns due to relative hypogammaglob. (clonal plasma cells suppress nl Ig)
- Neurologic: cord compression; POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome
- Hyperviscosity: usually when IgM >4 g/dL, IgG >5 g/dL, or IgA >7 g/dL
- Coagulopathy: seen in amyloid due to binding & depletion of Factor X
- AL amyloidosis (see "Amyloidosis")

Diagnostic and staging evaluation (*Lancet Onc* 2014;15:e538)

- **Dx:** BM plasma cells ≥10% or bx-proven plasmacytoma & ≥1 **MM-defining event**:
  (a) myeloma-related organ or tissue impairment (**ROTI**) = lytic bone lesions, Ca >11 mg/dL, Cr >2 mg/dL, or Hb <10 g/dL
  (b) any of the following biomarkers: BM plasma cells ≥60%, serum free light chain (FLC) ratio ≥100:1, >1 focal lesion on MRI
- **Variants**
  Solitary bone or extramedullary plasmacytoma: no periph plasmacytosis or other ROTI
  Plasma cell leukemia: plasma cell count >2000/μL in peripheral blood
  Nonsecretory MM (~2% of MM Pts; MM without M protein)

- ✓ Peripheral smear for rouleaux (see insert), Ca, alb, Cr; ↓ anion gap, ↑ globulin, ↑ ESR
- **Protein electrophoresis and immunofixation**
  - **Serum protein electrophoresis (SPEP):** quantitates M component; ⊕ in >80% of Pts
  - Ddx of M component: MM, MGUS (vide supra), CLL, lymphoma, sarcoidosis, RA Polyclonal hypergam seen in inflammatory states: HIV, rheumatic diseases, cirrhosis
  - Urine protein electrophoresis (UPEP): detects Pts who secrete only light chains (= Bence Jones proteins), which are filtered rapidly from the blood
  - Immunofixation: shows component is monoclonal and identifies Ig type → IgG (50%), IgA (20%), IgD (2%), IgM (0.5%), light chain only (20%), nonsecretors (<5%)
  - **Serum FLC assay:** important for dx (esp. light chain-only Pts) and f/up response to Rx
- β_2-microglobulin (β_2M) and LDH levels reflect tumor burden
- **BM bx cytogenetics:** normal karyotype better than abnl. **Standard risk** = hyperdiploidy or t(11;14); **high risk** = hypodiploidy, del. 17p13 (~10% of Pts), t(4;14) & t(4;16).
- **Skeletal survey** (plain X-rays) to identify lytic bone lesions and areas at risk for pathologic fracture. Whole-body PET-CT (scalp to toe) or MRI often used to detect bone lesions.

Multiple Myeloma Staging Systems (OS does not account for cytogenetics)

Stage	ISS Criteria*	Durie-Salmon (DS) Criteria	ISS Median OS
I	β_2M <3.5 mg/L *and* albumin >3.5 g/dL	*All:* Hb >10 g/dL; Ca ≤12 mg/dL; 0–1 lytic bone lesions; IgG <5 g/dL or IgA <3 g/dL or urine light chain <4 g/24 h	62 mo
II	Fulfilling criteria for neither I nor III		44 mo
III	β_2M >5.5 mg/L	*Any:* Hb <8.5 g/dL; Ca >12 mg/dL; >5 lytic bone lesions; IgG >7 g/dL or IgA >5 g/dL or urine light chain >12 g/24 h	29 mo (30 mo if Cr <2 mg/dL; 15 mo if Cr ≥2 mg/dL)

*Consider R-ISS incl chrom abnl & LDH (*JCO* 2005;23:3412 & 2015;61:2267).

Treatment and prognosis (*NEJM* 2016;375:754 & 1319; 2018;378:518 & 379:1811)

- Decisions dictated by risk stratification and transplant eligibility; generally incurable. Stratify via ISS criteria; R-ISS which includes chrom abnl & LDH (*JCO* 2015;61:2267).
- Rx incl. **proteasome inhibitors:** bortezomib (V), carfilzomib (K), ixazomib (I); **immunomodulators:** lenalidomide (R), thalidomide (T), pomalidomide (P); **immunotherapy:** daratumumab (anti-CD38, Dara), elotuzumab (anti-SLAMF7, Elo)
  Other active drugs: dexamethasone (D), melphalan, panobinostat, cyclophosphamide
- **Induction Rx** w/ best response rate: proteasome inhib (V or K) + immunomod (eg, R). Triplet Rx ↑ OS vs. double (*Lancet* 2017;389:519). RVD most common regimen in US; KRD if high-risk (*NEJM* 2014;371:906 & 2016;374:1621). Dara-RD an option (*NEJM* 2019;380:2104). Quad Rx (Dara-RVD) may improve response rates (*Blood* 2020;136:936).
- If *not* transplant eligible: **induction Rx** ↑ survival, not curative; consider maint chemo
- If transplant *eligible:* after induction chemo then **high-dose melphalan** + **auto-HSCT.** Not curative, but ↑ progression-free survival (PFS) vs. chemo alone (*NEJM* 2014;371:895, *Lancet Onc* 2015;16:1617). Offer if good perf. status & no prohibitive comorbid. Maint Rx w/ R improves PFS/OS (*NEJM* 2014;371:10). Timing of HSCT (upfront vs. relapse) debatable.
- Relapsed/refractory: HSCT (if good prior response, no prior HSCT), Elo-PD, Dara-PD, venetoclax (anti-Bcl-2) + dex in t(11;14); rarely use Allo-SCT. CAR-T w/ idecabtagene vicleucel (anti-B-cell maturation antigen) after >3 prior Rx: response rates >70% (*NEJM* 2019;380:1726 & 2021;384:705).
- Local radiation for solitary or extramedullary plasmacytoma
- Adjunctive Rx: *bone:* **bisphosphonates** (*JCO* 2007;25:2464), XRT for sx bony lesions
  renal: avoid NSAIDs & IV contrast; consider plasmapheresis for acute renal failure
  hyperviscosity syndrome: plasmapheresis; *infxns:* consider IVIg for recurrent infections
- Common **toxicities** of Rx: melphalan → myelosuppression; lenalidomide → low plts & thromboembolism; bortezomib → periph.

neuropathy; steroids → hyperglycemia, infxn

WALDENSTRÖM'S MACROGLOBULINEMIA (WM)

Definition (*Blood* 2009;114:2375; *NEJM* 2012;367:826)

- B-cell neoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- 91% w/ *MYD88* (NF-κB pathway) L265P mut., may distinguish from MM
- *No evidence of bone lesions* (IgM M component + lytic bone lesions = "IgM myeloma")

Clinical manifestations

- **Fatigue** from anemia is most common sx
- **Tumor infiltration:** BM (cytopenias), hepatomegaly, splenomegaly, lymphadenopathy
- **Circulating monoclonal IgM**
  - **Hyperviscosity syndrome** (~15%): *Neurologic:* blurred vision ("sausage" retinal veins), HA, dizziness, Δ MS. *Cardiopulmonary:* congestive heart failure, pulm. infiltrates.
  - Type I **cryoglobulinemia → Raynaud's phenomenon**
  - Platelet dysfxn → mucosal bleeding
- **IgM deposition** (skin, intestine, kidney); amyloidosis and glomerulopathy
- **Autoantibody activity of IgM:** *Chronic AIHA* (prominent **rouleaux;** 10% Coombs' ⊕ = AIHA). *Peripheral neuropathy:* may be due to IgM against myelin-associated glycoprotein.

Diagnostic evaluation

- SPEP + immunofixation with IgM >3 g/dL; 24-h urine for UPEP (only 20% have ⊕ UPEP)
- Bone marrow biopsy: ↑ plasmacytoid lymphocytes; β_2-microglobulin for prognostic eval
- **Relative serum viscosity:** ratio serum viscosity to H_2O (nl 1.8); hyperviscosity when >5–6

Treatment

- Hyperviscosity: **plasmapheresis;** limit transfusions if possible (worsen hyperviscosity)

- Sx (eg, prog. anemia): ritux ± chemo (eg, bendamustine, Cy, etc.); ritux + ibrutinib (*NEJM* 2018;378:2399); zanubrutinib (*Lancet Haem* 2020;7:e837); everolimus or HSCT in salvage

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of donor pluripotent cells that can reconstitute all recipient blood lineages

Categories of Stem Cell Transplantation		
Feature	**Allogeneic (Allo)**	**Autologous (Auto)**
Donor–recipient relationship	Immunologically distinct	Donor is also recipient
Graft-vs.-host disease	***Yes***	***No***
Graft-vs.-tumor effect	***Yes***	***No***
Risk of graft contam. w/ tumor	No	Yes
Relapse risk (leukemia)	Lower	Higher
Transplant-related mortality	***Higher***	***Lower***

- **Types of Allo HSCT:** *based on donor/recipient matching of major HLA antigens on Chr. 6* (4 principal genes for serotyping: *HLA-A*, *-B*, *-C*, & *-DR;* each w/ 2 alleles ∴ 8 major Ag)
  - *Matched related* (MRD, sibling 8/8 major Ag match): lowest GVHD; **preferred donor**
  - *Matched unrelated (MUD):* ↑ risk of GVHD; ∴ matching of 10 HLA alleles (*DQ* also) to ↓ risk; chance of match correlates w/ ethnicity (*NEJM* 2014;371:339)
  - *Mismatched related* (eg, 1/8 Ag mismatch): ↑ available donor pool, but ↑ GVHD, rejection; ∴ need additional immunosuppression
  - *Haploidentical*: typically, between parents and young children or sibs (“half” match); early post-tx cyclophosphamide reduces GVH by destroying proliferating alloreactive T-cells
  - *Umbilical cord blood:* HSC processed at birth & stored. Yields lower cell number. Need 2 cords per adult. Neonatal immune cells:

HLA-mismatch tolerated better, ↓ GVHD, slow immune reconstitution → ↑ late viral infections (*Blood* 2010;116:4693).

- **Graft-vs.-host disease (GVHD):** *undesirable* side effect of allo HSCT allogeneic T cells view host cells as foreign; ↑ incid. w/ mismatch or unrelated donors
- **Graft-vs.-tumor (GVT):** *desired* effect in allo-SCT; graft T cells attack host tumor cells

Indications (*BBMT* 2015;21:1863; BMT 2015;50:1037)

- **Malignant disease:**
  Auto HSCT allows *high-dose myeloablative chemo* and then rescue what would be otherwise lethal cytopenias with autologous stem cells. Used in chemosensitive diseases such as relapsed/refractory DLBCL, MM, testicular germ cell tumor.
  Allo HSCT produces **graft-vs.-tumor** (GVT) effect, in addition to hematopoietic rescue (used for AML, ALL, MDS, CML-blast crisis, CLL, lymphoma)
- **Nonmalignant disease:** allo HSCT replaces abnl lymphohematopoietic system w/ one from nl donor (eg, immunodeficiencies, aplastic anemia, hemoglobinopathies)

Transplantation procedure (for Allo HSCT)

- **Pre-Tx conditioning regimen goal:** immunosuppression to allow donor cell engraftment & anti-tumor efficacy to ↓ relapse risk. Type and dose of agents determine this balance.
  Myeloablative conditioning: high-dose chemo and/or total body irradiation. Low relapse rates, high immunosuppression, higher transplant-related morbidity.
  Reduced-intensity conditioning ("RIC"): lower dose of chemo → ↓ transplant-related morbidity/mortality, but ↑ relapse b/c it relies more on GVT effect (*Blood* 2015;126:23). Allows allo HSCT for older adults (>60) or Pts w/ comorbidities.
- **Sources of hematopoietic stem cells** (*NEJM* 2012;367:1487)
  Bone marrow (BM): original source, preferred in non-malignant disease, ↓ GVHD rates
  Peripheral blood stem cells (PBSC): easier to collect, more commonly used. BM vs. PBSC ≈ survival; BM ↓ chronic GVHD, PBSC ↓ graft failure, faster engraftment.

Umbilical cord blood stem cells (UCB): see above in Types of Allo HSCT

- **Engraftment:** absolute neutrophil count (ANC) recovers to 500/μL w/in ~2 wk w/ PBSC, ~2.5 wk w/ BM, ~4 wk w/ UCB. G-CSF accelerates recovery by 3–5 d in all scenarios.

Complications

- Either **direct chemoradiotoxicities** associated with preparative regimen or consequences of **interaction between donor and recipient immune systems**
- **Engraftment syndrome***:* fever, rash, noncardiogenic pulm. edema, abnl LFTs, AKI, wt gain. Dx of exclusion: r/o infection, GVHD; Rx w/ 1 mg/kg steroids, rapid taper over 3–4 d.
- **Sinusoidal obstruction syndrome (SOS):** incidence ~10%, mortality ~30%
  Previously known as **veno-occlusive disease (VOD)** (*BBMT* 2016;22:400). Mechanism: direct cytotoxic injury to hepatic venules → *in situ* thrombosis.
  Symptoms: tender hepatomegaly, ascites, jaundice, fluid retention with severe disease → liver failure, encephalopathy, hepatorenal syndrome
  Diagnosis: ↑ ALT/AST, ↑ bilirubin; ↑ PT with severe disease; Doppler U/S *may* show reversal of portal vein flow; ↑ hepatic wedge pressure; abnl liver bx
  Treatment: supportive; prophylaxis with **ursodiol;** treat w/ defibrotide (*Blood* 2016;127:1656)
- **Idiopathic pneumonia syndrome (IPS):** 5–25% of Pts, >50% mortality (*Blood* 2003;102:2777)
  Alveolar injury 2/2 direct toxicity → fever, hypoxia, diffuse infiltrates; occult infxn frequent
- **Bleeding**: incidence ~25%, 2/2 ↓↓ plts; sites: CNS, GI, pulm.; Ppx w plt transfusions
- **Diffuse alveolar hemorrhage (DAH):** Dx: bronchoscopy to exclude infection; ↑ bloody lavage fluid. Rx: 500–1000 mg Solu-Medrol × 3 d ± etanercept (*BBMT* 2015;1:67).
- **Acute GVHD** (usually within 6 mo of transplant; *NEJM* 2017;377:2167)
  Clinical grades I–IV based on scores for **skin** (severity of maculopapular rash), **liver** (bilirubin level) and **GI** (volume of

diarrhea); bx supports diagnosis

Prevention: **immunosuppression** (MTX + cyclosporine, or tacrolimus), T-cell depletion of graft, post-Tx cyclophos. for haploidentical, some high-risk allo (*BBMT* 2008;14:641)

Treatment: grade I → topical Rx; grades II–IV → associated with ↓ survival and ∴ treated with immunosuppressants (corticosteroids, CsA, tacrolimus, rapamycin, MMF)

- **Chronic GVHD** (developing or persisting >3 mo posttransplant; *NEJM* 2017;377:2565)

  Clinical: malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, bile duct degeneration, cholestasis, and many others. More common w/ PBSC than BM.

  Treatment: immunosuppression; rituximab; photopheresis; ibrutinib (*Blood* 2017;130:21), ruxolitinib (*NEJM* 2021; 385:228), belumosudil (*Blood* 2021;138:2278)

- **Graft failure**

  Primary = persistent neutropenia without evidence of engraftment

  Secondary = delayed pancytopenia after initial engraftment; either immune mediated via immunocompetent host cells (**graft rejection**) or non–immune mediated (eg, CMV)

- **Infectious complications**

  due to regimen-induced pancytopenia and immunosuppression

  auto HSCT recipients: no immunosuppression ∴ at ↑ risk only pre-/postengraftment

  both primary infections and reactivation events occur (eg, CMV, HSV, VZV)

Timing of Complications Following Allogeneic HSCT

	Time After Transplant and Associated Risk Factors		
	Days 0–30 Mucositis; organ dysfunction; neutropenia	**Days 30–90** Acute GVHD; ↓ cell immunity	>**90 Days** Chronic GVHD; ↓ cellular & humoral immunity
Viral infection	Respiratory and enteral viruses, BK virus		
	HSV*	CMV*, HHV 6 & 7	
		EBV-related lymphoma	
			VZV*, JC

Timing of Complications Following Allogeneic HSCT			
Bacterial infection	Gram ⊕ cocci (*Staph.*, *Strep. viridans*) GNRs (Enterobacteriaceae, *Pseudomonas, Legionella, S. maltophilia*)		Encapsulated bacteria
Fungal infection	*Candida* spp.		
	Aspergillus spp.		
Parasitic infection		*T. gondii* *P. carinii* *S. stercoralis*	*T. gondii* *P. carinii*
Regimen-related	Pancytopenia		Growth failure
	Mucositis, rash, alopecia		Hypogonadism/infertility
	Nausea, vomiting, diarrhea		Hypothyroidism
	Peripheral neuropathies		Cataracts
	Hemorrhagic cystitis		Avascular necrosis of bone
	Veno-occlusive disease		2^{nd} malignancy
	IPS/Interstitial pneumonitis		
Immune-mediated	Acute GVHD		Chronic GVHD
	Primary graft failure	Secondary graft failure	

*Primarily among persons who are seropositive before transplant.

Prophylaxis/Supportive Medications During HSCT		
Medication	**Prophylaxis Against**	**Duration**
Fluconazole or posaconazole	*Candida*	75 d
Acyclovir	HSV/VZV	365 d
Valganciclovir, ganciclovir, or letermovir if CMV ⊕	CMV	100 d or when no longer immunosuppressed
Antibiotics (eg, fluoroquinolone)	Bacterial infxn	While neutropenic
TMP-SMX or atovaquone	PCP	365 d or when off immunosupp.
Allopurinol	Hyperuricemia	Until d –1

LUNG CANCER

Epidemiology and risk factors

- Most common cause of cancer-related death for both men and women in the U.S.
- Two main types: **non-small cell** (NSCLC, ~85% of cases); **small cell** (SCLC, ~15%)
- **NSCLC** comprised of **adeno** (40%), **squamous cell** (SCC, 20%), & large cell (5%) carcinomas, as well as other / not classified (20%)
- **Cigarette smoking:** 85% of lung cancers occur in smokers; risk ∝ total pack-yrs, ↓ risk after quitting/reducing but not to baseline (*Int J Cancer* 2012;131:1210).
  SCC & SCLC almost exclusively in smokers, adeno most common type in nonsmokers.
- Asbestos: when combined with smoking, synergistic ↑ in risk of lung cancer
- Other: RT (for other cancer); HIV; environ. toxins (radon, 2nd-hand smoke); pulm. fibrosis

Screening (*JAMA* 2021;325:962)

- **Annual low-dose chest CT** in ≥20 pack-year current or former (quit w/in 15 y) smokers, age 50–80 y → 20% ↓ lung cancer-related mortality (*NEJM* 2020;382:503)
- High rates of screen-detected nodules. Multidisciplinary mgmt recommended (pulm., med onc, thoracic radiology & surgery; *NCCN Guidelines: Lung Cancer Screening* v.1.2022).

Clinical manifestations

- ~10% asymptomatic at dx, detected incidentally (only 16% w/ localized dis. at presentation)
- **Endobronchial growth** of 1° tumor: **cough**, **hemoptysis**, **dyspnea**, pain, wheezing, post-obstructive pneumonia; more common with squamous or small cell (central location)
- **Regional spread**: can cause dysphagia (esophageal compression), stridor (tracheal obstruction), hoarseness (recurrent laryngeal

nerve palsy). Pleural effusions & pleural metastases specifically = metastatic disease = Stage IV.

Pancoast's syndrome: apical tumor → brachial plexus involvement (C8, T1, T2) → Horner's syndrome, shoulder pain, rib destruction, atrophy of hand muscles

SVC syndrome (*NEJM* 2007;356:1862): central tumor → SVC compression → face/arm swelling (>80%), neck/chest vein distention (~60%), SOB/cough (~50%), HA (~10%); Rx = steroids, diuretics, RT ± chemo, SVC stent if severe sx, anticoag if clot

- **Extrathoracic metastases:** brain (~25% of patients at dx), bone, liver, adrenal
- **Paraneoplastic syndromes**

Endo: **SIADH** (SCLC); ACTH (SCLC) → **Cushing's;** PTH-rP (SCC) → **hyperCa**

Skeletal: digital clubbing (NSCLC), **hypertrophic pulm. osteoarthropathy** (adenocarcinoma) = symmetric polyarthritis and proliferative periostitis of long bones

Neuro (SCLC): **Eaton-Lambert** (anti-P/Q-type voltage-gated Ca^{2+} channel Abs), peripheral neuropathy (anti-Hu, anti-PCA-2, anti-CRMP5), cerebellar degeneration (anti-Hu, anti-Yo, anti-Ri, anti-Tr), encephalomyelitis (anti-Hu, anti-Ma1/2, anti-CRMP5)

Hematologic: hypercoagulable state (adenocarcinoma), DIC

Diagnostic and staging evaluation (*NCCN Guidelines* v.7.2021)

- **Staging:** based on tumor size and extent of invasion (T), regional LN involvement [N: N0 (none), N1 (ipsilat. hilar), N2 (ipsilat. mediast.), N3 (contralat., supraclav.)] and presence of metastases (M) (*Chest* 2017;151:193). Pleural effusions/implants = Stage IV.

  5-y survival: ~70–90% for stage I, 50–60% stage II, 15–35% stage III, 0–10% stage IV (*J Thorac Oncol* 2016;11:39); survival improving with newer therapies (*NEJM* 2020;383:640).
- **Imaging: CT w/ contrast** of chest & abd/pelvis to assess for mets (adrenal, liver, bones).

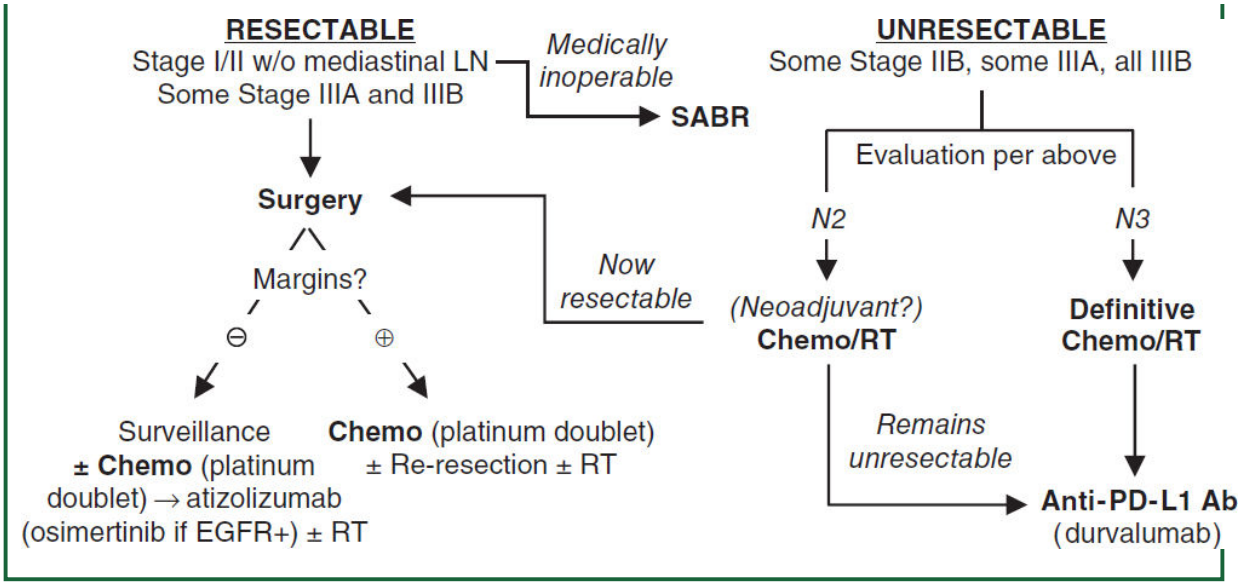
  PET-CT more Se than CT alone for detecting mediastinal and distant mets as well as bone mets (*NEJM* 2009;361:32). **Brain MRI** for all Pts except stage IA.

- **Pathology:** via **bronchoscopy** (central lesions) or **CT-guided needle bx** (peripheral lesions or accessible sites of suspected metastasis); mediastinoscopy (LN bx / eval), VATS (eval. of pleural peripheral lesions), thoracentesis if pleural effusion (cytology).
- **Genetics** (usually just in adv/metastatic disease)**:** ✓ *EGFR* (include in stage IIA-IIIB), *ALK, ROS1, MET, KRAS, RET, BRAF, NTRK* fusion for all non-squamous disease (incidence lower in SCC but still consider testing); PD-L1 expression
- PFTs w/ quant V/Q if Rx includes resection; need 30% nl predicted lung fxn *after* resection

NSCLC Treatment (*NCCN Guidelines* v.7.2021; *Lancet* 2021;398:535)

- Localized disease: surgery if possible; RT (eg, stereotactic ablative radiotherapy [SABR]) vs. chemo/RT if not (see Figure 5-7)
- Metastatic disease: >20 new Rx since 2015. Some targeted Rx substantially improves survival & are better tolerated (see Stage IV Rx table); however, 5-y survival still poor.
    - First-line immunotherapy (IO) ± chemo for most Pts w/o targetable mutations.
    - Pemetrexed + pembrolizumab often continued as maintenance when used.
    - Palliative care ↑ survival (*NEJM* 2010;363:733); palliative RT for local sx from tumor/mets.
- Avoid combining IO & targeted Rx, ↑↑ tox (eg, rash/diarrhea, lung/liver injury [can be fatal])
- Solitary brain metastasis (oligomet): surgical resection + brain radiation may ↑ survival

Figure 5-7 Localized NSCLC treatment algorithm



(*NCCN Guidelines* v7.2021; *NEJM* 2017:377:1919, 2018;378:113, & 2020;383:1711; *Lancet* 2021;398:1344)

Stage IV NSCLC Treatment			
Type	**Genetics**	**%**	**Treatment**
Adeno or Other	*EGFR*	~15	1st line: osimertinib if L858R, ex19del (*NEJM* 2018;378:113)
	EGFR ex20 insertion	2–3	Subsequent Rx w/ amivantamab (*JCO* 2021;39:3391) or mobocertinib (*JAMA Onc* 2021;7:e214761) after platinum chemo
	ALK	~4	1st line: alectinib pref. b/c CNS activity (*NEJM* 2017;377:829)
	*ROS*1	2	Crizotinib pref. (*JCO* 2017;35:2613); entrectinib (*Lancet Onc* 2020;21:261)
	MET ex14 skip or amplif.	3	Capmatinib (*NEJM* 2020;383:944) or tepotinib (*NEJM* 2020;383:931)
	RET	1	Selpercatinib (*NEJM* 2020;383:813) or pralsetinib (*Lancet Onc* 2021;22: 959-969)
	BRAF V600E	1–3	Dabrafenib + trametinib (*Lancet Onc* 2016;17:984)
	NTRK fusions	<1	Larotrectinib (*NEJM* 2018;378:731)
	KRAS G12C	~13	Subsequent Rx w/ sotorasib (*NEJM* 2021;384:2371)
	PD-L1≥50%	30	Pembrolizumab or chemo + pembro (*NEJM* 2018;378:2078)
	No targets & PD-L1 <50%		Chemo (carbo/pemetrexed) + pembro (*NEJM* 2018;378:2078) *or* carbo/paclitaxel + anti-VEGF Ab (bevacizumab) + atezo (*NEJM* 2018;378:2288)

Stage IV NSCLC Treatment			
Squam	PD-L1 ≥50%		Pembrolizumab or chemo/pembro (*NEJM* 2016;375:1823)
	PD-L1 <50%		Chemo [carbo/paclitaxel] + pembro (*NEJM* 2018;379:2040)

Many are specific tyrosine kinase inhibitors ('tinibs) directed against EGFR, ALK, etc. Amivantamab is an EGFR- MET bispecific mAb. Pembrolizumab is a mAb against PD-1 on lymphocytes (ie, an immune checkpoint inhibitor).

SCLC staging and treatment (*NCCN Guidelines* v.1.2022)

- SCLC usually disseminated at presentation; poor overall survival
- Can be very responsive to chemotherapy, but rapidly develop resistance
- **Diagnosis:** all have Rb & p53 mutations (*Nature* 2015;524:47); 90% w/ neuroendo markers
- **Treatment:** primarily chemo (platinum + etoposide); adding anti-PD-L1 Ab (atezolizumab)
  ↑ survival (*NEJM* 2018;379:2220), as does concurrent thoracic RT in limited-stage disease

SCLC Staging Schema and Treatment				
Stage	**% at dx**	**Definition**	**1st-line Treatment**	**Median Survival**
Limited (LS-SCLC)	30–40	Confined to ipsilat. hemithorax. Within 1 radiation field / safely treated with definitive RT doses	Concurrent chemo + radiation (± PCI)	1–2 y
Extensive (ES-SCLC)	60–70	Beyond 1 radiation field / too extensive to be encompassed in a tolerable RT plan	Chemotherapy + atezolizumab	~1 y

- **Prophylactic cranial irradiation** (PCI) controversial. Offered to potentially ↑ survival for LS-SCLC in complete remission (*NEJM* 1999;341:476). Role in ES-SCLC being studied.
- **Second line**: low response rates, short survival. Options: lurbinectedin, single-agent chemo (eg, topotecan, docetaxel), reRx w/ platinum doublet, anti-PD-1 (eg, nivo).

BREAST CANCER

Epidemiology

- In U.S., most common cancer in women; 2nd leading cause of cancer death in women
- **Genetic risk:** 15–20% ⊕ FHx → 2× ↑ risk; ~45% familial cases a/w germline mutation.
  BRCA1/2*:** 35–85% lifetime risk of breast ca. Germline loss-of-function mutations in ***PALB2 a/w 35% ↑ risk breast cancer by age 70. Moderate risk mutations ***CHEK2*** and ***BARD1*** a/w 15–30% lifetime risk of breast cancer (*NEJM* 2021;384:428).
- **Estrogen:** ↑ risk with early menarche, late menopause, late parity or nulliparity (*NEJM* 2006;354:270); ↑ risk with prolonged HRT (RR = 1.24 after 5.6 y; *JAMA* 2003;289:3243); OCP use a/w extremely low to no ↑ risk (*NEJM* 2017:317:2228; *JAMA Oncol* 2018;4:516)
- Benign breast conditions: ↑ risk if atypia (atypical ductal or lobular hyperplasia; *NEJM* 2015;372:78) or proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; *no* ↑ risk w/ cysts, simple fibroadenoma, or columnar changes
- ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin lymphoma

Prevention (if high-risk: eg, FHx, LCIS, atypical hyperplasia)

- Tamoxifen (contraindic. in preg): ↓ risk contralateral breast ca as adjuvant Rx. Approved for 1° prevent. if ↑ risk: ↓ invasive breast cancer, but ↑ DVT & uterine ca.
- Raloxifene (only if post-menopausal): ↓ risk of invas breast ca, vertebral fx, & uterine ca, ↑ risk stroke & DVT/PE (*NEJM* 2006;355:125); less effective than tamoxifen for prevention.
- Aromatase inhib. (post-menopausal): ↓ risk >50% (*Lancet* 2014;383:1041), ↑ osteoporosis
- *BRCA1/2* ⊕: intensified surveillance vs. prophylactic bilat. mastectomy which ↓ risk ~90%; bilat. salpingo-oophorectomy ↓ risk of ovarian *and* breast cancer (*NEJM* 2016;374:454)

Clinical manifestations

- Breast mass (hard, irregular, fixed, nontender), nipple discharge (higher risk if unilateral, limited to 1 duct, bloody, associated with mass)
- Special types: **Paget** disease → unilateral nipple eczema + nipple discharge; **inflammatory** breast cancer → skin erythema and edema *(peau d'orange)*
- Metastases: lymph nodes, bone, liver, lung, brain

Screening (*JAMA* 2015;314:1599; *Annals* 2019;170:547)

- **Mammography:** ~20–30% ↓ **in breast cancer mortality**, smaller abs. benefit in women <50 y (*JAMA* 2018;319:1814); digital breast tomosynthesis (3-D) ↑ specificity (*JAMA* Oncol 2019;5:635); suspicious findings: clustered **microcalcifications**, **spiculated**, **enlarging**
- ACS: annual mammo starting at 45 (consider biennial after 54), cont. if life expect ≥10 y
- USPSTF: screen biennially ages 50–75 (some may want to begin at 40)
- ↑ risk: screen earlier w/ exam and mammo (age 25 in *BRCA1/2* carrier, 5–10 y before earliest FHx case, 8–10 y after thoracic RT, upon dx of ↑ risk benign disease)
- **MRI:** superior to mammo in high-risk and young Pts; consider annually if >20% lifetime risk (eg, ⊕ FHx, *BRCA1/2*, prior chest RT) (*Lancet* 2011;378:1804)
- **Germline genetic testing:** if metastatic, TNBC, ♀, age ≤45y, or by FHx (*NCCN* v1.2022)

Diagnostic evaluation

- **Palpable breast mass:** age <30 y → observe for resolution over 1–2 menstrual cycles; age <30 y, unchanging mass → **U/S** → aspiration if mass not simple cyst;
  age >30 y *or* solid mass on U/S *or* bloody aspirate *or* recurrence after aspiration → **mammo** (detect other lesions) *and* either **fine-needle asp.** or **core-needle bx**
  clearly cancerous on exam or indeterminate read or atypia on bx → **excisional bx**
- **Suspicious mammogram** with normal exam: stereotactically guided bx

- MRI: detects contralateral cancer in 3% of Pts w/ recently dx breast cancer & contra-lateral mammo (but PPV only 21%) (*NEJM* 2007;356:1295); utility remains unclear

Staging

- **Anatomic:** tumor size, chest wall invasion, axillary LN mets (*strongest prognostic factor*)
- **Histopathologic:** type (little prognostic relevance) & grade; lymphatic/vascular invasion
  - ***In situ*** carcinoma: no invasion of surrounding stroma
  - **Ductal** (DCIS): ↑ risk of invasive cancer in *ipsilateral* breast (~30%/10 y)
  - **Lobular** (LCIS): benign entity; marker of ↑ risk of inv. cancer in *either* breast (~1%/y)
  - **Invasive** carcinoma: infiltrating ductal (70–80%); invasive lobular (5–10%); tubular, medullary and mucinous (10%, better prognosis); papillary (1–2%); other (1–2%)
  - **Inflammatory breast cancer** (see above): not a histologic type but a clinical reflection of tumor invasion of dermal lymphatics; very poor prognosis
  - **Paget disease** (see above)**:** ductal cancer invading nipple epidermis ± associated mass
- **Tissue biomarkers:** estrogen and progesterone receptor (ER/PR), HER2
- Oncotype DX 21-gene expression recurrence score predicts which ER ⊕, HER2 ⊖ will have minimal benefit from adjuvant chemo in LN ⊖ (*NEJM* 2018;379:111) and LN ⊕ (1–3) disease (*NEJM* 2021;385:2336)

Simplified Staging & 5-y Dis. Specific Survival (*CA Cancer J Clin* 2017;67:290; *SEER* 2017)

Stage	Characteristics	Description	5-y DSS
I	Tumor ≤2 cm	Operable locoregional	99%
IIA	Tumor >2 cm or *mobile* axillary nodes		98%
IIB	Tumor >5 cm or 2–5 cm w/ mobile nodes		96%
IIIA	Internal mammary or *fixed* axillary nodes	Locally advanced	95%
IIIB/C	Chest wall, skin, infra or supraclavic. nodes	Inoperable	80–85%
IV	Distant metastases	Metastatic	27%

General Approach to Treatment (*JAMA* 2019;321:288 & 1716)	
DCIS	Mastectomy or lumpectomy ± RT ± chemoprevention (*Lancet* 2016;387:849 & 866)
I	Surgery + RT
II	+ adjuv. chemo if ↑ risk: tumor >2 cm *or* ⊕ LN *or* triple ⊖ *or* Oncotype DX-guided + hormonal Rx for ER/PR ⊕: add ovarian suppression if ↑ risk (*NEJM* 2018; 379:122) + anti-*HER2* Rx and chemo if *HER2* ⊕ and tumor ≥1 cm or ⊕ LN
III	Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + hormonal Rx for ER/PR ⊕: add ovarian suppression if premenopausal + anti-*HER2* Rx for *HER2* ⊕: usually trastuzumab + pertuzumab
IV	ER/PR ⊕: combined aromatase & CDK4/6 inhibitors (*NEJM* 2016; 375:1925) ER/PR ⊖*/HER2* ⊕: chemo + anti-*HER2* therapy Triple ⊖: chemo ± immune checkpoint inhibitor Bony mets: bisphosphonates & denosumab ↓ fractures (*Cochrane* 2017;CD003474)

Surgery and Radiation for Local Control	
Intervention	**Indication**
Breast conserving	Stage I–II, lumpectomy + sentinel lymph node biopsy* + RT
Modified radical mastectomy	Large tumor relative to breast, multicentric dis., prior chest RT, diffuse microcalcifications, ⊕ margins after lumpectomy
Post mastectomy Radiation	≥4 ⊕ LN, tumor >5 cm, ⊕ surgical margins, chest wall or skin involvement (*Lancet* 2014;384:1848)

*Axillary lymph node dissection indicated for palpable axillary LNs

Systemic Therapy		
Indic.	**Class**	**Examples**
ER/PR ⊕ (*Lancet* 2017;389: 2403)	Endo (*NEJM* 2019;380: 1226)	**Tamoxifen:** adjuvant Rx for low-risk pre-meno; ↓ recurrence & ↓ mortality; 10 y superior to 5 y (*Lancet* 2011;378:771 & 2013;381:805) **Aromatase inhib** (AI; anastrozole, letrozole, exemestane): adjuvant Rx for post-meno; ↑ OS vs. tam. (*Lancet* 2015;386:1341); 7 y of Rx ↑ DFS vs. 5 y of Rx (*NEJM* 2021;385:395) Adding selective ER degrader (fulvestrant) to AI ↑ OS if mets
	Ovarian suppress.	**LHRH agonists** (eg, leuprolide) or oophorectomy: adjuvant Rx for high-risk pre-meno combined with tam. or AI (*NEJM* 2018;379:122)
	Cell prolif. (*NEJM* 2012;366: 520)	**CDK 4/6 inhib** (eg, palbociclib, abemaciclib, ribociclib): + AI (1st-line metastatic Rx) or fulvestrant ↑ PFS (& OS for ribociclib) in stage IV vs. AI alone (*NEJM* 2018;379:1926; *JCO* 2017;35:3638); + AI for adjuvant (*Ann Onc* 2021;32:1571) **mTOR inhib** (everolimus): + AI (exemestane) ↑ OS in stage IV
PIK3CA ⊕	PI3K inhib	**Alpelisib** + fulvestrant ↑ PFS in met HR⊕ (*NEJM* 2019;380:1929)

Systemic Therapy		
HER2 ⊕ (*Lancet* 2017;389:2415)	HER2-targeted	**Trastuzumab** (anti-HER2): 1st-line Rx combined w/ chemo **Trastuzumab emtansine** (mAb linked to chemo): ↓ risk of recurrence/death if residual disease post neoadj. Rx (*NEJM* 2019;380:617); preferred 2nd line Rx for met. disease **Trastuzumab deruxtecan** (mAb linked to chemo): emerging data as 2nd line Rx for met disease, ↓ risk disease progression vs. trastuzumab emtansine, ↑ lung toxicity (*NEJM* 2022;386:1143) **Margetuximab** (anti-HER2): combined w/ chemo preferred after 2+ lines of Rx (*JAMA Oncol* 2021;7:573)
Stage I–III (above)	Chemo	**Neoadjuvant:** to conserve breast & evaluate Rx efficacy, equivalent OS as adjuvant (*JCO* 2008;26:778) **Adjuvant:** use anthracycline ± taxane. Nb, endocrine only for some ER/PR ⊕ based on oncotype Dx (see staging).
Triple ⊖	Immune	**Pembrolizumab** (anti-PD-1 mAb) + chemo 1st-line for early stage (*NEJM* 2020;382:810) & PD-L1 ⊕ met dis. (*Lancet* 2020;396:1817)
	Ab-drug conjugate	**Sacituzumab govitecan**: anti-trop-2 Ab linked to chemo ↑ PFS & OS in heavily pre-Rx'd metastatic disease (*NEJM* 2019;380:741)
BRCA ⊕	PARP inh	**Olaparib & talazoparib** (*NEJM* 2017;377:523 & 2018;379:753)

DFS, disease-free survival; OS, overall survival; PFS, progression-free survival

PROSTATE CANCER

Epidemiology and risk factors (*NEJM* 2003;349:366)

- Most common cancer in U.S. men; 2nd most common cause of cancer death in men
- Lifetime risk of prostate cancer dx ~16%; lifetime risk of dying of prostate cancer ~3%
- ↑ risk with ↑ age (rare if <45 y), in African Americans, ⊕ FHx, BRCA mutations

Clinical manifestations

- Most prostate cancers (78%) are asymptomatic and localized at diagnosis
- Metastatic dis. sx primarily from bone mets: bone pain, spinal cord compression, cytopenias

Screening (*JAMA* 2014;311:1143; *Lancet* 2014;384:2027)

- **PSA:** 4 ng/mL cut point neither Se nor Sp; can ↑ with BPH, prostatitis, acute retention, after bx or TURP, and ejaculation (*no significant ↑ after DRE, cystoscopy*); 15% of men >62 y w/ PSA <4 & nl DRE have bx-proven T1 cancer (*NEJM* 2004;350:2239)
- Digital rectal exam no longer recommended due to limitations, no mortality benefit
- ACS rec: ≥50 y (or ≥45 y AA or ⊕ FHx) discuss PSA screening, informed decision making
- USPSTF (*JAMA* 2018;319:1901) rec discuss pros/cons w/ Pt (no ↓ in prostate ca-related mort.)

Diagnostic evaluation, staging, and treatment (*NCCN Guidelines* v1.2022)

- **Transrectal ultrasound** (TRUS) **guided biopsy** (6–12 cores)
- Multiparametric MRI (± endorectal coil): improves detection (*NEJM* 2018;378:1767)
- **Gleason score & grade group (histology):** Gleason score determines Grade Group. 1 = best → 5 = worst. Group 1: 3+3=6

(most common histologic pattern is 1st #, next is 2nd #), Group 2: 3+4=7, Group 3: 4+3=7, Group 4: 4+4=8, Group 5: all higher.

Risk Stratification & Treatment of Localized Prostate Cancer (JAMA 2017;317:2532)				
Risk	**T stage**	**Gleason Score & Path**	**Imaging**	**Treatment**
Very low*	T1c	Grade Group 1, <3 cores ⊕, <50% ⊕ in any core, *and* PSA <10 ng/mL & density <0.15 ng/mL/g	Not Indic.	Active surveillance strongly considered if very low risk, *or* EBRT (external beam RT), *or* Radical prostatectomy (RP) RP vs. EBRT based on Pt, long-term tox† of Rx
Low*	T1-2a	Grade Group 1, *and* PSA <10 ng/mL		
Intermed*	T2b-T2c	Grade groups 2–3, *or* PSA 10–20 ng/mL	Bone scan & CT A/P	RP *or* EBRT+ADT (4–6 mo)
High Very high	T3a-T4	Grade Groups 4–5, *or* PSA >20 ng/mL		EBRT+ADT (18–36 mo) *or* RP

*In asx Pts w/ life expect ≤5 y & very low-to-intermed risk dis., no w/up or Rx until sx. *NCCN Guidelines* v1.2022

†RP more short-term impotence (unless ADT) & incont than RT; over yrs → similar (*NEJM* 2016;375:1425)

Treatment of Metastatic Prostate Cancer (*NCCN Guidelines* v1.2022)	
Androgen deprivation therapy (ADT)	Prostate ca requires androgen signaling for growth. ADT backbone of Rx. Med: 1. Luteinizing hormone-releasing hormone (LHRH) agonist (eg, leuprolide) ± 1st-gen anti-androgen (nilutamide, bicalutamide), *or* 2. LHRH antagonist (degarelix) Surgery: bilateral orchiectomy
Hormone- sensitive prostate cancer (HSPC)	**Def:** ADT sensitive (ie, PSA ↓ w/ Rx): all prostate ca initially sensitive **Workup/testing:** PEx & PSA q 3–6 mos; sx-guided imaging **Rx:** 1. ADT alone (only if minimal disease, eg, rising PSA); *or* 2. ADT + abiraterone/pred or enza/apalutamide (↑ OS vs. ADT alone); *or* 3. Docetaxel + ADT (↑ OS vs. ADT alone, espec. in high-volume disease)

Treatment of Metastatic Prostate Cancer (*NCCN Guidelines* v1.2022)	
Castration-resistant prostate cancer (CRPC) *Always continue ADT*	**Def:** All met. HSPC eventually becomes CRPC (ie, progression despite castration androgen levels on ADT), due to re-estab. of androgen signaling via other mech. ∴ more potent anti-androgens are needed. **Rx:** New-gen. anti-androgens: abiraterone (biosynth inhib.) + pred, or enza/daro/apalutamide (receptor blocker) ↑ PFS & OS **Targeted:** *BRCA*1*/2, ATM* (homologous recomb genes, ~20%): olaparib; *MSI-H*/Lynch syndrome (2–5%): pembro*; Cancer vaccine:* Sipuleucel-T **Chemo:** doce/cabazitaxel +pred/dex+Luetitium-177 (*NEJM* 2021;385:1091) **Bone-active agents:** 1. denosumab or zoledronic acid ↓ skeletal-related events (SREs); 2. radium-223 used in bone-only dis, ↓ SREs & ↑ OS

(*NEJM* 2017;377:338 & 352; 2019;381:121; 2019;381:13; *Lancet* 2016;387:1163)

Prognosis and monitoring

- PSA level, Gleason score/grade group and age are predictors of metastatic disease
- In surgically treated Pts, 5-y relapse-free survival >90% (excellent) if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
- PSA q6mo for 5 y if curative Rx; consider PET Axumin scan if ↑ PSA ± equivocal bone scan

COLORECTAL CANCER (CRC)

Epidemiology and risk factors (*CA Cancer J Clin* 2018;68:7)

- 4th most common cancer in U.S. men & women; 2nd leading cause of all cancer death
- 90% of cases occur after age 50. ~75% are sporadic.
- IBD a/w ~0.3%/y ↑ risk of CRC. ↑ risk w/ ↑ extent and duration of disease.

Heritable Genetic Syndromes			
Disorder	**CRC risk**	**Pathophysiology**	**Assoc Cancers**
Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch)	~80% lifetime	Most common hered. CRC (~3%). Mismatch repair mut (eg, *MSH2*, *MLH*1). Dx: ≥3 family HNPCC cancer, 1 dx before 50 y, involves 2 gen. Typically **right-sided**.	**Endometrial**, ovarian, stomach, urothelial, small bowel & pancreas
Familial adeno polyposis (FAP)	100% lifetime	Mutation in *APC* gene → 1000s of polyps at young age	Thyroid, stomach, small bowel
MUTYH-assoc. polyposis (MAP)	40–100% lifetime	Autosomal *recessive;* consider if mult. polyps but ⊖ for FAP	Duodenal, ovarian, bladder, skin

- ASA rec for 1° prev. if 50–59 y & ≥10% 10-y CRC risk. Must take for at least 10 years.

Screening (*JAMA* 2021;325:1965)

- *Average-risk Pts*: start at age 45, repeat q1–10y based on screening modality
- ↑ *risk Pts*: ⊕ FHx: screen age 40 or 10 y before index dx, then q5y. IBD: colo 8–10 y after dx, then q1–2y. Suspect familial syndrome: genetic counsel, screen age 20–25, yearly.
- **Colonoscopy:** *preferred*; 90% Se for lesions >1 cm. If polyp, re ✓ in 3–5 y. Adenomatous polyp removal a/w ↓ CRC mortality (*NEJM* 2012;366:687). *Adenoma*: ↑ risk of malig. if >2.5 cm, villous, or sessile; can progress to CRC over ~10 y interval (sporadic & familial).

- **Sigmoidoscopy:** benefit w/ 1-time flex-sig (*Lancet* 2017;389:1299); less Se than colo or CTC
- **CT colonography (CTC):** ~90% Se for lesions ≥1 cm but less if smaller (*NEJM* 2008;359:1207). If high-risk, Se only 85% for neoplasia ≥6 mm (*JAMA* 2009;301:2453).
- **Combo DNA + Hb immunoassay** w/ ~90% Se & Sp (*NEJM* 2014;370:1287)
- Occult blood (FOBT): use 3-card home testing (Se 24%) yearly

Clinical manifestations

- Distal colon: Δ **bowel habits/ caliber**, **obstruction**, colicky abd. pain, **hematochezia**
- Proximal colon: **iron defic. anemia**, dull vague abd pain, liquid stool
- Associated with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis

Cancer genetics (*Nature* 2014;513:382)

- **Microsatellite stable (MSS) vs. high instability (MSI-H):** latter sign of mismatch repair gene failure, accounts for 15% CRC, presents more often as early stage, ~5% of met dis.
- **Mutations:** *APC* (~80%); *KRAS* (~40%); *TP53* (50–70%); *DCC*, *SMAD4*, *BRAF* (~15%), *HER2* amplification (<5%)

Staging and treatment (*NCCN Clin Pract Guidelines;* version 3.2021)

- TNM staging, including CT chest and abdomen/pelvis with contrast ± MRI pelvis for rectal
- Baseline **CEA**: monitor post resection or follow response; *not* for screening
- **Chemo options** (*Lancet* 2014;383:1490): 5-FU/leucovorin (LV) foundation. 5-FU/LV + oxaliplatin &/or irinotecan (FOLFOX, FOLFIRI, FOLFOXIRI, resp). Capecitabine oral 5-FU prodrug. TAS102 (trifluridine + tipiracil) in progressive disease (*NEJM* 2015;372:1909). *Anti-VEGF* (bevacizumab) added to chemo ↑ OS in all subsets of mCRC.
- **Targeted therapy:** *anti-EGFR mAb* (cetuximab or panitumumab) in unmutated *KRAS/NRAS/BRAF* (*NEJM* 2013;369:1023), better for L-sided disease; encorafienib + cetuximab + binimetinib in *BRAF* V600E (*NEJM* 2019;381:1632)

- **ImmunoRx**: anti PD-1 (*NEJM* 2020;383:2207) ± CTLA-4 in MSI-H/ MMRd met CRC
- **Radiation:** loc. adv. rectal (T3/N+) & colon (unresectable); consider for oligo-mets

TNM	Path. Criteria	5-y Surv.	Treatment
I	Submucosa/muscularis	94–97%	Surgery alone (resect & analyze ≥12 LN)
IIA	Serosa	83%	Surgery. Consider adjuvant chemo for high-risk Stage II: obstruction, perf, adherence, inadequate LN sampling (<12 LNs).
IIB	Peritoneum	74%	
IIC	Direct invasion	56%	
IIIA	≤6 ⊕ LNs	86%	Surgery + FOLFOX (6 mo) or CAPOX (3–6 mo) (*NEJM* 2018;378:13) Pre RT ± chemo if rectal (*NEJM* 2006;355:1114)
IIIB	Varying # ⊕ LNs & local invasion	51–77%	
IIIC		15–47%	
IV	Distant metastases* (*NEJM* 2014;371:1609)	5%	Chemo (FOLFOXIRI if high-risk) ± anti-PD-1 (MSI-H only) ± resect isolated mets

*Oligometastatic dis (few, limited mets) sometimes still curable w/ chemo + metastatectomy/radiation

PANCREATIC TUMORS

Genetics and path (*Nat Rev Dis Primers* 2016;2:16022)

- Histologic types: **adenocarcinoma** (~85%), acinar cell carcinoma, endocrine tumors, cystic neoplasms (<10%); rarely, mets to pancreas (eg, lung, breast, renal cell)
- Location: ~60% in head, 15% in body, 5% in tail; in 20% diffuse infiltration of pancreas
- Adeno. mut.: *KRAS* (>90%), *p16* (80–95%), *p53* (50–75%), *SMAD4* (~55%), *BRCA* (10%)

Epidemiology and risk factors (*Lancet* 2016;388:73)

- 4th leading cause of cancer death in U.S.; 80% panc adeno in ages 60–80 y; M>F (1.3:1)
- Acquired risk factors: **smoking** (RR ~1.5; 25% cases), obesity, chronic pancreatitis, T2DM
- Hereditary (5–10%): familial breast/ovarian CA (*BRCA2*); *hereditary chronic pancreatitis* (mutation in cationic trypsinogen gene (*PRSS1*, *SPINK1*); *familial cancer syndromes:* atypical multiple mole melanoma (*CDKN2A/p16*), Peutz-Jeghers (*LKB1*), ataxia-telang.

Clinical manifestations

- **Painless jaundice** (w/ pancreatic head mass), **pain** radiates to back, ↓ **weight** & appetite
- New-onset atypical DM (25%); migratory thrombophlebitis (Trousseau's syndrome)
- Exam: jaundice, RUQ/epigastric nontender mass, palpable gallbladder (Courvoisier's sign); hepatomegaly; ascites; L supraclavicular node (Virchow's)
- Laboratory tests may show ↑ bilirubin, ↑ alk phos, anemia

Diagnostic and staging evaluation (*NCCN Guidelines* v.2.2021)

- **Pancreatic protocol CT scan** (I^+ w/ arterial & venous phase imaging) or **MRI w/ contrast**

- *If no lesion seen but concerning signs & sx as above* → EUS, ERCP, or MRCP
- **Biopsy pancreatic lesion** via EUS-guided FNA (pref. for surgical candidates) or CT-guided (risk of seeding); if possible metastases, biopsy those for staging *and* dx.
- ✓ **CA19-9** preop (nb, can be ↑ in benign liver/biliary dis.); may be useful to trend postop
- **Germline genetic testing** for all Pts with pancreatic cancer

Clinical (Radiologic) Staging Pancreatic Adenocarcinoma	
Resectable	No extrapanc. dis. or bulky LAN; no **arterial** tumor contact [celiac axis (CA), SMA, common hepatic (CHA)]; and no **venous** contact [SMV, portal vein (PV)] or ≤180° + patent veins (ie, no tumor thrombus)
Borderline resectable	No extrapanc dis. or bulky LAN. **Head/uncinate:** contact w/ CHA (no extension to CA or HA bifurcation), SMA contact ≤180°, variant anatomy. **Body/tail:** contact CA ≤180° or >180° but w/o gastro-duodenal art. or aortic. **Venous:** SMV & PV contact ≤180° w/ contour irreg; contact w/ IVC.
Unresect.	**Distant mets**; or **head/uncinate:** contact >180° SMA, CA; or **Body/tail:** contact >180° SMA or CA; CA & aortic involvement; or **Venous:** SMV/PV involvement/not reconstructible

Treatment of pancreatic adenocarcinoma (*Lancet* 2016;388:73)

- **Resectable:** pancreaticoduodenectomy (**Whipple procedure**) + adjuvant chemo:
  modified FOLFIRINOX (5-FU + leucovorin, irinotecan, oxaliplatin) if ECOG 0-1 (*NEJM* 2018;379:2395), o/w gemcitabine + capecitabine (*Lancet* 2017;389:1011). Gemcitabine monoRx recently standard, but now w/ ↓ role. Role of RT is controversial.
- **Borderline:** goal to ↓ tumor to allow complete resection (R0 – neg margin at histology) using neoadjuvant Rx (various approaches tested). General schema: **chemo ± RT → restage & potential resection** depending on response**.** May need vasc. reconstruction during resection. Regimens include: FOLFIRINOX; gemcitabine + nab-paclitaxel.

- **Locally advanced** (ie, unresectable): Rx is typically palliative. However, in highly select Pts recent trend toward Rx w/ FOLFIRINOX plus XRT followed by laparotomy for response assessment (imaging can be unreliable) and potential resection.
- **Metastatic:** *clinical trials preferred;* Rx based on performance status (PS)
  Good PS: **FOLFIRINOX**, **gemcitabine** + nab-paclitaxel (*NEJM* 2013;369:1691); germline *BRCA1/2* mut: maintenance olaparib (*NEJM* 2019;381:317) also ↑ response to platinum combination chemo (eg, cisplatin w/ gemcitabine), ICI for MSI-high.
  Poor PS: gemcitabine; capecitabine; continuous infusion 5-FU
- **Palliative care:** *Biliary/gastric outlet obstruct.:* endoscopic stenting, IR drain, surg bypass. *Pain:* opiates, celiac plexus neurolysis, XRT. *Wt loss:* enzyme replacement.

Prognosis

- Resectable: if Rx'd w/ adjuvant FOLFIRINOX, 50+ mos, o/w ~30 mos
- Unresectable: if locally advanced ~1–2 y; if metastatic, ~1 y

Cystic lesions of the pancreas (*Am J Gastroenterol* 2018;113:464)

- **Serous cystadenoma:** usually benign; central scar or honeycomb appearance on imaging
- **Mucinous cystic neoplasm** (MCN): predominantly young females; multiloculated tumors in body or tail w/ ovarian-type stroma and mucin-rich fluid w/ ↑ CEA levels; precancerous
- **Intraductal papillary mucinous neoplasm** (IPMN): arises in main panc duct or branch

OTHER SOLID TUMORS

HEPATOCELLULAR CARCINOMA (HCC)

Risk factors (globally, 3rd leading cause of cancer death, espec. in Africa & Asia)

- **Cirrhosis:** present in 70–90% HCC cases
- **Infectious:** HCV & HBV (~75%), HBV/HDV coinfection; HBV can cause HCC w/o cirrhosis
- **Toxic:** EtOH (⅓ cases in U.S.), tobacco, aflatoxin from *Aspergillus*
- **Metabolic disorders:** NASH, DM, autoimmune hepatitis, hemochromatosis

Screening (screen high-risk Pts: cirrhosis, chronic HBV)

- **Ultrasonography** (U/S) + AFP q 6 mos; if high-risk may alternate U/S w/ **MRI**
- If lesion found or increasing AFP, perform **3-phase contrast CT** or **MRI**

Clinical manifestations

- Exam: nonspec. c/w liver dysfxn (eg, hepatomegaly, ascites, jaundice, encephalopathy)
- Labs: coagulopathy, low albumin, elevated LFTs; r/o other etiologies of liver dysfxn

Diagnosis

- Can diagnose w/o biopsy in high-risk Pts with **3-phase contrast CT** or **MRI**
- Only 15% of liver masses are HCC; liver metastases from other 1° more common

Treatment (*NEJM* 2019;380:1450)

- Localized disease (goal = cure) → **resection** if feasible (preferred), ablation, transarterial chemoembolization, or radiotherapy (SBRT)

also options. Inadequate hepatic reserve → **liver transplant** if able (*NEJM* 1996;334:693); non-surgical local and/or systemic Rx if not.
- Systemic Rx: atezolizumab (anti-PD-L1) + bevacizumab preferred (*NEJM* 2020;382:1894), 2nd line: kinase (lenvatinib, sorafenib) or PD-(L)1 inhib (*Lancet* 2017;389:2492 & 2018;391:1163)

GASTRIC/ESOPHAGEAL CANCER

Epidemiology (*Lancet* 2017;390:2383 & 2020;29:635)
- **Esophageal:** Predominantly adenocarcinoma in U.S. (>60%), squamous cell (SCC) more common globally. Risk factors: GERD → Barrett's esoph (adeno), smoking/EtOH (SCC)
- **Gastric:** Predominantly adenocarcinoma. Risk factors include *H. pylori*, FHx & cancer syndromes (eg, Lynch syndrome), nitrosamines in diet, smoking/EtOH.

Screening
- **Esophageal:** screen for Barrett's w/ endoscopy if multiple risk factors (eg, hiatal hernia, age ≥50, male, chronic GERD, obese, smoking, FHx). Repeat q3–5y if Barrett's.
- **Gastric:** typically not screened in U.S. More common in regions w/ higher incidence (eg, Japan, Korea, Chile) w/ endoscopy or barium radiographs.

Clinical manifestations
- Dysphagia, wt loss, early satiety, nausea, typically occult GI bleed, vague abd discomfort
- Exam: diffuse seborrheic keratoses (Leser-Trélat sign, though non-specific)

Diagnosis and staging
- Both diagnosed w/ **endoscopic biopsy**. CT chest/abd/pelvis for staging. If no mets → PET/CT (occult mets). If neg → endoscopic ultrasound for locoregional assessment.
- Staging laparoscopy needed for gastric cancer
- Molecular: ✓ HER2, PD-L1, microsatellite instability & mismatch repair

Treatment (*NCCN Guidelines* v5.2021 Gastric & v4.2021 Esophageal)

- If localized disease and good performance status/fit, goal is cure with surgery
- **Localized**: resection. Periop or neoadjuvant chemo/chemoRT if stage IB or higher (*NEJM* 2012;366:2074). Adjuvant nivolumab (*NEJM* 2021;384:1191).
- **Advanced**: sequential chemo w/ platinum/fluoropyrimidine (+ trastuzumab if HER2⊕, + nivolumab if PD-L1⊕), ramucirumab (VEGF, 2nd line), nivolumab/pembrolizumab (PD-1, 3rd line)
- **Supportive care**: pain/nausea mgmt. Consider G/G-J tube if obstruction, IVF prn.

MELANOMA

Clinical presentation and workup (*NCCN Guidelines* v1.2022)

- Suspicious skin lesion (ABCDE: asymm, border, color, diameter >6 mm, evolution) → bx
- **Staging:** I & II = no regional/distant mets. III = regional LN ⊕ or in-transit/satellite mets. Ulceration & thickness confer substage within I–III. IV = distant mets.
- **Prognosis:** excellent if localized dis., ≤1 mm thickness. Varies widely stage IIIA–IIID based on nodal burden (5yr OS 20–70%; ulceration, mitotic rate, & invasion depth predictive).
- Molecular diagnostics: check for *BRAF* V600E (present in ~50% of melanomas)

Treatment (*NCCN Guidelines* v1.2022; *NEJM* 2021;384:2229)

- Wide surgical excision + sentinel node mapping (unless *in situ* or low risk of node ⊕).
  If sentinel node ⊕, nodal dissection vs. observation. No difference in survival w/ observation (*Lancet Oncol* 2016;17:757, *NEJM* 2017;376:2211).
- **Checkpoint inhibitors** (CPI = pembrolizumab, nivolumab, nivolumab/ipilimumab)
- ***BRAF/MEK* inhibitors** (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib) if activating *BRAF V600E* mutation present
- Adjuvant for high-risk node ⊕ disease: CPI (↑ RFS, *Lancet Onc* 2020;21:1465 & *JCO* 2020;38:3925) or dabrafenib/trametinib (BRAF ⊕, ↑

OS, *NEJM* 2020;383:1139)
- Metastatic: CPI mono vs. dual (ipi+nivo a/w improved response rate especially for intracranial mets, *NEJM* 2018;379:722). Consider targeted Rx if BRAF ⊕.

OVARIAN CANCER

Histopathology
- Epithelial ovarian carcinoma (EOC, 95%): high-grade serous (most common, often dx at late stage, poor prognosis), low-grade serous, endometroid, clear cell, mucinous
- Non-epithelial (~5%): germ cell, sex cord-stromal. Rare: small cell, sarcoma.

Risk factors for EOC (*Nat Rev Dis Primers* 2016;2:16061)
- Nulliparity, early menarche, late menopause; EOC risk ↑ 2–7% each additional ovulatory yr
- **Genetics:** germline testing / genetics referral for all Pts (25% w/ heritable mutation), can inform Rx (eg, PARPi maintenance, *JCO* 2020;38:1222). 5% risk if one 1st-degree relative w/ ovarian cancer, 3.5% risk if one 2nd-degree relative (*Obstet Gynecol* 1992;80:700). ↑↑ risk w/ hereditary syndromes: *BRCA1/2* (lifetime risk 17%/44%), Lynch syndrome (non-serous).
- History of pelvic radiation, endometriosis, or obesity (risk association less clear)

Clinical manifestations
- Nonspecific history of bloating, pelvic/abdominal pain, bowel sx, urinary sx
- Exam may reveal palpable pelvic mass, abdominal distention, or ascites

Diagnosis
- No screening modalities have shown survival benefit; no data to support at this time
- If concerning signs/sx (above), obtain pelvic U/S and/or CT A/P or pelvic MRI, CA-125
- Pathologic dx based on biopsy of lesion or sampling of ascitic fluid

Treatment

- Cytoreductive surgery: survival benefit even for stage IV and relapsed disease (*Gynecol Oncol* 2013;130:493; *NEJM* 2021;385:2123). Consider neoadj. chemo to ↑ likelihood of maximal cytoreduction at surgery and reduce surgical morbidity.
- Chemo: 1st line (neoadj., adj., adv.): carboplatin+paclitaxel (CP). PARPi maintenance (olaparib, niraparib, rucaparib; esp if homologous recombination deficient [eg, *BRCA1/2*]) or bevacizumab maintenance if homologous recombination proficient.
- Recurrence at >6 mos = **platinum sensitive** → Rx w/ platinum doublet. If <6 mos = **platinum resistant** → single agent chemo (eg, liposomal doxorubicin, gemcitabine) ± bevacizumab.

Primary CNS Tumors and Brain Metastases

Presentation and diagnosis

- Suspect if new focal neurologic deficits, seizure, memory or balance issues, or evidence of ↑ intracranial pressure (HA, n/v, vision change)
- **MRI brain** for suspected CNS tumors; CT less Se. Consider LP if c/f CNS lymphoma.

Primary CNS tumors

- **Meningioma:** histopath. grading (WHO grades). Grade 1 = benign, asx/small → observe. Large or sx → resection if able, radiation if not. Grade 2–3 → resection + adjuvant RT (defer if risk of RT complication high and tumor totally resected).
- **Glioma:** histopath. grading, Grade 1/2/3: astrocytoma, oligodendroglioma most common; Grade 4: glioblastoma. Grade 3/4 = "high grade" (*Neuro Oncol* 2021;23:1231).
- Notable testing: 1p/19q, *IDH*, *MGMT* methylation (predicts sensitivity to temozolomide)
- Treatment: **max resection as feasible** → adjuvant RT + temozolomide → surveillance. Steroids if neuro sx, hold until biopsy if c/f 1° CNS lymphoma. Anti-epileptics if seizures.
- Prognosis based on grade & histology. For glioblastoma, overall survival 12–15 mos, based on extent of tumor resection (*J Neurosurg* 2014;120:31).

Metastatic CNS Lesions

- ↑ incidence than 1° CNS. Most common: lung, breast, melanoma, RCC, gastro-esoph.
- **Surgery** if oligomet disease or symptomatic & resectable, steroids if neuro sx
- **Radiation** particularly if multiple mets or inoperable. Consider WBRT if many mets.
- Some systemic therapies (checkpoint inhibitors, targeted Rx in NSCLC) have CNS activity

IMMUNOTHERAPY & CELLULAR THERAPY

IMMUNE CHECKPOINT INHIBITORS (ICI)

Overview (*Science* 2018;359:1350)

- Immune checkpoints: co-inhibitory signaling molecules that limit immune responses
- Cytotoxic T-lymphocyte-assoc. protein 4 (CTLA-4): ↓ T cell activation via negative signals and ligand competition w/ CD28 (activating co-stim. molecule).
- Programmed cell death protein 1 (PD-1): on activated T cells, turns off T cell responses
- Prog. death-ligand 1 (PD-L1): PD-1 ligand expressed on tumor and/or immune cells

ICIs (*Annals of Oncol* 2017;28:2377)

Target	Drugs	Select Indications	Common Adverse Events (approx. incidence, any grade)
PD-1	Nivolumab Pembrolizumab Cemiplimab Dostarlimab	Melanoma, NSCLC, RCC, HNSCC, esoph., endometrial, MSI-high tumors	Rash (12%); hypothyroid (5%); pneumonitis (2%); colitis (<1%); hepatitis (<1%); type 1 DM (<1%)
PD-L1	Atezolizumab Avelumab Durvalumab	Urothelial carcinoma, NSCLC, SCLC, HCC (atezo)	Rash (5%); hypothyroid (2%); adrenal insufficiency (<1%); colitis (<1%); pneumonitis (<1%)
CTLA-4	Ipilimumab	Melanoma, RCC (w/ PD1), mesothelioma (w/ PD1)	Rash (21%); colitis (5%); hypophysitis (1%); hypothyroid (1%); pneumonitis (<1%); hepatitis (<1%)

ICI toxicities (*Nat Rev Dis Primers* 2020;6:38; *Curr Cardiol Rep* 2021;23:98)

- ICIs can cause inflammation of any tissue (lungs, liver, colon, joints, skin, etc.)
- Common **immune-related adverse events (IRAEs)** above; ↑ incidence w/ combinations.

- Rare: myocarditis (can be fulminant), myositis, myelitis, uveitis, diabetes
- Workup: CT chest for dyspnea; colonoscopy and infectious workup for colitis; TSH, FT4, a.m. cortisol, glucose. Trend comprehensive metabolic panel and TSH while on ICI.
- IRAEs graded 1 (mild) to 4 (severe) (*NCCN Guideline* v4.2021)

ICI toxicity treatment *(multidisciplinary care)*

- Most IRAEs reversible with steroids
- Mild symptoms (grade 1): supportive care, can often continue Rx; moderate symptoms (grade 2): hold ICI, consider steroids; severe symptoms (grades 3–4): often requires admission to hospital, hold ICI, IV steroids, targeted therapies (eg, enteracept)
- Endocrinopathies (hypophysitis, hypothyroid) are not reversible, Rx hormone replacement
- Managing IRAEs with steroids likely does not reduce ICI efficacy (*J Clin Oncol* 2019;37:1927)
- If ICI is restarted, Pts at increased risk for recurrent IRAE

CHIMERIC ANTIGEN RECEPTOR (CAR)-T CELLS

Overview (*Nat Rev Cancer* 2021;21:145)

- Autologous T cells w/ chimeric receptor: antibody variable region fused to T cell co-stimulatory intracellular signaling domains → MHC independent Ag recognition
- CAR-T cells targeting CD19 used for ALL, DLBCL, FL, MCL. Targeting B-cell maturation antigen (BCMA) for MM. Strategies for solid tumors in development.

Toxicities

- **Cytokine release syndrome (CRS)**: fever, HoTN, shock secondary to overwhelming cytokine release from proliferating T cells
- **Immune effector cell-associated neurotoxicitiy synd. (ICANS)**: cerebral edema → HA, aphasia, delirium, lethargy/obtundation. Graded using ICE score (vide infra).

CAR-T Toxicity (*Biol Blood Marrow Transplant* 2019;25:625)

Type	Grade	Mechanism & Manifestations	Treatment
CRS	1	Fever (≥38°C) ± other sx	Supportive (fluids, O_2), ±

		CAR-T Toxicity (*Biol Blood Marrow Transplant* 2019;25:625)	
	2	Fever + HoTN not needing pressors ± O_2 by nasal cannula	steroids ± anti-IL-6 (tocilizumab or siltuximab), depending on severity
	3	Fever + pressor ± O_2 > nasal cannula	
	4	Fever + >1 pressor ± ⊕ pressure vent	
ICANS	1	ICE 7–9 pts	Steroids, anticonvulsants for seizures
	2	ICE 3–6 pts	
	3	ICE 0–2 pts	
	4	Unarousable & unable to perform ICE	

ICE score: orientation (4 pts), name 3 objects (3 pts), follow commands (1 pt), write sentence (1 pt), count backward from 100 by 10 (1 pt)

ONCOLOGIC EMERGENCIES

FEVER AND NEUTROPENIA (FN) (*NCCN Guidelines* v.1.2021)

Definition

- Fever: single oral temp ≥38.3°C (101°F) or ≥38°C (100.4°F) for ≥1 h
- **Neutropenia:** ANC <500 cells/μL or <1000 cells/μL with predicted nadir <500 cells/μL

Pathophysiology and microbiology

- Predisposing factors: catheters, skin breakdown, GI mucositis, obstruction (lymphatics, biliary tract, GI, urinary tract), immune defect associated with malignancy
- Often thought due to seeding of bloodstream by GI flora, eg, GNRs (esp. *P. aeruginosa*)
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- Gram ⊕ infections have recently become more common (60–70% of identified organisms)
- Fungal superinfection often results from prolonged neutropenia & antibiotic use

Prevention (only if intermediate or high-risk)

- Bacterial: consider FQ if neutropenic esp steroids+ALL; ↓ mortality (*Cochrane* 2012 CD004386)
- Fungal: consider during neutropenia in blood cancers (posa/fluconazole, micafungin)
- Viral: consider during active Rx in blood cancers (acyclovir, famciclovir, valacyclovir)

Role of hematopoietic growth factors (*NCCN Guidelines* v.4.2021)

- Granulocyte (G-CSF) and granulocyte-macrophage (GM-CSF) colony-stimulating factors can be used (*but not in AML*) as 1° Ppx when expected FN incidence >20% or as 2° Ppx after FN has

occurred in a prior cycle (to maintain dose-intensity for curable tumors)
- CSFs ↓ rate of FN but have not been shown to affect mortality (*Cochrane* 2014 CD003039)

Diagnostic evaluation

- Exam: skin, oropharynx, lung, perirectal area, surgical & catheter sites; *avoid rectal exam*
- Studies: U/A, blood (periph & through each indwelling catheter port), urine, & sputum cx; for localizing s/s → ✓ stool (*C. diff*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s → CNS, sinus, chest or abdomen/pelvis CT
- Caveats: neutropenia → impaired inflammatory response → *exam and radiographic findings may be subtle;* absence of neutrophils by Gram stain does *not* r/o infection

Risk stratification (factors that predict lower risk)

- History: outPt, ECOG 0–1, age <60 y, solid tumor, no sx, no major comorbidities, no h/o fungal infection, MASCC Risk Index ≥21 (*Support Care Cancer* 2013;21:1487)
- Exam: temp <39 °C, no tachypnea, no HoTN, no Δ MS, no dehydration
- Labs: ANC >100 cells/μL, anticipated duration of neutropenia ≤100 cells/μL <7 d

Initial antibiotic therapy (*NCCN* Guidelines v.1.2021)

- Empiric regimens should include **antipseudomonal activity**; consider VRE coverage if ⊕
- **Low risk:** PO abx or home IV abx may be considered in select Pts (*JCO* 2013;31:1149)
  PO options: cipro+amoxicillin-clavulanate; levofloxacin; moxifloxacin (avoid if FQ Ppx)
- **High risk: hospital admission & IV abx;** *monotherapy preferred*
  options: **cefepime**, imipenem, meropenem, piperacillin/tazobactam, ceftazidime
- Antifungal Rx added for neutropenic fever ≥4 d despite abx: **micafungin**, liposomal amphotericin B, caspofungin, anidulafungin, voriconazole, & posaconazole are options

Modification to initial antibiotic regimen based on site-specific evaluation

- **Vancomycin** *only if* HoTN, PNA, clinically apparent catheter-related or soft-tissue infxn, gram ⊕ BCx, mucositis + on quinolone Ppx; d/c when BCx ⊖ × 48 h for GPCs
- Mouth/esoph (ulcer, thrush): anaerobic (if necrotizing), anti-HSV and/or antifungal Rx
- Sinus/nasal: add vanc if periorbital cellulitis, ampho if concern for Aspergillus/Mucor
- Abd pain/diarrhea: PO vanc if concern for *C. diff*; ensure adequate anaerobic coverage
- Lung infiltrates: consider atypical coverage; vanc/linezolid if c/f MRSA; TMP/SMX if c/f PCP
- CNS: ID consult; empiric meningitis Rx (incl. *Listeria*), high-dose acyclovir for encephalitis

Duration of therapy

- Known source: complete standard course (eg, 14 d for bacteremia)
- Unknown source: continue antibiotics until afebrile *and* ANC >500 cells/μL
- Less clear when to d/c abx when Pt is afebrile but prolonged neutropenia

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Spinal Cord Compression

Clinical manifestations (*Lancet Neuro* 2008;7:459)

- Metastases located in vertebral body extend and cause epidural spinal cord compression
- **Prostate**, **breast**, and **lung** cancers are most common, followed by RCC, NHL, myeloma
- **Site of involvement: thoracic** (60%), lumbar (25%), cervical (15%)
- Signs and symptoms: **pain** (>95%, *precedes neuro* Δs), **weakness**, **autonomic dysfunction** (urinary retention, ↓ anal sphincter tone), **sensory loss**

Diagnostic evaluation

- Always take back pain in Pts w/ cancer seriously. Urgent **whole-spine MRI**; CT if unable.

- **Do *not* wait for neurologic signs to develop** before initiating evaluation b/c duration & severity of neuro dysfunction before treatment are best predictors of neurologic outcome

Treatment (*NEJM* 2017;376:1358)

- **Dexamethasone** (10 mg IV × 1 STAT, then 4 mg IV or PO q6h)
  initiate immediately while awaiting imaging if back pain + neurologic deficits
- Emergent RT or surgical decompression if confirmed compression/neuro deficits
- Surgery + RT superior to RT alone for neuro recovery in solid tumors (*Lancet* 2005;366:643)
- If pathologic fracture causing compression → surgery; if not surgical candidate → RT

TUMOR LYSIS SYNDROME

Clinical manifestations (*NEJM* 2011;364:1844)

- Large tumor burden or a rapidly proliferating tumor → spontaneous or chemotherapy-induced release of intracellular electrolytes and nucleic acids
- Most common w/ treatment of **high-grade lymphomas** (**Burkitt's**) and **leukemias** (**ALL**, **AML**, **CML in blast crisis**). *Very rare w/ solid tumors*; rarely due to spont. necrosis.
- Electrolyte abnormalities: ↑ K, ↑ uric acid, ↑ PO_4 → ↓ Ca; **renal failure** (urate nephropathy)

Prophylaxis

- Allopurinol 300 mg qd to bid PO or 200–400 mg/m^2 IV (adjusted for renal fxn) & aggressive hydration prior to beginning chemotherapy or RT

Treatment

- *Avoid* IV contrast and NSAIDs; treat hyperK, hyperPO_4, and only *symptomatic* hypoCa
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP for goal 80–100 cc/h
- Rasburicase (0.1–0.2 mg/kg or 6 mg IV fixed dose) for ↑↑ uric acid esp. in aggressive malig (*JCO* 2003;21:4402; *Acta Haem* 2006;115:35). ***Avoid***

in G6PD def (hemolytic anemia). Consider G6PD testing in Jehovah's Witnesses especially if Black (12% prevalence).

- Hemodialysis may be necessary; early renal consultation for renal insufficiency or ARF

CHEMO SIDE EFFECTS

Nausea & vomiting common (*NEJM* 2016;374:1356; 375:134 & 177)

Select Adverse Effects from Chemotherapy*		
Toxicity	**Common Agents**	**Comments**
Cardiotoxicity (*NEJM* 2016;375;1457)	**Anthracyclines**	Dose-dependent CMP; ✓ EF pre-Rx
	5-FU	Spasm → ischemia; CCB may prevent
	Trastuzumab	CMP, esp w/ anthracycline, TTE's for EF
	Tyrosine kinase inhib (TKI)	QTc prolongation, CMP, angina
	Cyclophosphamide	Myopericarditis (esp. in BMT)
	Cisplatin	AKI → HypoMg / HyperK → arrhythmia
Pulmonary (*Sem Oncol* 2006;33:98)	Busulfan	~8% fibrosis or DAH; if severe → steroids
	Bleomycin	~10% IPF; ✓ PFTs pre-Rx; Rx: steroids
	TKI (esp. dasatinib)	Pleural effusion
	Cyclophosphamide	Pneumonitis, progressive fibrosis; Rx: d/c
	Bevacizumab	Pulm. hemorrhage (esp. lung SCC)
Nephrotoxicity/ urologic toxicity	Platinum Rx (**cisplatin**)	Esp. proximal tubule; pretreat w/ IV saline
	Methotrexate	Via deposition; Rx: alkalinize urine, IVF
	Cyclophosphamide	Hemorrhagic cystitis; Rx: Mesna
Neurotoxicity (*Sem Oncol* 2006;33:324)	Platinum Rx (**cisplatin**)	"Stocking-glove" neuropathy; ototoxicity
	Cytarabine	Cerebellar toxicity (irreversible 5–10%)
	Methotrexate (esp. intrathecal)	Late leukoenceph, meningitis; reverse w/ intrathecal glucarpidase, leucovorin
	Ifosfamide	Enceph; Rx: methylene blue, thiamine
	Taxanes, vincristine	Sensorimotor long fiber neuropathy
Hepatotoxicity (*Sem Oncol* 2006;33:50)	TKI (eg, imatinib, nilotinib)	↑ LFTs, rarely necrosis; Rx: d/c ± steroids
	Gemcitabine	Common ↑ ALT/AST; ↓ dose if ↑ bili
	Methotrexate	↑ ALT/AST, rarely fibrosis

Select Adverse Effects from Chemotherapy*		
Dermatologic	TKI (eg, imatinib)	Dermatitis, can be severe (eg, SJS)

*See “ImmunoRx” section for cytokine release and immune effector cell-associated neurotoxicity syndromes

PNEUMONIA

Definitions and clinical manifestations

- Pneumonia: s/s (fever, cough, purulent sputum, dyspnea) + new infiltrate on chest imaging
- Community-acquired pneumonia (CAP): pneumonia acquired outside of hospital setting
- Hospital-acquired pneumonia (HAP): pneumonia acquired ≥48 hrs after hospitalization
- Ventilator-associated pneumonia (VAP): pneumonia acquired ≥48 hrs after intubation
- Lung empyema: accumulation of pus in pleural space
- Lung abscess: parenchymal necrosis with confined cavitation
- Aspiration pneumonitis: acute lung injury after inhalation of gastric contents without infection, though bacterial infection can occur within 24–72 hrs of injury

Microbiology of Pneumonia	
Clinical Setting	**Etiologies**
CAP (*AJRCC* 2019;200:7)	*No pathogen identified in 50–60%*, virus alone in ~25%, bacteria alone in ~10%, virus-bacteria coinfection in <5% Viruses: influenza, RSV, hMPV, parainfluenza, rhinovirus, coronavirus *S. pneumoniae* (most common bacterial cause) *S. aureus* (espec. post-influenza) *Mycoplasma*, *Chlamydia* (espec. in young & healthy) *H. influenzae, M. catarrhalis* (espec. in COPD) *Legionella* (espec. in elderly, smokers, ↓ immunity, TNF inhibitors) *Klebsiella* & other GNR (espec. in alcoholics & aspiration)
HAP/VAP	*S. aureus, Pseudomonas, Klebsiella, E. coli, Enterobacter, Acinetobacter, Steno*. IV abx w/in 90 d risk factor for MDR. Viral ~20% cases.
Empyema	*S. pneumo, S. aureus, E. coli*, *Klebsiella*, *H. influenzae*, anaerobes
Lung abscess	Often polymicrobial, incl. oral flora. *S. aureus,* anaerobes*, Strep* (*anginosus,* GAS), GNR *(Klebsiella, E. coli, Pseudomonas), Nocardia, Actinomyces,* fungi, mycobacteria, *Echinococcus*

Microbiology of Pneumonia	
Immunosupp.	Above + *Pneumocystis*, *Cryptococcus*, *Nocardia*, non-TB mycobacteria (NTM), CMV, invasive molds

Diagnostic studies (*AJRCC* 2019;200:e45)

- **Sputum Gram stain/Cx:** reliable if high quality (ie, sputum not saliva; <10 squam cells/lpf). If bacterial PNA should be purulent (>25 PMN/lpf). Yield ↓ >10 h after abx (*CID* 2014;58:1782).
- **Procalcitonin:** ↑ in acute bacterial (not viral) PNA. Consider stopping abx if levels <0.25 ng/ml (<0.5 ng/mL in ICU Pts) or ↓ ≥80% from peak. ↓ abx exposure by 2–3 d (*Lancet* ID 2016;16:819 & 2018;18:95). Not validated in immunosuppressed hosts. Levels harder to interpret in CKD. False ⊕ in cardiac arrest, shock, burns, surgery.
- **CXR** (PA & lateral; see Radiology inserts)
- HIV test (if unknown); MRSA nares swab in HAP/VAP (if ⊖ 96% NPV for MRSA PNA)
- Consider in severe disease (otherwise not recommended):
  - *Legionella* urinary Ag (detects *L. pneumophila* L1 serotype, 60–70% of clinical disease)
  - *S. pneumoniae* urinary Ag (Se 70%, Sp >90%)
  - Blood cultures (*before antibiotics!*): ⊕ in ~10% of inPts, depending on pathogen
- If clinical suspicion for mTB: (induced) sputum AFB stain ×3 q ≥8h (w/ ≥1 early morning). Mycobact. cx (*empiric respiratory isolation while pending*); MTb DNA PCR if smear ⊕.
- **Viral testing** (DFA or PCR) on nasopharyngeal swab or sputum
- Bronchoscopy: immunosupp., critically ill, failure to respond, suspected PCP, inadequate/ ⊖ sputum cx (send Gram stain/cx, *Legionella* cx, fungal cx/wet prep, mycobacterial cx/smear, modified AFB stain, galactomannan)
- Reasons for failure to improve on initial treatment:
  - Insufficient time: may take ≥72 h to see improvement (fever persists >4 d in ~20%)
  - Insufficient drug levels for lung penetration (eg, vanco trough <15–20 µg/mL)

Resistant organisms or superinfxn: eg, MRSA, *Pseudo.;* consider **bronchoscopy**

Wrong dx: fungal/viral, chemical pneumonitis, PE, CHF, ARDS, DAH, ILD; **consider CT**

Parapneumonic effusion/empyema/abscess: if CXR ⊖, **consider bedside US or CT**. If effusion >1 cm, drain & send fluid pH, gluc, Gram stain & Cx.

Metastatic infection (eg, endocarditis, septic arthritis)

Triage

- **qSOFA** predicts poor outcomes, prolonged ICU stay, and in-hospital mortality if >2 of 3: RR>22, AMS, SBP<100 (*JAMA* 2016; 315:801)

Treatment (*NEJM* 2019;380:651; *AJRCC* 2019;200:e45)	
Scenario	**Regimen**
CAP (outPt)	Amoxicillin, azithro, or doxy (*avoid* latter two if >25% resistance locally)
CAP (ward)	[3rd-gen ceph + azithro] *or* levoflox; omadacycline ≈ FQ (*NEJM* 2019;380:517)
CAP (ICU)	3rd-gen ceph + azithro. Only cover MRSA or *Pseudomonas* if risk factors (prior PsA PNA, MRSA infection, recent hospitalization, IV abx)
HAP/VAP	[Pip-tazo *or* cefepime *or* carbapen.] + [vanc or linezolid]. May add resp FQ or azithro if concerned for atypicals. Daptomycin not active in lungs.
Empyema/ abscess	[3rd-gen ceph + MNZ] *or* amp-sulbactam. Only cover *Pseudomonas* or MRSA if risk factors. Empyema: drain if >1 cm ± chest tube. Abscess: drainage not required. De-escalate to PO abx based on clinical improvement & micro.

- Avoid quinolones if suspect TB. When possible, de-escalate abx based on sensitivities.
- Steroids: not unless indicated for shock or COPD exacerbation; may ↓ mortality, mech vent, & ARDS in severe CAP (*Cochrane* 2017;12:CD007720). *Avoid* in influenza.
- Duration: CAP: 5–7 days, can de-escalate IV abx to PO after clinical improvement. HAP/VAP: 7 days. Empyema/abscess: 2–6 wks based on complexity, drainage.

Prevention

- All persons >65 or age 19–64 w/ CHF, lung disease, cirrhosis, DM, EtOH, smoker, immunosupp. (eg, ESRD, organ transplant, HIV, leukemia, lymphoma, asplenia)
- PCV20 vaccine or PCV15 + PPSV23 1 yr later

Viral Respiratory Infections

URI, bronchitis, bronchiolitis, pneumonia (*Lancet* 2011;377:1264)

Microbiology & epidemiology (http://www.cdc.gov/flu/weekly)

- Typical pathogens: Short, mild = rhinovirus, other non-SARS-CoV-2 coronavirus.
  Longer, more severe or complicated = **influenza**, parainfluenza, RSV, adenovirus, metapneumovirus, COVID-19 (vide infra). Can be esp. severe in immunosupp.

Diagnosis

- Sx: fever, cough, myalgias, SOB, wheezing, sore throat, rhinorrhea, malaise, confusion
- Respiratory viral panel on nasal swab or sputum/BAL; rapid flu *nasopharyngeal swab* preferred to nasal swab (Se 50–70%, Sp >90%); RT-PCR for flu A/B (>95% Se & Sp)

Treatment (*NEJM* 2017;390:697)

- **Influenza (A & B):**
- Neuraminidase inhib. (eg, oseltamivir); must start w/in 48 h of sx for low-risk; for critically ill or immunosupp., start ASAP even if >48 h. Peramivir IV if unable to tolerate PO.
- Endonuclease inhib. (baloxavir), superior to oseltamivir in ↓ sx & viral load on 1st day of Rx, but resistance emerging; no data in severe influenza (*NEJM* 2018; 379:913)
- **RSV:** can consider inhaled ribavirin in immunosupp, but very expensive & rarely used

Prevention

- Inactivated **influenza vaccine**: rec for *all* >6 mo of age.
- Isolation, droplet precautions for inpatients strongly recommended
- Ppx for high-risk contacts of confirmed influenza: oseltamivir × 7 d or baloxavir single dose

CORONAVIRUS (COVID-19) / SARS-COV-2 INFECTION

Microbiology & epidemiology

- Person-to-person transmission via respiratory particles; asx & pre-sx transmission can occur
- Incubation period: up to 14 days, median time of 4–5 days from exposure to sx onset

Presentation

- Ranges from asx to severe illness. Of those with sx, 81% mild-to-moderate, 14% severe (hypoxia), 5% critical (ARDS, shock, multiorgan failure) (*JAMA* 2020:323;13)
- Common sx: fever, chills, cough, dyspnea, myalgias, HA, N/V, diarrhea, loss of smell/taste
- Risk factors for severe illness: age ≥65, CVD, DM, stroke, lung dx, CKD, obesity

Diagnosis

- RT-PCR testing of nasopharynx, lower respiratory tract, or anterior nares
- Rapid antigen testing of anterior nares (less Se than PCR)
- CXR: typically bilateral opacities (esp peripheral), can be nl early; consider CT if dx ?

Treatment (https://www.covid19treatmentguidelines.nih.gov/)

- Non-hospitalized: mAb, paxlovid and molnupiravir if risk factors for severe disease
- Hospitalized w/ suppl O_2: dexamethasone ± remdesivir (inhibits vRNA polymerase)
- Hospitalized w/ mechanical ventilation or ECMO: dexamethasone + anti IL6 (tocilizumab/ sarilumab) or anti JAK (baricitinib/tofacitinib) if rapidly ↑ O_2 requirement but not intubated
- Anticoag. due to high rate of thrombosis; Ppx vs. Rx dosing based on severity and risk

Prevention

- Vaccines against spike protein highly effective. Infxn may occur but severity much lower.

- See CDC website for quarantine guidelines
  (https://www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html)

FUNGAL INFECTIONS

Fungal diagnostics

- **Antigen detection**
  - **1,3-β-D glucan** (Se 75%, Sp 85%): **Candida, Aspergillus, Histo, Coccidio, PCP**, *for invasive infxn in immunocomp host*. *Cannot* detect Mucor, Rhizopus, Blasto, Crypto.
  - **Galactomannan** (Se 71%, Sp 89%): **Aspergillus**. BAL preferred. Test *serum* only if heme malig or HSCT. Not for screening or Rx monitoring in solid organ Tx, chronic granulomatous disease (false ⊕ w/ colonization).
  - **Histo urine/serum Ag**: Se of urine Ag 90% (serum 80%) if dissem; Sp limited by X-react
  - **Crypto Ag** (serum, CSF): sAg >90% Se & Sp in invasive, less for pulm. only unless HIV+
  - **Blastomyces:** urine >serum Ag, high Se but modest Sp given X-react w/ other fungi
- **Culture**: *Candida* grows in blood/urine Cx, but ↓ Se of BCx in deep tissue infection; others (eg, *Crypto*, *Histo*) ↓↓ Se of BCx; if suspect *Coccidio* alert lab *(biohazard)*
- **Antibody detection**: useful for *Coccidio* (serum IgG and IgM 7–21 days post exposure)
- **Biopsy**: no grinding of tissue if Zygomycetes suspected

Candida species

- **Microbiology:** normal GI flora; *C. albicans* & nonalbicans spp.
- **Epidemiology:** neutropenia, immunosupp., broad-spectrum abx, intravascular catheters (esp. if TPN), IVDU, abd surgery, DM, renal failure, age >65
- **Clinical manifestations:**
  - Mucocutaneous: cutaneous (eg, red, macerated lesions in intertriginous zones); oral thrush (exudative, erythematous or atrophic; if unexplained, r/o HIV); esophageal (odynophagia; ± oral thrush); vulvovaginal, balanitis

Candiduria: typically *colonization* due to broad-spectrum abx and/or indwelling catheter

Candidemia: ⊕ *blood cx are never a contaminant!* R/o retinal involvement (ophtho consult) & endocarditis w/ TTE ± TEE (esp. w/ prosthetic valve) as req ↑ Rx duration. May present w/ erythematous papules or pustules in immunosupp.

Candida in sputum: usually not a clinically significant pathogen

Hepatosplenic: typically, after prolonged neutropenia as cell counts are recovering

Treatment (*CID* 2016;62:409)	
Mucocutaneous	Clotrimazole, nystatin, fluconazole, itraconazole
Candiduria (*if pyuria or sx of infxn*)	Fluconazole or intravesical ampho if severe infxn, immunosupp. or planned GU procedure.
Candidemia w/o neutropenia	**Echinocandin** (mica 1st line) if stable w/o prior azole exposure can consider fluc; *remove CVC*; test for azole-resist.
Candidemia w/ neutropenia	**Echinocandin** *or* ampho; *remove CVC*; test for azole-resist.

Aspergillosis (*Lancet* 2021;397:499)

- **ABPA:** airway hypersensitivity secondary to aspergillus colonization
- **Chronic pulmonary aspergillosis:** includes aspergilloma (fungus ball), pulm. nodules, chronic cavitary and chronic fibrotic pulmonary aspergillosis that can present with subacute cough, dyspnea, hemoptysis; aspergilloma/nodules can be asymptomatic
- **Invasive aspergillosis:** seen in immunosupp., esp prolonged neutropenia. Primarily pulmonary, ie, PNA w/ *chest pain*, cough, *hemoptysis;* CT: solid/cavitary nodules, halo sign. Non-pulm. manifestations: rhinosinusitis (like Zygomycetes), CNS (brain abscesses, mycotic aneurysm), endophthalmitis (eye pain, visual changes), cutaneous, GI (typhlitis)

  Rx: voriconazole or posaconazole preferred over ampho. For aspergilloma, ± resection.

Zygomycetes (eg, ***Mucor, Rhizopus***)

- **Epidemiology: diabetes** (espec. those w/ prior DKA), heme malignancy, neutropenia, transplant, chronic steroids, iron overload, trauma, h/o voriconazole Rx or Ppx

- **Clinical: rhinocerebral** = severe periorbital/facial pain, swelling, vision changes, sinusitis, opthalmoplegia, nasal ulcerations/ necrosis, HA. Other: **pulm.** (PNA w/ infarct & necrosis); **cutaneous** (indurated painful cellulitis ± eschar); **GI** (necrotic ulcers); **renal** (flank pain, fever).
- **Treatment** (high mortality): 1st line is debridement + ampho. Can deescalate to posaconazole or isavuconazole if improving after debridement.

ENDEMIC FUNGI

Cryptococcus (*CID* 2010;50:291)

- **Epidemiology:** immunosupp. most susceptible (espec. AIDS, transplant recipients, and cirrhosis); can occur in healthy hosts (esp *C. gattii)*
- **Clinical manifestations**
  - **CNS** (meningoencephalitis): subacute HA, fever, meningismus, CN abnl, ± stupor
  - Other sites: pulm., GU, cutaneous, CNS cryptococcoma. *With any crypto dx, LP all Pts.*
- **Dx:** CSF cell counts vary in HIV vs. non-HIV; serum/CSF CrAg (Se 99%, Sp 86–100%); cx
- **Treatment**
  - CNS Rx has induction (ampho ± flucytosine × 2 wks), consolidation and maintenance (fluconazole) phases (*NEJM* 2013;368:1291); if ↑ ICP, may need repeat LP/VP shunt
  - Non-CNS disease (pulm., skin, bone, blood) in HIV ⊖ Pts: consider fluconazole

Histoplasmosis (*CID* 2007;45:807)

- **Epidemiology**: endemic to central & SE U.S., but sporadic cases throughout U.S.
- **Clinical manifestations**
  - Acute: PNA ± hilar LAN, often subacute, but high inoculum can cause acute severe PNA
  - Chronic lung disease: cough + B sx ± cavitary lesions (Ddx TB, blasto)

Disseminated (seen in immunosupp.): fever, fatigue, wt loss, mucocutaneous lesions, ΔMS, arthritis, pericarditis, interstitial infiltrates HSN, LAN, cytopenias

- **Treatment:** mild to mod: itraconazole; disseminated/severe: ampho → itraconazole

Coccidioidomycosis (*CID* 2016;63:112)

- **Epidemiology**: endemic to SW U.S., Central and South America
- **Clinical manifestations**
  - Acute: subclinical PNA, arthralgias, rash (erythema nodosum)
  - Chronic lung disease (seen in immunosupp): dyspnea, chest pain, hemoptysis, "B" sx
  - Disseminated (immunosupp, pregnant): meningitis, osteo, monoarthritis, cutaneous
- **Treatment:** no Rx for mild PNA in immunosupp.; ampho for severe/CNS involvement; azoles for extrathoracic w/o CNS involvement; some cases require debridement

Blastomycosis (*CID* 2008;46:1801)

- **Epidemiology** endemic to the eastern ½ of U.S.
- **Clinical manifestations**
  - Acute: PNA w/o hilar LAN that can progress to ARDS
  - Chronic: cough + "B" sx, fibronodular infiltrates, masses ± cavitary lesions (Ddx TB, histo)
  - Disseminated (seen in immunosupp.): rash (verrucous, ulcerated lesions), subcutaneous nodules, osteo, GU (prostatitis, epididymoorchitis), CNS involvement uncommon
- **Treatment:** mild to mod: itraconazole; disseminated/severe/CNS: ampho → itraconazole

INFXNS IN IMMUNOSUPPRESSED HOSTS

Overview

- Many Pts have ≥1 risk (eg, DM, ESRD, transplant, extremes of age)
- Accurate dx of opportunistic infections and targeted Rx key in this population
- The following is not an exhaustive list, but a delineation of common or classic etiologies

Predisposition	Classic Infectious Etiologies
Humoral immune dysfunction (eg, CVID, myeloma) and **asplenia**	**Encapsulated bacteria:** *S. pneumo*, *H. flu*, *N. meningitidis* (vaccinate against these 3, ideally prior to splenectomy) **Other bacteria:** *E. coli* and other GNRs, *Capnocytophaga* **Parasites:** *Babesia, Giardia;* **Viruses:** VZV, echovirus, enterovirus
Granulocytopenia or neutropenia (includes DM, ESRD → functional impairment)	**Bacteria:** Gram positive: coag ⊖ staph, *S. aureus*, viridans strep, *S. pneumo*, other strep; *Corynebacterium* spp., *Bacillus* spp. Gram negative: *E. coli*, *Klebsiella*, *Pseudomonas* **Fungi:** Yeast: *Candida albicans* and other *Candida* spp. Molds: *Aspergillus, Mucor* spp., endemic fungi and others **Viruses:** VZV, HSV1 and 2, CMV
Impaired cell-mediated immunity (CMI) (eg, HIV/AIDS, chronic steroids, posttransplant, DM, ESRD, autoimmune dis.)	**Bacteria:** *Salmonella spp., Campylobacter, Listeria, Yersinia, Legionella* (*Lancet* 2016;387:376)*, Rhodococcus, Nocardia,* TB, non-TB mycobacteria **Fungi:** *Candida, Crypto, Histo, Coccidio, Aspergillus, Pneumocystis, Zygomycetes* spp. and other molds **Viruses:** HSV, VZV, CMV, EBV, JC virus, BK virus **Parasites:** *Toxoplasma, Cryptosporidium, Isospora, Microsporidia Babesia; Strongyloides*
Organ dysfunction	**Liver (esp. cirrhosis):** *Vibrio* spp., encapsulated bacteria **ESRD:** impaired granulocyte fxn and CMI as above Iron overload (or deferoxamine Rx): *Yersinia*, *Zygomycetes*
Biologics (eg, TNF inhibitors, anti-B- cell Rx; ✓ for TB before starting)	**Bacteria:** sepsis, septic arthritis, TB, NTM, *Listeria*, *Legionella* **Fungi:** *Pneumocystis, Histo, Coccidio, Aspergillus*, endemic fungi **Viruses:** JC virus (PML), EBV, HSV, VZV, HBV **Parasites:** *Strongyloides* reactivation

(*NEJM* 2007;357:2601; *Am J Med* 2007;120:764; *CID* 2011;53:798)

URINARY TRACT INFECTIONS

Definitions

- **Asymptomatic bacteriuria:** presence of bacteria in urine without signs or sx of infection
- **Uncomplicated:** confined to bladder. No upper tract or systemic infection signs.
- **Complicated:** extends beyond bladder (pyelonephritis, renal/perinephric abscess, prostatitis) with symptoms of fever, rigors, malaise, flank pain, CVA tenderness or pelvic/perineal pain. More likely to develop bacteremia or sepsis. Men, those w/ nephrolithiasis, strictures, stents, urinary diversions, immunosupp, DM, are not automatically complicated. Pregnant & renal Tx *are* considered complicated.

Microbiology

- Uncomplicated: ***E. coli*** (80%), *Proteus*, *Klebsiella*, *S. saprophyticus* (*CID* 2004;39:75). In healthy, nonpregnant women, lactobacilli, enterococci, Group B strep, and coag-neg staph (except *S. saprophyticus*) are likely *contaminants* (*Annals* 2012;156:ITC3).
- Complicated: as above + PsA, enterococci, staph (uncommon 1° urinary pathogen w/o catheter or recent instrumentation; ? bacteremia w/ hematogenous spread). ↑ MDR.
- Catheter-associated: *E. coli* most prevalent, candida, *Enterococcus,* PsA, other GNR
- Urethritis: *Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Trichomonas vaginalis, Mycoplasma genitalium*, HSV

Clinical manifestations

- **Cystitis: dysuria**, **urgency**, **frequency**, hematuria, suprapubic pain; fever *absent.* R/o vaginitis if symptoms of cystitis & urethritis. Neurogenic bladder Pts may have atypical sx (↑ spasticity, autonomic dysreflexia, malaise).

- **Urethritis:** dysuria, urethral discharge (see "STI")
- **Prostatitis**
  Chronic: similar to cystitis + *symptoms of obstruction* (hesitancy, weak stream)
  Acute: perineal pain, fever, tenderness on prostate exam
- **Pyelonephritis:** fever, chills, flank or back pain, nausea, vomiting, diarrhea
- **Renal abscess**: pyelonephritis sx + *persistent fever on appropriate antibiotics*

Diagnostic studies (*NEJM* 2016;374:562)

- **Urinalysis: pyuria** + bacteriuria ± hematuria ± nitrites
- **Urine Cx** (clean-catch midstream or straight-cath)
  Obtain cx only if symptoms (although in ill Pts, can include ΔMS, autonomic instability)
  ⊕ if: ≥10^5 CFU/mL, though <10^5 but ≥10^2/mL may still indicate UTI in some scenarios
  Pyuria & ⊖ UCx=sterile pyuria. Ddx: prior abx, nephrolithiasis, interstitial nephritis, tumor, TB, urethritis (see "STI")
- **Catheter-associated:** requires (1) s/s (incl atypical) + (2) urine Cx w/ 1 species ≥10^3 colonies from clean urine sample (**after** replacing Foley). Pyuria alone *not* sufficient to dx
- Blood cultures: obtain in febrile Pts; consider in complicated UTIs
- For all men w/ UTI, consider prostatitis: ✓ prostate exam
- CT A/P: consider in severely ill, obstruction, persistent sx after 48–72 hours of approp abx

Treatment of UTIs (*CID* 2011;52:e103; *JAMA* 2014;312:1677)

Scenario	Empiric Treatment Guidelines (narrow based on UCx)
Asymptomatic bacteruria	Do *not* treat. Exceptions: pregnant women, renal transplant, prophylaxis prior to invasive urologic procedures (*CID* 2019;68:1611).
Cystitis (*JAMA* 2014;16:1677)	Uncomp: nitrofurantoin (Macrobid 100 mg PO q12h or Macrodantin 100 mg PO q6h) × 5 d *or* TMP-SMX DS × 3 d *or* fosfomycin (3 g × 1). Refer to dosing guidelines for ↑ Cr. Complicated: outPt FQ or TMP-SMX PO × 7–14 d FQ or TMP-SMX superior to β-lactams (*NEJM* 2012;366:1028) InPt: CTX or FQ; PO if improving, if growing GPC add vancomycin If catheterized **remove or exchange catheter**.
Prostatitis	FQ or TMP-SMX PO × 14–28 d (acute) or 6–12 wk (chronic)

Treatment of UTIs (*CID* 2011;52:e103; *JAMA* 2014;312:1677)	
Pyelonephritis	OutPt: FQ × 7 d *or* TMP-SMX PO × 14 d (*Lancet* 2012;380:452) InPt: CTX × 14 d; if at risk for MDR pathogen cefepime, pip-tazo, carbapenem, or plazomicin (*NEJM* 2019;380:729) (Δ IV → PO when clinically improved & afebrile 24–48 h, tailor to Cx)
Renal abscess	Drainage + antibiotics as for pyelonephritis

SEXUALLY TRANSMITTED INFECTIONS

Risk Factors and Screening (*MMWR* 2021;70:1)

- **High risk:** >10 lifetime sexual partners, prior STI, MSM, sex workers
- Screening recommendations: differ based on sexual practices and risk. All adults should have one-time HIV Ag/Ab, HCV Ab. Consider q3mo testing for STIs if high risk.

Genital Lesions (*MMWR* 2021; 70:1)		
	Disease	**Symptoms**
Painless	Syphilis *(T. pallidum)*	1°: **chancre** = firm, indurated, clean base 2°: fever, LAN, rash palms/soles, uveitis, condylomata lata 3°: aortitis/aneurysm, gumma, CN palsies (7/8), tabes dorsalis, aseptic meningitis Latent = asx; early latent <1yr; late >1yr/unknown
	LGV (*C. trachomatis, L1–L3*)	1°: transient papule 2°: 2–6 wks later, painful inguinal LN (buboes) 3°: Anorectal syndrome w/ proctitis, ulcers
	Donovanosis/GI (*K. granulomatis*)	Multiple beefy, firm, irregular ulcers ("granuloma inguinale"), no LAN; in tropics
Painful	Genital herpes (HSV 2>1)	Prodrome: multiple painful vesicles 1° outbreak: more severe ± LAN/fever
	Chancroid (*H. ducreyi*)	Multiple ulcers ± LAN, in tropics

Diagnosis (*MMWR* 2021;70:1; *JAMA* 2022;327:161)

- Syphilis: 1st step is treponemal test: IgG to *T. pallidum*. ⊕ for life.
  2nd step: confirm w/ non-treponemal test (VDRL/RPR titer). Should ↓ 4-fold w/ Rx.
  Neurosyphilis: LP not needed if only ocular or otic sx. CSF VDRL may be ⊖.

- LGV: clinical dx + ⊕ rectal *C. trachomatis* NAAT + r/o other causes of proctitis
- Donovanosis: bx w/ Donovan bodies (encapsuled GNR) in monocytes/macrophages
- Genital herpes: clinical dx; confirm w/ PCR, viral cx from lesion
- Chancroid: clinical dx; r/o syphilis & HSV

Treatment (*MMWR* 2021;70:1; *JAMA* 2022;327:161)

- Syphilis
  1°/2°/early latent: PCN G benzathine 2.4 mil U IM × 1
  3°/late latent: PCN G 2.4 mil U IM × 3
  Neuro: IV PCN G 4 mil U q4h 10–14 d (*CID* 2011; 53:S110)
- LGV: doxy 100 mg BID × 21 d + aspiration of buboes
- Donovanosis: azithro 1g qwk × 3 wks, until healed (*MMWR* 2015;64)
- Genital herpes: valacyclovir 1g bid × 7–10 d. Consider suppression if >6 outbreaks/yr.
- Chancroid: azithro 1g × 1 PO *or* cipro 500 mg bid × 3 d

Genital Discharge (*MMWR* 2021;70:1)

Disease	Symptoms
Gonorrhea *(N. gonorrhoeae)* & Chlamydia (*C. trachomatis*)	♀: Mucopurulent cervicitis, dysuria, PID; can be asx ♂: Urethritis, infxn of epididymis/prostate All: pharyngitis
Mycoplasma genitalium	Suspect in Pts w/ urethritis/cervicitis after Rx for GC/CT
Trichomoniasis (*T. vaginalis*)	♀: Malodorous purulent discharge, dysuria, dyspareunia ♂: Asymptomatic
Bacterial vaginosis (*Gardnerella vaginalis*)	♀: Malodorous grey/white discharge, no dyspareunia

♀ denotes all persons with a vagina. ♂ denotes all persons with a penis.

Diagnosis (*MMWR* 2021;70:1; *JAMA* 2022;327:161)

- NAAT (vaginal/cervical/urine ♀; urine ♂), mycoplasma testing not widely available
- For GC/CT, strongly suggest urine + rectal/pharyngeal swab if history of oral or anal sex
- Trichomoniasis: motile trichomonads on wet mount
- Bacterial vaginosis: clue cells on wet mount; ⊕ whiff test; vaginal culture

Treatment (*MMWR* 2021;70:1; *JAMA* 2022;327:161)

- GC: CTX 500 mg IM × 1 (if wt >150 kg, 1 g). CT: doxy 100 mg PO bid × 7 d (preferred) or azithro 1 g PO × 1. Do *not* need to treat both if neg NAAT. Retest at 3 mos.
- *M. gen.*: doxy 100 mg PO bid × 7 d, then: moxifloxacin 400 mg PO qd × 7 d
- Trich: ♀ → MNZ 500 mg PO bid *or* tinidazole 2 g PO qd × 7 d. ⇕ → MNZ 2 g PO × 1.
- Bacterial vaginosis: MNZ 500 mg PO bid × 7 d *or* vaginal Rx w/ MNZ gel daily × 5 d

SKIN AND SOFT TISSUE INFECTIONS

Definitions

- **Cellulitis:** infection of dermis and subcutaneous tissue characterized by erythema, warmth, tenderness, and swelling; often occurs as a result of skin breaches (*JAMA* 2016;315:3)
- **Skin abscess:** subcutaneous collection of pus
- Staph toxic shock syndrome: rapid onset fever, rash, hypotension, and multiorgan injury. *Staph aureus* cx are not necessary for dx. Often associated with packing (tampon, nasal packing). Management may require surgical debridement + abx.

Risk Factors

- Trauma, edema, preceding skin inflammation or infection, obesity, DM, other immunosupp.

Microbiology (*CID* 2014;59:e10)

- Purulent: **MRSA** (*NEJM* 2006;355:666) causes up to 75% of purulent skin/soft tissue infections, followed by MSSA and strep
- Non-purulent: *Strep*, MSSA, aerobic GNRs. MRSA less commonly unless significant risk factors (prior MRSA infection, IVDU, HD, recent abx or hospitalization).
- Bites: **skin** (***Strep*, *Staph*** [MRSA only if risk factors]) and **oral flora** (including anaerobes) + special exposures:

Feature	Microbiology	Clinical	Treatment
Cat bite*	*Pasturella spp*	Rapid onset erythema, swelling, lymphangitis, fever	Amox/clav
Dog bite	*Pasturella & Capnocytophaga spp*	Can cause severe sepsis w/ DIC & gangrene in asplenic/cirrhotics and other immunosupp.	Amox/clav If Capno. suspected: pip/tazo or carbapenem
Penetrating injury	*Pseudomonas*	Can be a/w deep tissue abscess	Directed based on suscept.

Gardening	*Sporothrix*	Ulcerating nodules, lymphatic spread	Itraconazole
Salt H_2O or raw oysters/fish	*V. vulnificus*	Hemorrhagic bullae & sepsis (esp. in cirrhotics)	Doxy + Ceftaz/CTX
	Mycobacterium marinum	Indolent, nodules on extremities/ superficial lymphadenitis	Macrolide + rifampin/ ethambutol
Fresh H_2O	*Aeromonas*	Myonecrosis/rhabdo can occur.	FQ, TMP-SMX, or CTX

*Cat scratch disease caused by *Bartonella* acquired via cat scratch or bite. Results in lymphadenitis.

Diagnosis

- Clinical diagnosis based on physical examination
- Cultures from intact skin are not helpful and should *not* be performed (*CID* 2014;59:e10)
- BCx are typically low yield (~5–10%)
- Ultrasound can be used to identify deep abscesses and facilitate drainage. If abscess is found, incision/drainage is key to treatment.
- Aspirate from an abscess may provide microbiologic dx

Cellulitis Treatment (*NEJM* 2014;370:2238; *CID* 2014;59:e10; *JAMA* 2016;316:325 & 2017;317:2088)

Purulent	Usual Micro	Severity	Treatment
No	β-hemolytic *Strep* >*S. aureus*	Mild	Oral: PCN VK, cephalosporin
		Mod	IV: PCN, ceftriaxone, cefazolin
		Severe	IV: vanc + pip/tazo (± clinda for toxic shock syndrome)
Yes	*S. aureus* (incl. MRSA) >> β-hemolytic *Strep*	Mild	Consider I&D only vs. I&D + clinda or TMP-SMX (*NEJM* 2017;376:2545)
		Mod	I&D + TMP-SMX or doxycycline
		Severe	I&D + IV vanc, daptomycin or linezolid (± clinda for toxic shock syndrome)

Mild: abscess <2 cm, no systemic signs of infection, immunocompetent, no indwelling hardware; moderate: systemic signs; severe: SIRS or immunosuppressed

- **Limb elevation;** erythema may *worsen* after starting abx b/c bacterial killing → inflam.
- In obese Pts, adequate drug dosing important to avoid treatment failure (*J Infect* 2012;2:128)

• **Duration:** 5 to up to 14 d based on severity and response to treatment. Take pictures & draw margins to track progress.

NECROTIZING SOFT-TISSUE INFECTIONS (*NEJM* 2017;377:2253)

Definition

• Fulminant tissue destruction, systemic toxicity & high mortality. **Surgical emergency**.
• May include cellulitis, fasciitis, myositis, myonecrosis (gas gangrene).

Risk factors

• Can affect healthy individuals via skin/mucosal breach or traumatic wound, but ↑ risk w/ DM, PVD, EtOH abuse, IVDU, cirrhosis, or other immunosupp.

Microbiology

• **Necrotizing fasciitis**
• Type I: polymicrobial (mixed aerobes & anaerobes), typically in older Pts w/ above RFs. **Fournier's gangrene** involves genitalia and/or perineum
Head and neck NSTI evolve from oral flora including anaerobes
• Type II: monomicrobial, usually group A strep, less likely *Staph, Vibrio, Aero.*; a/w TSS
• **Clostridial myonecrosis (gas gangrene):** *C. perfringens; C. septicum* (large Gram ⊕ rods w/ blunt ends on Gram stain). A/w traumatic wounds that create an anaerobic environment ideal for *Clostridia*.

Clinical manifestations

• Erythema, edema, warmth + **systemic illness** ± **crepitus,** bullae, necrosis
• **Rapid progression** of clinical signs
• **Pain out of proportion** to apparent cellulitis; skin hyperesthetic and later anesthetic

Diagnosis

• Clinical dx is sufficient to initiate **urgent surgical exploration**

- Aspiration of necrotic center; BCx; Gram stain; lactate, AST, & CK for deep tissue necrosis
- Imaging: **noncontrast CT**, but do not delay Rx/surgery (*Arch Surg* 2010;145:452)
- Microbiologic dx from Gram stain and culture of surgical specimens

Treatment (*CID* 2014;60:169)

- Urgent surgical exploration with debridement of necrotic tissue and ID consultation
- Empiric antibiotics: [pip/tazo *or* ceftriaxone + metronidazole *or* carbapenem] + [vanco or linezolid]. For Group A Strep: penicillin + clindamycin + consideration of IVIG for toxic shock.

Diabetic Foot Infections

Microbiology and severity (*CID* 2004;39:885)

- **Mild** (superficial ulcer, no involvement of deeper structures, surrounding erythema <2 cm, and no systemic illness): usually *S. aureus* or aerobic streptococci
- **Moderate** (ulcer with involvement of deeper structures, surrounding erythema >2 cm, or lymphangitic streaking and no systemic illness): more likely to be chronic and polymicrobial (PsA, enterococci, enteric GNR, anaerobes)
- **Severe** (moderate + systemic illness or metabolic instability): anaerobic streptococci, enteric GNR, PsA, *Bacteroides*, *Clostridium*

Initial evaluation

- Cleanse, debride, probe, and obtain deep anaerobic + aerobic cultures
- Assess for PVD: sensation, pulses, ABIs

Diagnosis

- **Deep tissue wound cx** at time of debridement (ideally prior to antibiotics). Superficial swabs are typically of limited utility due to colonization.
- For mod/severe: obtain blood cx, ESR, CRP
- **Osteomyelitis should always be ruled out.** At ↑ risk if: grossly visible bone or able to probe to bone, ulcer >2 cm, ulcer duration

>1–2 wk, ESR >70. If suspicious for osteo, obtain plain films ± MRI (see osteomyelitis below).

Treatment (*CID* 2012;54:e132)

- **Mild infxn:** oral abx. Target GPCs (diclox, cephalexin, or amox/clav); use TMP-SMX or doxy for MRSA.
- **Mod/severe infxn:** IV abx. Target GPCs (vanco, linezolid,dapto) + GNRs (CTX, levo, or amp/sulb) ± anaerobes (metronidazole or clinda). Add PsA coverage (cefepime or pip- tazo) if: macerated wound, significant water exposure, warm climate
- Elevation, non–weight-bearing status, wound care, glycemic control, Rx for venous insufficiency and arterial ischemia
- **Many require surgery:** early, aggressive, and repeated debridement; revascularization or amputation may be necessary

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OSTEOMYELITIS

Infection of bone due to hematogenous seeding or direct spread from contiguous focus

Etiology (*Lancet* 2004;364:369)

- **Hematogenous: *S. aureus***; mycobacterial infection of vertebral body = Pott's disease
- **Contiguous focus** (may be acute or chronic)
  - Open fracture, orthopedic surgery, etc.: ***S. aureus*** and ***S. epi***
  - Skin breakdown + vasc. insuffic. (eg, diabetic foot, pressure ulcer): **polymicrobial**
  - GU source (GNR, *Enterococcus*)

Clinical manifestations

- Surrounding soft-tissue compromise ± fistula to superficial skin
- ± Fever, malaise, and night sweats (more common in hematogenous than contiguous)
- Vertebral osteomyelitis (esp. IVDU): unremitting, focal back pain, ± fever (*NEJM* 2010;362:1022)

Diagnosis (*JAMA* 2008;299:806)

- Crucial to obtain cx data of causative organism to avoid long-term empiric abx

- **Bone biopsy** or **tissue cx** obtained surgically or via percutaneous biopsy (send aerobic, anaerobic, mycobacterial, and fungal cultures + pathology) unless ⊕ blood cx. Do not rely on swabs of ulcers or fistulae drainage.
- Physical exam: high suspicion in diabetic foot (see above) if can probe ulcer to bone or ulcer >2 cm^2 (Sp 83%, 90% PPV)
- **Blood cultures before antibiotics** (more often ⊕ w/ acute hematogenous osteomyelitis)
- CBC, CRP, ESR (>70 greatly ↑ likelihood of osteo)
- Imaging
  - Plain radiographs: normal early in disease; lytic lesions seen after 2–6 wk
  - **MRI:** preferred imaging study (overall Se 90%, Sp 82%; *Archives* 2007;167:125)
  - CT: can demonstrate periosteal reaction and cortical and medullary destruction
  - CT & MRI very Se but ↓ Sp; false ⊕ if contig focus w/ periosteal reaction, Charcot Δs
  - Radionuclide imaging: very Se but non-Sp (false ⊕ if soft-tissue inflammation)

Treatment

- **Antibiotics:** based on cx data. If clinically stable, consider holding antibiotics until bone bx obtained. Duration depends on Rx strategy/goals of Rx management (eg, 6 wks for vertebral osteo; *Lancet* 2015;385:875). After ≥7 days from either start of IV abx or surgery, if doing well consider (in consultation with ID!) Δ'ing IV to PO (if good bioavailability and bone penetration) (*NEJM* 2019;380:425).
- **Surgery** should be considered for any of the following: acute osteo that fails to respond to medical Rx, chronic osteo, complications of pyogenic vertebral osteo (eg, neurologic compromise, spinal instability, epidural abscess) or infected prosthesis

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Epidural Abscess

Etiology

- Hematogenous spread (⅔): skin infection, soft tissue (dental abscess), or endocarditis

- Direct extension (⅓): vertebral osteo, sacral ulcer, spinal anesthesia or surgery, LP
- Risk factors: IVDU diabetes, renal failure, alcoholism, immunosuppression
- ***S. aureus*** most common pathogen; in immunosuppressed, consider fungal, TB, and *Nocardia*

Clinical manifestations

- **Back pain** with spinal or paraspinal tenderness + **fever** ± followed by radiculopathy. *Sx of cord compression or cauda equina is a surgical emergency.*

Diagnostic studies

- **MRI** with contrast
- Aspiration of abscess fluid for Gram stain & cx or operative Gram stain & cx
- Blood cx (frequently ⊖)

Treatment

- **Antibiotics** (typically MRSA and gram-negative coverage initially then narrowed based on culture data) ± **surgery** (decompressive laminectomy and debridement) for failure to improve on medical Rx. Emergent surgery for early s/s of cord compression (w/ vertebral osteo and epidural abscess).

INFECTIONS OF THE NERVOUS SYSTEM

ACUTE BACTERIAL MENINGITIS

Definition

- Inflammation of tissue around the brain/spinal cord
- Usually arising from nasopharynx (hematogenous spread), bacteremia, or direct inoculation (surgery, contiguous infection, trauma, foreign body [eg, CSF shunt])

Microbiology in Bacterial Meningitis (*NEJM* 2011;364:2016)	
S. pneumoniae (30–60%)	Look for preceding infection (bacteremia, pneumonia, endocarditis) Drug-resistant *S. pneumoniae:* ~40% PCN-resistant (even *intermediate* resistance problematic) ~<10% 3rd-gen. cephalosporin-resistant See "Pneumonia" for *S. pneumoniae* vaccination recs
N. meningitidis (10–35%)	Primarily in age <30 y; associated petechiae or purpura ↑ risk in asplenia, complement defic., HIV, SCT, unvaccinated Vaccine rec for all age 11–18 y, HIV infection, asplenia, C5-9 deficiency
H. influenzae (<5%)	↑ risk in asplenia, complement defic., HIV, SCT, unvaccinated, CSF leak, trauma/surgery, mastoiditis Vaccine rec for all children; markedly ↓ incidence
L. monocytogenes (5–10%)	↑ in immunosupp (glucocorticoids, transplant), elderly, malignancy, pregnant, cirrhosis. Outbreaks a/w contaminated dairy & raw veg.
GNRs (1–10%)	More common in health care associated meningitis (*E. coli, Klebsiella sp., Pseudomonas aeruginosa)*
Staphylococci (5%)	Preceding infection (endocarditis, bacteremia), post CNS surgery, foreign bodies (CSF shunt, intrathecal pump)
Mixed infection	Suspect parameningeal focus or CSF leak, post CNS surgery

Clinical manifestations (*Lancet* 2016;339:16)

- Headache (84%), fever (74%), stiff neck (74%), photosensitivity, GCS <14 (71%), nausea (62%), seizure (23%); **95% have 2 of 4:**

HA, fever, stiff neck, ΔMS

- Presentation may be *atypical* (eg, lethargy w/o fever) in elderly and immunosupp.

Physical exam (*CID* 2002;35:46; *Am J Emerg Med* 2013;31:1601)

- Nuchal rigidity (Se 30%, Sp 68%), Kernig's sign (Se 5%, Sp 95%), Brudzinski's sign (Se 5%, Sp 95%), jolt sign (HA worsens w/ horizontal rotation) (Se 64%, Sp 43%)
- ± Focal neuro findings (~30%; hemiparesis, aphasia, visual field cuts, CN palsies)
- ± HEENT findings: sinus tenderness, clear rhinorrhea (CSF leak)
- ± Skin and joint findings: petechial rash (*N. meningitidis*), genital or oral ulcers (HSV), arthritis with joint effusion (*N. meningitidis*)

Sequential management of bacterial meningitis

1. **Blood cx**, initiate **empiric antibiotics**, consider corticosteroids (vide infra)
2. **CT head** if indicated (see below)
3. **LP** ASAP (if not contraindicated); yield of CSF cx unlikely to be changed if obtained w/in ~4 h of initiation of abx

Diagnostic studies (*NEJM* 2017;388:3036)

- **Blood cultures** ×2 *before abx*
- WBC count: >10,000 in >90% of bacterial meningitis in healthy hosts
- Head CT to r/o mass effect before LP *if ≥1 high-risk feature:* immunosupp., h/o CNS disease, new-onset seizure, focal neuro findings, papilledema, GCS <15 (*CID* 2004;39:1267)
- **Lumbar puncture** with opening pressure (*NEJM* 2006;355:e12)
  - Send CSF for cell count and differential, glucose, protein, Gram stain, bacterial cx
  - Additional CSF studies based on clinical suspicion: AFB smear/cx (or MTb PCR), cryptococcal Ag, fungal cx, VDRL, PCR (HSV, VZV, enteroviral), cytology
  - CSF Gram stain has 30–90% Se; cx 80–90% Se if LP done prior to abx though abx should not be delayed for LP if there is concern for bacterial meningitis
  - *Rule of 2s:* CSF WBC >2k, gluc <20, TP >200 has >98% Sp for bacterial meningitis

Repeat LP only if no clinical response after 48 h of appropriate abx or CSF shunt

Metagenomic next-generation sequencing ↑ dx yield (*NEJM* 2019;380:2327)

Typical CSF Findings in Meningitis					
Type	**Appearance**	**Pressure (cm H_2O)**	**WBC/mm^3 Predom Type**	**Glc (mg/dL)**	**TP (mg/dL)**
Normal	Clear	9–18	0–5 *lymphs*	50–75	15–40
Bacterial	Cloudy	18–30	100–10,000 *polys*	<45	100–1000
TB	Cloudy	18–30	<500 *lymphs*	<45	100–200
Fungal	Cloudy	18–30	<300 *lymphs*	<45	40–300
Aseptic	Clear	9–18	<300 *polys → lymphs*	50–100	50–100

Empiric Treatment of Bacterial Meningitis (*Lancet* 2012;380:1693)	
Adults <50 y	Ceftriaxone + vancomycin (trough 15–20), consider acyclovir IV
Adults >50 y	Ceftriaxone + vancomycin + ampicillin, consider acyclovir IV
Immunosuppressed	[Cefepime *or* meropenem] + vanc ± amp (not nec. if on meropenem), consider acyclovir IV & fungal coverage
Healthcare assoc. infection (eg, surgery, CSF shunt)	[Cefepime *or* meropenem *or* ceftazidime] + vancomycin
When possible, organism-directed Rx, guided by sensitivities or local patterns of drug resistance should be used	
Confirm appropriate dosing as *higher doses are often needed in meningitis* (though may need to be adjusted for renal function)	
Corticosteroids: If causative organism is unknown, dexamethasone 10 mg IV q6h × 4 d recommended prior to or with initiation of abx. Greatest benefit in *S. pneumoniae* and GCS 8-11 (↓ neuro disability & mortality by ~50%). Avoid in crypto (*NEJM* 2016;374:542).	
Prophylaxis: for close contacts of Pt w/ *N. meningitidis*; rifampin (600 mg PO bid × 2 d) or ciprofloxacin (500 mg PO × 1) or ceftriaxone (250 mg IM × 1). See Microbiology in Bacterial Meningitis Table for available vaccinations.	
Precautions: droplet precautions until *N. meningitidis* is ruled out	

ASEPTIC MENINGITIS

Definition

- Clinical/lab evidence of meningeal inflammation with negative bacterial cx (CSF & blood)

Etiologies (*Neurology* 2006;66:75)

- **Viral**: enteroviruses are most common cause (summer/fall; rash, GI, URI sx), HIV, HSV, VZV, mumps (parotitis), lymphocytic choriomeningitis virus (rodent exposure), encephalitis viruses, adenovirus, polio, CMV, EBV, WNV
- **Focal bacterial infection**: brain/epidural/subdural abscess, CNS septic thrombophlebitis
- **Partially treated bacterial meningitis**
- **Other infectious**: TB, fungal (cryptococcus, coccidiodes), Lyme, syphilis, leptospirosis
- **Neoplasm**: intracranial tumors (or cysts), lymphomatous or carcinomatous meningitis
- **Drug-induced** meningitis: NSAIDs, IVIG, antibiotics (TMP-SMX, PCN), anti-epileptics
- **Systemic autoimmune illness**: SLE, sarcoidosis, Behçet's, Sjögren's syndrome, RA
- Mollaret's: recurrent lymphocytic meningitis, spontaneously resolving (often HSV-2)

Diagnosis

- Obtain LP for CSF analysis: lymphocytic pleocytosis common in viral etiologies (see Typical CSF Findings in Meningitis table above)
- Consider CSF cytology and MRI brain/spine to evaluate for malignancy
- Consider serum autoimmune and serum viral testing in appropriate settings if CSF is unrevealing and there is no improvement with empiric treatment

Empiric treatment

- Suspected bacterial meningitis: see empiric treatment of bacterial meningitis above
- Suspected viral meningitis: if concern for HSV meningoencephalitis → IV acyclovir

- Unclear etiology: consider initiation of empiric bacterial meningitis treatment while observing and awaiting CSF studies

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ENCEPHALITIS (*NEJM* 2018;379:557)

Definition

- Inflammation of brain parenchyma characterized by impaired cerebral function (AMS, neurologic deficits) often due to primary viral infection or post-viral inflammation

Etiologies (specific etiology found in <20% of cases; *Neurology* 2006;66:75; *CID* 2008;47:303)

- **HSV-1** all ages/seasons. If sxs recur after Rx, consider viral relapse vs. autoimmune encephalitis b/c high rates of autoimmune disease wks later (*Lancet Neurol* 2018;17:760).
- **VZV** 1° or reactivation; ± vesicular rash; all ages (favors elderly), all seasons
- **Arboviruses:** evaluate for exposure to vector/geography. Mosquitoes: West Nile, Eastern/Western equine, St. Louis, La Crosse; Ixodes tick: Powassan.
- Enteroviruses (coxsackie, echo): preceding URI/ GI sx; peaks in late summer/early fall
- Other infectious: CMV, EBV, HIV, JC, measles, mumps, rabies, adeno, influenza, Lyme
- Non-infectious: autoimmune/paraneoplastic (anti-NMDAR, anti-Hu, anti-Ma2, anti-CRMP5, anti-mGluR5), post-infxn demyelination (eg, ADEM)

Clinical manifestations

- **Fever** + **ΔMS** (subtle to severe), seizure, focal neuro deficit, HA in meningoencephalitis

Diagnostic studies (*CID* 2013;57:1114)

- CSF analysis: **lymphocytic pleocytosis**; PCR for HSV (95% Se & Sp), VZV; consider other PCR based on risk factors (CMV/EBV, HIV, JC, adeno/enterovirus, WNV)
- Consider testing for autoimmune etiologies and serologic viral testing in appropriate settings if CSF is unrevealing and there is no improvement with empiric HSV/VZV Rx

- **MRI** (CT if unavailable); HSV temporal lobe; W. Nile & Powassan thalamic hyperintensity
- EEG to r/o seizure; findings in encephalitis are nonspecific (temporal lobe focus in HSV)

Treatment

- HSV/VZV: IV acyclovir 10 mg/kg IV q8h; consider *empiric treatment* given frequency

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Bell's Palsy

Definition & clinical manifestations

- Acute idiopathic unilat. **facial nerve palsy** (CN VII), often presumed HSV reactivation
- P/w unilateral facial muscle weakness, hyperacusis, ↓ taste, lacrimation, & salivation
- Risk factors: pregnancy (preeclampsia), obesity, HTN, diabetes, preceding URI

Diagnosis (*Otol Head Neck Surg* 2013;149:656)

- Labs, imaging, EMG not needed in routine cases
- Ddx: Bilateral: Lyme, GBS, sarcoid. Additional neuro sx: stroke, tumor. Rash: herpes zoster. Other: otitis media, HIV, Sjögren.

Treatment and Prognosis (*CMAJ* 2014;186:917)

- 70% recover spontaneously w/in 6 mos, >80% recover with glucocorticoid treatment
- Oral corticosteroids started w/in 72 hrs of sx onset improve odds of recovery; dose varies based on severity (House-Brackmann grading). No conclusive data on antivirals.
- If eyelid closure is compromised, eye protection is crucial to prevent trauma

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Herpes Zoster (Shingles)

Definition & etiology

- Painful vesicular rash in a peripheral nerve distribution due to reactivation of VZV

- Spread by contact with active lesion (prior to crusting) in uncomplicated zoster or via airborne transmission in disseminated zoster

Clinical manifestations & complications

- **Uncomplicated**: pain in a dermatomal distribution → dermatomal eruption of erythematous papules → vesicles → crusted plaques in varying stages of evolution
- **Disseminated**: vesicles across multiple dermatomes, visceral organ involvement (pneumonia, hepatitis, CNS) seen in immunosupp. (eg, transplant, malignancy)
- **Zoster opthalmicus**: ocular involvement (V1 of CN V) requires ***urgent ophtho eval***
- Post-herpetic neuralgia: neuropathic pain lasting >90 d after dx

Diagnosis

- Clinical diagnosis if uncomplicated. Confirm with PCR (most sensitive), DFA, and viral culture (allows for resistance testing) of vesicular fluid (scrape from unroofed vesicle).

Treatment & prevention

- Uncomplicated: acyclovir, valacyclovir, or famciclovir x 7 d; initiate w/in 72 h of onset for greatest benefit; consider after 72 h if new lesions present; minimal benefit after crusting
- Superimposed bacterial cellulitis is common; if suspected, treat with appropriate antibiotics
- Disseminated/immunosupp.: IV acyclovir, eval for visceral spread, droplet precautions
- Prevention: Shingrix (2 doses) for all Pts >50; consider in younger if immunosupp.

BACTEREMIA & ENDOCARDITIS

BACTEREMIA

Definitions

- 1° bacteremia: bloodstream infection due to direct inoculation of the blood
- Central line associated bloodstream infection (CLABSI): bacteremia in which the same organism is growing from peripheral and catheter cultures (*CID* 2009;49:1)
- 2° bacteremia: infection of another site (eg, UTI, PNA, colitis, etc.) spreading to blood
- Contaminant: bacteria growing in a blood culture that does not represent a true infection

Risk factors for bloodstream infections (*JAMA* 2012;308:502; *CID*;2020;71)

- Syndromes with high likelihood of bacteremia:
  - Sepsis
  - Endovascular infxns: endocarditis, infection of pacemaker, vascular graft or IV catheter
  - Vertebral osteomyelitis, epidural abscess, septic arthritis
- Risk factors: indwelling lines, IVDU, immunosupp. (neutropenic, transplant)
- Organisms
  - **More likely pathogenic**: *S. aureus*, β-hemolytic strep, enterococci, GNR, *S. pneumo, Neisseria, Candida*
  - **Less likely pathogenic**: coag-neg staph, diphtheroids, *Cutibacterium*
- Time to growth: <24 h → higher risk, >72 h → lower risk (except slow-growing, eg, HACEK)
- **Factors increasing likelihood of endocarditis:** high-grade bacteremia w/o source, persisting after line removal or drainage of

focal source, in hosts at risk for endocarditis or w/ organisms known to cause IE; emboli

Diagnosis

- ≥2 sets BCx prior to abx (set = aerobic + aneaerobic cx) at separate puncture sites
- If proven bacteremia, daily surveillance cxs until 48 hrs of ⊖ cxs. May not need for GNRs (*CID* 2017;65:1776).
- TTE/TEE if concern for endocarditis (see IE section)
- TTE and urgent ophthalmology evaluation if yeast is growing in BCx

Treatment (*CID* 2009;49:1; *JAMA* 2020;323:2160)

- Empiric abx based on Gram stain, cx, & clinical syndrome, then tailor based on sensi

Short-Term Central Venous Catheter-Related Bloodstream Infxns	
S. aureus	Risk of endocarditis in bacteremia: ~25% (*JACC* 1997;30:1072). ID consult a/w ↓ mortality (*CID* 2015;60:1451). Remove CVC, evaluate for endocarditis, osteo, hardware infections. Preferred abx: *MSSA* → nafcillin, oxacillin, or cefazolin. *MRSA* → vancomycin. Duration: 2 wks if normal host, no implants, no e/o endocarditis or metastatic complications. Otherwise 4–6 wks.
Coag-neg staphylococci	CVC retention does not ↓ rate of resolution, but a/w ↑ rate of recurrence (*CID* 2009;49:1187). If CVC left, treat 10–14 d; if removed 5–7d.
Enterococcus	Remove CVC & treat for 7–14 d
GNR	Remove CVC esp if *Pseudomonas.* Rx for 14 d (7 if uncomplicated).
Yeast	Remove CVC & treat for 14 from first ⊖ BCx. ID consult a/w ↓ mortality.

- **Persistently ⊕ BCx:** remove CVCs, look for metastatic infxn (endocarditis, septic arthritis, osteo), infected thrombosis, or prosthetic material (vascular graft, PPM)

Bacterial Endocarditis

Definition

- Infection of endothelium of heart (including but not limited to the valves) including both prosthetic valve endocarditis (PVE) and

native valve endocarditis (NVE)

Risk Factors

- **Abnormal valve** (*JAMA* 1997;277:1794; *JACC* 2018;72:2443)
  High risk: prior endocarditis, prosthetic valve or ring, some congenital heart disease (unrepaired cyanotic; shunt/conduit; prosthesis in past 6 mos), transplant heart, valvulopathy, VAD
  Medium risk: previous rheumatic fever, non-rheumatic valve disease (including MVP w/ MR or thickened leaflet), HCM, bicuspid AoV
- **Risk of bacteremia:** IVDU, indwelling venous catheters, hemodialysis, prosthetic material in heart (eg, pacemaker, ICD, graft), poor dentition

Microbiology of Endocarditis				
	Native Valve (NVE)		Prosthetic Valve (PVE)	
Etiology	**Non-IVDA**	**IVDU**	**Early** (≤60 d)	**Late** (>60 d)
S. viridans et al.	**36%**	**13%**	<5%	**20%**
Enterococcus	**11%**	5%	8%	13%
S. aureus	**28%**	**68%**	**36%**	**20%**
S. epidermidis	**9%**	<5%	**17%**	**20%**
GNR	<5%	<5%	**6%**	<5%
Other	<5%	<5%	10%	10%
Fungal[a]	1%	1%	9%	3%
Culture ⊖[b]	11%	<5%	17%	12%

[a]↑ risk w/ DM, indwelling lines, immunosupp. [b]Cx ⊖ = abiotrophic strep, HACEK (*Haemophilus para-influenzae & aphrophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella*), *T. whipplei, Bartonella, Coxiella, Chlamydia, Legionella, Brucella* (*JAMA* 2007;297:1354; *Annals* 2007;147:829; *J Clin Microbiol* 2012;50:216)

Clinical manifestation (*Lancet* 2016;387:882)

- **Persistent bacteremia → fever** (80–90%), rigors, night sweats, anorexia, myalgias
- **Valvular or perivalvular infection → HF**, conduction abnormalities (eg, AVB)
- **Septic emboli**: stroke, embolic MI, renal/splenic/pulmonary infarcts, septic arthritis, osteo
- Immune complex phenomena: arthritis, glomerulonephritis

- Subacute endocarditis can present with subacute progressive "B" sx (fatigue, wt loss)

Physical exam

- **Cardiac murmur** (85%), s/s of new HF (pulmonary edema, JVP elevation, edema)
- Skin/ocular changes (uncommon but highly specific)
  - Janeway lesions (painless hemorrhagic macules on palms/ soles due to septic emboli)
  - Osler's nodes (painful nodules on pads of digits due to immune complex deposition)
  - Splinter hemorrhages in fingernails or toenails
  - Roth spots (retinal hemorrhages)
- MSK: point tenderness along spine, red/hot joints
- Neurologic deficits c/f embolic stroke; vertebral tenderness c/f osteo or epidural abscess
- Devices: evaluate CVCs, PM/ICD pocket, and sites of other hardware/ prosthetics

Diagnosis (*CID* 2010;51:131; *EHJ* 2015;36:3075; *Circ* 2015;132:1435)

- **Blood cultures** (*before abx*): 3 sets (aerobic & anaerobic bottles) from different sites, ideally spaced ≥1 h apart. ✓ BCx (at least 2 sets) after appropriate abx have been initiated to document clearance; repeat q24–48h until ⊖.
- Serial **ECGs** to assess for conduction disease and ↑ PR interval (c/f perivalvular abscess)
- **Echocardiogram:** TTE in all Pts. **TEE** if (i) TTE abnl but nondx, (ii) TTE ⊖ but high suspicion, (iii) complications suspected or present (eg, AVB), (iv) high-risk (prosthetic valve, CIED, prior IE, congenital heart dis.), (v) *S. aureus*, enterococcus, or fungus, (vi) Δ in signs or sx (eg, new conduction abnl, regurgitation, etc.) (vii) if considering a shortened course (10–14 d) of abx (vide infra)

	Sensitivity		
	NVE	**PVE**	**Abscess**
Transthoracic (TTE)	39–58%	33%	18–63%
Transesophageal (TEE)	>90%	86%	76–100%

(*Mayo Clin Proc* 2014;89:799; *Circ* 2015;132:1435; *Eur Radiol* 2015; 25:2125; *J Am Soc Echo* 2016;29:315)

- Gated cardiac CT useful if TTE/TEE equivocal or suspected paravalvular abscess
- PET/CT using FDG useful for suspected PVE or CIED infxn if TTE/TEE equivocal
- Brain/spine imaging if concern for CNS spread (mycotic aneurysms, embolic stroke) or spinal involvement (vertebral osteo, epidural abscess)
- **Cx ⊖ endocarditis:** may be due to abx prior to BCx. PCR, bacterial 16S ribosomal RNA, serol. may be helpful. Detailed hx: animal exposure, travel, unpast. dairy, etc. ID eval. Consider organisms listed in Cx ⊖ footnote in microbiology table (vide supra).

Modified Duke Criteria	
Definitive: 2 major *or* 1 major+3 minor *or* 5 minor; **Possible**: 1 major+1 minor *or* 3 minor	
Major	**Minor**
• **BCx** with common endocarditis pathogen (grown in 2 separate cx) • *Coxiella* serology ≥1:800 • **Endocardial involvement**: vegetation, abscess, prosthetic dehiscence or **new valvular regurgitation**	• Predisposing condition (see risk factors) • Fever • Vascular phenomena: septic arterial or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions • Immune phenomena: ⊕ RF, GN, Osler's nodes, Roth spots • ⊕ BCx not meeting major criteria

Se ~90%, Sp >95%, NPV ≥92% (*CID* 2000;30:633).

Treatment (ID consult is strongly recommended)

Treatment (*Circ* 2015;132:1435)	
Empiric	NVE or PVE >12 mos post-op: vanc + CTX PVE <12 mos post op: vanc + CTX ± gentamicin (if OK renal fxn)
Strep	Penicillin, ampicillin, cftx; if PVE consider gentamicin in discussion w/ ID
Staph (S. aureus and *lugdunensis)*	MRSA: vanc or dapto MSSA: nafcillin, oxacillin, or cefazolin (avoid if CNS involvement due to poor penetration); vanc inferior to β-lactam for MSSA For PCN allergy w/ MSSA consider desensitization Consider rifampin / gentamicin in PVE in discussion w/ ID
Enterococci	Ampicillin + [CTX or gent]; if VRE: linezolid, dapto, ampicillin if sensitive

Treatment (*Circ* 2015;132:1435)	
Gram negatives	HACEK: CTX, ampicillin or FQ. *Pseudomonas*: 2 anti-Pseudomonal agents [eg, β-lactam + (aminoglycoside or FQ)]
Fungi (candida, aspergillus)	*Candida*: amphotericin B ± flucytosine or micafungin *Aspergillus*: amphotericin B or voriconazole Ophtho consult for fungemia to rule out endophthalmitis

- De-escalate abx to organism-directed therapy based on speciation and sensitivities
- If on anticoagulation or antiplatelet, typically can continue unless concern for stroke, intracranial hemorrhage, or need for emergent surgery
- Monitor for complications of endocarditis (CHF, conduction block, osteomyelitis, new embolic phenomenon) which can occur even on abx
- Duration is usually **4–6 wks**
  - After ≥10d IV abx can consider Δ'ing to PO if clinically appropriate and available PO abx in consultation with ID (*NEJM* 2019;380:415)
  - Uncomplicated right-sided NVE or PCN-S *Strep* spp → 2 wks may be adequate
- IVDU-associated best managed by multidisciplinary teams including Addiction Medicine

Indications for surgery (consult early; *JTCS* 2017;153:1241; *Circ* 2021;143:e72)

- Emergent if refractory cardiogenic shock
- Urgent (during initial hospitalization):
  - **Sx HF**
  - **Penetrating infection**: periannular abscess, heart block, fistula, worsening conduction
  - **Persistent infection**: ⊕ BCx after >5 d of appropriate abx, ↑ or ? large vegetation
  - **Emboli**: recurrent or w/ residual large (>10 mm) vegetation & severe AR/MR. Cerebral emboli *not* contraindic. unless severe stroke or hemorrhage (*Stroke* 2006;37:2094).
  - *S. aureus*, fungal or multiRx-resistant organisms
  - PVE (emergent if dysfunction or dehiscence)

Endocarditis Prophylaxis (*Circ* 2007;116:1736)

Endocarditis Prophylaxis (*Circ* 2007;116:1736)	
Cardiac conditions*	**Prosthetic valve; previous endocarditis; congenital heart disease** (CHD) including unrepaired or incompletely repaired cyanotic CHD (palliative shunts or conduits), 1st 6 mo after completely repaired CHD using prosthetic material; cardiac transplant recipients w/ valvulopathy. (Prophylaxis no longer rec. in acquired valvular dysfxn, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCM.)
Procedures*	**Dental:** manipulation of gingival tissue or periapical region of teeth or perf oral mucosa (eg, extraction, periodontal, implant, root canal, cleaning)
Regimens	Oral: **amoxicillin 2 g 30–60 min before** Unable to take PO: amp 2 g IM/IV or cefazolin or CTX 1 g IM/IV PCN-allergic: cephalexin or azithro or claritho or doxy

*Pts should meet both indications (high-risk condition & high-risk procedure) to qualify for Ppx

TUBERCULOSIS

Definitions

- **Primary**: new *Mycobacterium tuberculosis* (TB) in a naïve host; symptomatic or asymptomatic; 90% of infected normal hosts will never develop clinically evident disease
- **Latent**: well-controlled infection without clinical or radiographic evidence of active disease; can persist for years to decades
- **Reactivated**: activation of latent; more likely in the setting of immunosuppression.
- **Milliary**: disseminated lympho-hematogenous spread due to primary or reactivated TB
- **Multidrug-resistant (MDR):** resistant to isoniazid (INH) & rifampin. Can occur as 1° infxn.
- **Extensively drug-resistant (XDR):** resistant to INH, rifampin (RIF), fluoroquinolones (FQ), and at least one of amikacin, kanamycin, or capreomycin

Epidemiology (*NEJM* 2016;375:1081)

- Transmission via aerosols; untreated active dx requires airborne isolation in healthcare facilities and community isolation measures; must involve local public health authorities
- Acquisition: residents/travel in TB-endemic area, IVDU, resident/worker in correctional facility or homeless shelter, close contact w/ active TB
- Reactivation: risk is 5% in first 2 yr, 5–10% overall; ↑ if HIV ⊕, immunosupp. (anti-TNF, steroids), ESRD, DM, cancer, transplant, malnourished, smoker, substance use disorder

Screening for latent TB

- Whom to screen: high likelihood of exposure and/or high risk of progression to active disease including HIV ⊕ and prior to immunosuppression (pre-transplant or anti-TNF)

- Relies on host immune system, so limited Se in immunosuppressed individuals
- Nb, testing for host exposure & immune response to TB, ***not whether TB active*** (vide infra)
- Screening tests
  - IFN-γ release assays (IGRA): preferred test; Ag-stimulated IFN-γ release from Pt's T-cells. ↑ Sp over TST/PPD in BCG vaccinated Pts.
  - Tuberculin skin test (TST/ PPD): inject purified protein intradermally, examine for wheal 48–72 hrs later. Interpret based on max diameter of induration, not erythema.

Size of Reaction	**Persons Considered to Have ⊕ Test** (*NEJM* 2002;347:1860)
>5 mm	HIV ⊕ or immunosupp. (eg, prednisone 15 mg/d × >1 mo) Close contacts of Pt w/ active TB; CXR c/w prior active TB
>10 mm	All other populations with ↑ prevalance/risk. Healthcare workers, recent conversion (↑ induration by >10 mm in 2 y).
>15 mm	No risk factors
False ⊖	Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB mycobacteria (NTM), malignancy
False ⊕	Improper reading, cross-reaction with NTM, BCG vaccination (although usually <10 mm by adulthood)
Booster effect	↑ in duration b/c immunologic boost by prior skin test in prev sensitized individual (by TB, NTM, or BCG). Test ⊖ → ⊕ but *not* true conversion due to *recent* infxn. 2nd test true baseline. Can be 1 y after initial test.

Clinical manifestations (*Lancet* 2016;387:1211)

- **Constitutional symptoms are common in all manifestations, but may be absent**
- **Primary TB pneumonia:** middle or lower lobe consolidation, ± effusion, ± cavitation
- TB pleurisy: pulmonary effusion ± pericardial and peritoneal effusions secondary to granuloma breakdown and local inflammation; can occur in primary or reactivation
- **Reactivation TB pulmonary disease**: upper lobe infiltrate ± volume loss ± cavitation

- **Milliary TB**: diffuse millet seed-sized lesions, more common in immunosupp.
- Extrapulmonary TB: lymphadenitis, pericarditis, peritonitis, CNS disease including meningitis, GU tract disease ± sterile pyuria, osteoarticular disease (vertebral = Pott's disease), granulomatous hepatitis, splenitis, cutaneous disease
- TB and HIV: HIV ⊕ at ↑ risk infxn, reactivation (8–10%/yr without ART, higher w/ ↓ CD4), and progressive 1° infxn. CXR can be atypical espec. if CD4 ≤200 (*JAMA* 2005;293:2740).

Diagnostics for active TB (*CID* 2017;64:11)

- **Pulmonary TB**: common CXR findings discussed above; induced sputum **AFB smear** & **culture** (3 samples at least 8 h apart) ± NAAT/ PCR (GeneXpert); consider bronchoscopy + BAL ± transbronchial biopsy. GeneXpert can also detect RIF resistance (non-bloody sputum only). Sp 98%/Se 74%, independent of HIV status.
- **Extrapulmonary TB**
  - *Pleural/pericardial effusions or ascites:* fluid sampling for AFB cx/smear, NAAT/ PCR, cell counts. Adenosine deaminase (ADA) can be ↑, best validated in ascites. Free INFγ can be elevated in pleural/ascitic fluid (not validated in pericardial effusions). Higher diagnostic yield with pleural/pericardial biopsies for disease at these sites.
  - *CSF:* fluid sampling for AFB cx/smear (submit at least 10 mL), NAAT/PCR, cell count (lymphocyte predominanace), glucose (low), protein (high), ADA (high)
  - *Soft tissue:* tissue biopsy with AFB staining, pathology w/ granulomas

Treatment of latent TB

- If screening test ⊕ and no risk factors, confirm prior to treatment; if ⊕ w/ risk factors, proceed to treatment (*CID* 2017;64:11).
- **Prior to treatment of latent TB, active TB must be ruled out** with, at a minimum, ROS for symptoms (cough, fever, night sweats, weight loss), physical exam, and CXR (though may be normal in immunosupp.)

Scenario	Prophylaxis Regimen
PPD/IGRA ⊕ (regardless of HIV status)	1st line: Rifampin × 4 mo *or* INH/rifampin daily x 3 mos *or* INH/rifapentine weekly × 12 wks) (*MMWR* 2020; 69:1) *Alternative:* INH + vitamin B_6 × 6–9 mos
Contact case known or suspected to have MDR TB	No proven regimen: ? PZA + EMB, ? PZA + FQ

- ✓ LFTs monthly if receiving INH (risk ↑ w/ age; *Chest* 2005;128:116): if AST/ALT ↑ 5× ULN *or* sx (nausea, vomiting, abd pain) → stop TB meds & re-eval

Patient isolation

- Decision based on likelihood of active disease. Consider when cough, dyspnea, hemoptysis, ≥1 risk factor (HIV ⊕, foreign born, substance use disorder, homeless, recent incarceration, prior TB or exposure).
- Discontinue if alternative dx and AFB smear neg ×3, or TB treated for 2 wk & AFB neg ×3

Treatment of active tuberculosis (*NEJM* 2015;373:2149; *Lancet* 2016;387:1211)

- Prior to treatment, **consult ID**, check LFTs, Cr, **HIV** & hepatitis A/B/C screen, DM screen, pregnancy screen, vision testing for acuity and color, EtOH use history
- Treatment requires several drugs to prevent resistance (see below)
- **Suspect MDR TB** if prior TB Rx (esp. if poor adherence), travel to area w/ ↑ rates of MDR (India, China, Eastern Europe including Russia, South Africa), exposure to person w/ likely MDR-TB (*NEJM* 2008;359:636)
- "Paradoxical *worsening*" of sx can occur after starting Rx. More common w/ extrapulm. TB & more frequent/severe w/ concurrent immune reconstitution (eg, HIV ⊕ Pts started on ART, Pts taken off immunosuppression). **Must r/o Rx failure** (repeat Cx, imaging), consider checking drug levels.
- Duration of treatment varies based on host, clinical manifestation, and improvement/ progression on treatment

Antituberculous Medications	
Drug	**Adverse Effects***

Antituberculous Medications	
Isoniazid (INH)	Hepatitis (avoid EtOH), periph neuropathy (↓ risk by suppl. vit B_6), drug-induced lupus
Rifampin (RIF)	Orange tint of body fluids, GI upset, hepatitis (avoid EtOH), hypersensitivity, fever, drug interactions
Pyrazinamide (PZA)	Hepatitis (avoid EtOH), hyperuricemia, arthritis
Ethambutol (EMB)	Optic neuritis
Streptomycin (SM)	Ototoxicity, nephrotoxicity
Amikacin (AMK)	Ototoxicity, nephrotoxicity
Quinolone (moxifloxacin, levofloxacin)	GI upset, tendinopathy, ↑ QTc

*Risk of hepatitis ↑ w/ pre-existing liver disease. Consult ID, consider holding/replacing PZA or INH.

Scenario	Antituberculous Treatment Regimens
Pulmonary TB **≥4% INH-resist. in community** (incl. most of U.S.)	INH + RIF + PZA + EMB until suscept. known If *sensitive* to INH & RIF → INH + RIF + PZA × 2 mo, *then* → INH + RIF × at least 4 mo If *resistant*, see next row
Drug-resistant TB (INH-R, RIF-R, or MDR/XDR)	*Consult ID specialist* (*NEJM* 2008;359:636)
Extrapulmonary TB	*Consult ID specialist*
TB in HIV ⊕ patient	*Consult ID specialist*

HIV/AIDS

Definition & Clinical Manifestations

- Acute HIV: rash, lymphadenopathy, fever, oral ulcers, pharyngitis, myalgias, diarrhea Presents ~2–6 wk after exposure; not all HIV infections result in symptoms of acute HIV
- AIDS: HIV + CD4 <200/mm^3 *or* AIDS-defining opportunistic infection (OI) or malignancy

Epidemiology

- ~1.2 million Americans living w/ HIV (13% unaware); ~37 million worldwide
- **High risk groups:** MSM, transgender women, IVDU, sex worker, partners of high-risk Pts
- Transmission: sexual (risk 0.1–1% per sex act w/o ARV), needlesticks (occupational or IVDU), vertical (15–40% w/o ARV), transfusions, organ transplant (uncommon in U.S.)

Prophylaxis (*NEJM* 2015;373:2237; *Lancet* 2016;387:53; *J Infect Dis* 2018;218:16; CDC 2021)

- **Pre-exposure** (PrEP): TDF/FTC daily, ↓ transmission >90% if adherent. Consider for serodiscordant partners, condomless sex in high-risk groups, STI w/in 6 mo, IVDU w/ equipment sharing. **Rule out HIV prior to initiation**, ✓ renal fxn, STIs, & HIV q3 mo.
- **Post-exposure** (PEP): start ASAP (within 72 hr) after high-risk exposure from HIV ⊕ source (case-by-case decision if HIV status ?). Test baseline HIV, STIs, HBV, HCV. Rx: 2 NRTIs (usually TDF/FTC) + RAL or DTG × 4 wks. Consider initiating PrEP afterwards.

Screening and Diagnosis (*JAMA* 2018;320:379)

- Screen all 13–64 yo at least once, every preg, if new STI dx; **screen high risk annually**
- **HIV Ab/p24Ag** (ELISA assay): ⊕ 1–12 wk after acute infxn; >99% Se; 1° screening test

- If ⊕, Ab differentiation assay confirms and differentiates HIV-1 vs. -2 (*MMWR* 2013;62:489)
- **HIV RNA PCR viral load (VL)** in plasma; assay range is 20–10 million copies/mL; false ⊕ can occur, but usually low # copies; in contrast, VL should be high (>750 k) in 1° infxn
- **CD4 count:** not a dx test, b/c can be HIV ⊕ w/ normal CD4 or be HIV ⊖ w/ low CD4

Approach to newly diagnosed HIV ⊕ Pt (*CID* 2020;73:e3572)

- Counsel re: excellent prognosis w/adherence to treatment, treatment options, & disclosure
- **Lab evaluation:** CD4 count, HIV VL & genotype, CBC w/ diff., BMP, LFTs, HbA1c, lipids, UA, PPD/ IGRA, syphilis Ab, *Chlamydia* & gonorrhea (3 site), Hep A/B/C, G6PD (if high-risk ethnicity), preg screen, HLA-B*5701 if Rx w/ abacavir. If AIDS: CMV IgG, Toxo IgG.
- Confirm all vaccinations (including annual flu) are up to date, avoid live vax if CD4 ≤200
- **Initiate ARV early** (same day, preferably after labs/genotype and w/ *guidance from HIV specialist*) regardless of CD4 level because ↓ mortality (*NEJM* 2015;373:795)
- **Treatment prevents transmission to partners.** Risk of transmission w/ unprotected sex w/ undetectable VL >6 months is ~0% (*JAMA* 2016;316:171; *Lancet* HIV 2018;5:e438).
- Regimens include: 2 NRTI (eg, TAF + FTC) + *either* INSTI or boosted PI (eg, DRV/r)

Common Antiretrovirals (ARVs)		Common Side Effects
NRTI	abacavir (ABC; Ziagen) emtricitabine (FTC; Emtriva) lamivudine (3TC; Epivir) tenofovir (TAF or TDF) zidovudine (AZT; Retrovir)	*Class:* GI intol, lipoatrophy, lactic acidosis ABC: hypersensitivity (3%), ✓ **HLA-B*5701** AZT: BM suppression (esp. macrocytic anemia) TDF: renal toxicity, bone density loss TAF: minimal renal toxicity
NNRTI	efavirenz (EFV; Sustiva) etravirine (ETR; Intelence) nevirapine (NVP; Viramune) rilpivirine (RPV; Edurant)	*Class:* rash, hepatitis, mixed CYP450 inducer/inhib EFV: CNS effects (incl depression) NVP: rash and hypersensitivity [risk factors are female, CD4 >250,

		pregnancy (∴ avoid)]
PI	atazanavir (ATV; Reyataz) darunavir (DRV; Prezista) lopinavir (LPV; Kaletra) *PIs given w/boosters ritonavir or cobicistat for ↑ PK*	*Class:* GI intol; hepatotoxicity; inhibit CYP450 (many DDIs, eg statins, steroids, DOACs); ↑ glc; hyperlipid (less w/ ATV); MI (*NEJM* 2007;356:1723) ATV: crystalluria → nephrolithiasis DRV: rash (10%); possible sulfa cross-reactivity
EI	maraviroc (MVC; Selzentry)	Dizziness, hepatotoxicity; ✓ CCR5 tropism assay
INSTI	bictegravir (BIC; Biktarvy) dolutegravir (DTG; Tivicay) elvitegravir (EVG; Vitekta) raltegravir (RAL; Isentress) cabotegravir (CAB; Vocabria)	Class: diarrhea; weight gain; ↑ CPK DTG/BIC ↑ metformin levels; monitor glc DTG a/w 0.003% risk of neural tube defects (*NEJM* 2019;381:827) CAB/RPV: injection site rxn

NRTI, nucleoside/tide reverse transcriptase inhib; NNRTI, nonnucleoside RTI; PI, protease inhib; EI, entry inhib (CCR5 antagonist); INSTI, integrase inhib; several multiclass combo pills exist

- Initiation of ARVs may *transiently worsen* existing OIs (TB, MAC, CMV, others) due to immune reconstitution inflammatory syndrome (IRIS). Prednisone during 1st 4 wks of ARVs ↓ risk for TB-associated IRIS, but not routinely given (*NEJM* 2018;379:1915).
- **Do not start ARVs** immediately if c/f cryptococcal or TB meningitis
- After ARV initiation, check VL q4 wks until undetectable, then monitor q3–4 mos

Approach to previously established HIV ⊕ Pt

- H&P (mucocutaneous, neurocognitive, OIs, malignancies, STDs); meds and adherence
- Review ARVs (past and current); if hospitalized typically continue ARVs, if any must be held, *stop all* to ↓ risk of resistance
- Regimen failure: cannot achieve undetectable VL after months on ARVs, viral rebound (VL >200 copies/mL ×2 after prior suppression), ↓ CD4 count or clinical worsening

OI Prophylaxis (https://aidsinfo.nih.gov/guidelines & *JAMA* 2018;320:379, HIV.gov:2020)		
OI	**Indication**	**1° Prophylaxis**
Tuberculosis	⊕ PPD (≥5 mm), IGRA, *or* high-risk exposure	See treatment for latent TB

OI Prophylaxis (https://aidsinfo.nih.gov/guidelines & *JAMA* 2018;320:379, HIV.gov:2020)		
Pneumocystis jiroveci (PCP)	CD4 <200/mm *or* CD4 <14% or thrush	TMP-SMX DS qd (first line) *or* dapsone qd *or* atovaquone qd *or* pentamidine inhaled q4wk
Histoplasmosis	CD4 <150/mm + endemic/ exposure	Itraconazole qd
Toxoplasmosis	CD4 <100/mm^3 *and* ⊕ *Toxo* IgG	TMP-SMX DS qd *or* dapsone 50 mg qd + pyrimeth. qwk + leucovorin 25 qwk
MAC	Ppx no longer rec. if effective ARVs initiated	
When to stop Ppx: PCP and toxo if CD4 >200 × 3 mos; Histo if CD4 >150 × 6 mos		

COMPLICATIONS OF HIV/AIDS

CD4 Count	Complications
Any	*S. pneumo*, TB, VZV, HPV complications, Kaposi's sarcoma, lymphoma, ↑ CVD risk, ↓ bone density.
<500	Constitutional sx. Mucocutaneous: seborrheic dermatitis; psoriasis; oral hairy leukoplakia; HSV. Recurrent bacterial infxns.
<200	PCP*, Toxo,* PML*, Crypto, candida, Histo/Coccidio* (endemic areas)
<50–100	CMV, MAC, CNS lymphoma, invasive aspergillosis, bacillary angiomatosis (dissem. *Bartonella*), death (<50 is medical emergency)

Fever workup in patient with HIV/AIDS

- Etiologies (*Infect Dis Clin North Am* 2007;21:1013)
  - **infxn** (82–90%): MAC, TB, CMV, early PCP, *Histo*, *Crypto*, *Coccidio*, *Toxo*, endocarditis
  - **noninfectious:** lymphoma, drug reaction. Non 1° HIV itself rarely (<5%) cause of fever.
- Workup: guided by CD4 count, s/s, epi, & exposures
  - CBC, BMP, LFTs, BCx, CXR, UA, mycobact. & fungal cx, ✓ meds, ? ✓ chest & abd CT
  - CD4 <100–200 → serum crypto Ag, urinary *Histo* Ag, CMV PCR
  - pulmonary s/s → CXR; ABG; sputum for bacterial cx, PJ stain, AFB; bronchoscopy
  - diarrhea → stool cx, O&P, AFB; direct visualization with bx on colonoscopy
  - cytopenias → BM bx for path & cx of aspirate including for mycobacteria & fungi

headache/visual Δs→ LP; send CSF for bacterial/fungal cx, CrAg, ? MTb PCR; send CMV PCR from serum; dilated eye exam with Ophtho

Cutaneous

- Eosinophilic folliculitis; **warts** (HPV); HSV & VZV; MRSA SSTI; scabies; candidiasis; eczema; prurigo nodularis; psoriasis; drug eruption; subungual onychomycosis
- Molluscum contagiosum (poxvirus): 2–5 mm pearly papules w/ central umbilication
- **Kaposi's sarcoma** (KSHV or HHV8): red-purple nonblanching nodular lesions
- Bacillary angiomatosis (disseminated *Bartonella*): friable violaceous vascular papules

Oral

- Aphthous ulcers; KS; **thrush/oral candidiasis** (curd-like patches, often painless)
- Oral hairy leukoplakia**:** painless proliferation of papillae w/ adherent white coating usually on lateral tongue, caused by EBV but not precancerous

Ophthalmologic

- **CMV retinitis** (CD4 usu <50); Rx: ganciclovir or valganciclovir, foscarnet, or cidofovir
- HZV, VZV, syphilis (any CD4 count, *treat as neurosyphilis*) or *Toxo* (CD4 usually <100)

Endocrine/metabolic

- Hypogonadism; adrenal insufficiency (CMV, MAC, TB, HIV, or med-related); sarcopenia; osteopenia/porosis/fragility fractures (at all CD4 counts)
- **Lipodystrophy**: central obesity, peripheral lipoatrophy, dyslipidemia, hyperglycemia

Cardiovascular (*JACC* 2013;61:511)

- Higher rates of CAD, stroke, VTE, dilated CMP; pulm. HTN; pericarditis/effusion

Pulmonary

Radiographic Pattern	Common Causes
Normal	Early PCP
Diffuse interstitial infiltrates	PCP, TB, viral, or disseminated fungal
Focal consolidation or masses	Bacterial or fungal, TB, KS
Cavitary lesions	TB, NTM, aspergillus, other fungal, bacterial (incl. *Staph aureus*, *Nocardia, Rhodococcus*)
Pleural effusion	TB, bacterial or fungal, KS, lymphoma

- ***Pneumocystis jiroveci* (PCP) pneumonia** (CD4 <200) (*NEJM* 1990;323:1444)
  fever, night sweats, dyspnea on exertion, dry ("doorstop") cough
  CXR w/ interstitial pattern, ↓ P_aO_2, ↑ A-a ∇, ↑ LDH, ⊕ PCP sputum stain, ⊕ β-glucan
  Rx if P_aO_2 >70: TMP-SMX 15–20 mg of TMP/kg divided tid, avg dose = DS 2 tabs PO tid
  Rx if P_aO_2 <70 or A-a gradient >35: prednisone before abx (40 mg PO bid; ↓ after 5 d)
  HIV ⊕ smokers much more likely to die from lung cancer than OI (*JAMA* 2017;177:1613)

Gastrointestinal & hepatobiliary

- Esophagitis: *Candida*, CMV (solitary, lg serpiginous), HSV (multiple, small shallow), giant aphthous ulcers, pills; EGD if no thrush or no response to empiric antifungals
- Enterocolitis: *bacterial* (esp. if acute: *Shigella*, *Salmonella*, *C. diff*); *protozoal* (esp. if chronic: *Giardia*, *Isospora*, *Cryptosporidium*, *Cyclospora*, *Microsporidium*, *Entamoeba*); *viral* (CMV, adeno); *fungal* (histo); MAC; AIDS enteropathy; TB enteritis
- GI bleeding: CMV, KS, lymphoma, histo; proctitis: HSV, CMV, *LGV, N. gonorrhoeae*
- Hepatitis: HBV, HCV, CMV, MAC, TB, histo, drug-induced
- AIDS cholangiopathy: often a/w CMV or *Cryptosporidium or Microsporidium* (at ↓ CD4)

Renal

- HIV-assoc. nephropathy (collapsing FSGS); **nephrotoxic drugs** (eg, TDF → prox tub dysfxn)

Hematologic/oncologic (*NEJM* 2018;378:1029)

- Cytopenia: ACD, BM infiltration by tumor/infxn (eg, MAC/TB), drug toxicity, hemolysis, ITP
- Non-Hodgkin lymphoma: ↑ frequency with any CD4 count, but incidence ↑ with ↓ CD4
- Hodgkin lymphoma (any CD4; impact of ART unclear)
- CNS lymphoma: CD4 count <50, EBV-associated
- **Kaposi's sarcoma** (HHV-8): at any CD4 count, incidence ↑ b/c CD4 ↓, usu. MSM
  Mucocut. (violacious lesions); *pulmonary* (nodules, infiltrates, LAN); *GI* (bleed, obstruct.)
- Cervical/anal CA (HPV high risk in MSM)
- ↑ rates of liver CA (a/w HBV/HCV), gastric CA

Neurologic/Psychologic

- **Meningitis**: *Crypto* (dx w/ CSF; serum CrAg 90% Se), bacterial (inc. *Listeria*), viral (HSV, CMV, 1° HIV), TB, histo, *Coccidio*, lymphoma; neurosyphilis (cranial nerve palsies)
- **Space-occupying lesions**: may present as HA, focal deficits or Δ MS. Workup: MRI, brain bx only if suspect non-*Toxo* etiology (*Toxo* sero ⊖) or no response to 2 wk of empiric anti-*Toxo* Rx (if *Toxo*, 50% respond by d3, 91% by d14; *NEJM* 1993;329:995)

Etiology	Imaging Appearance	Diagnostic Studies
Toxoplasmosis	Enhancing lesions, typically in basal ganglia (can be multiple)	⊕ *Toxo* serology (Se ~85%)
CNS lymphoma	Enhancing ring lesion (single 60% of the time)	⊕ CSF PCR for EBV ⊕ SPECT or PET scan
Progressive multifocal leukoencephalopathy (PML)	Multiple nonenhancing lesions in white matter	⊕ CSF PCR for JC virus
Other: abscess, nocardiosis, crypto, TB, CMV, HIV	Variable	Biopsy

- HIV-assoc. dementia: depressive sx, impaired attention/concentration, psychomotor slowing
- Depression: ↑ rates of suicide/depression

- Myelopathy: infxn (CMV, HSV), cord compression (epidural abscess, lymphoma)
- Peripheral neuropathy: meds (esp 1st gen NRTIs), CMV, diabetes

Disseminated *Mycobacterium avium* complex (DMAC)

- Fever, night sweats, wt loss, abd pain, diarrhea, pancytopenia. Can cause localized lymphadenitis. Rx: clarithro/azithro + ethambutol ± rifampin/rifabutin.

Cytomegalovirus (CMV)

- Retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis. CMV VL may be ⊖. Consider tissue biopsy. Rx: ganciclovir, valganciclovir, foscarnet, or cidofovir.

TICK-BORNE DISEASES

Distinguishing Features of Tick-Borne Illnesses					
Disease	**Rash**	**↓WBC**	**Anemia**	**↓ Plts**	**↑ LFTs**
Lyme	80%: erythema migrans	–	–	–	+
RMSF	90%: petechiae, palms/soles	–	+	+	+++
Borrelia miyamotoi	–	++	+	+++	+++
Ehrlichia	25%: maculopap, petechiae	+++	++	++++	++++
Anaplasma	–	+++	+	+++	++++
Babesia	–	+	++++ (lysis)	++++	+++

–: <15%, +: 15–25%, ++: 25–50%, +++: 50–75%, ++++: >75%

Tick prophylaxis: protective clothing, tick ✓ q24h, DEET/picardin, if bitten remove ASAP

LYME DISEASE

Microbiology & epidemiology

- Spirochete *B. burgdorferi* transmitted by *Ixodes scapularis* (deer tick)
- Humans contact ticks in low brush near wooded areas
- Infection usually requires tick attached >36–48 h
- Most common vector-borne illness in U.S.; peak in summer in NE/Mid-Atlantic/Midwest
- Consider coinfection w/ *Anaplasma, Babesia, B. miyamotoi*

Clinical Manifestations	
Stage	**Manifestations**
Early localized (w/in 1 month)	*General:* flu-like illness. *Derm* (~80%): **erythema migrans** (EM) = erythematous patch ± central clearing, ~6–38 cm.

Clinical Manifestations	
Early disseminated (wks to mos)	*General:* fatigue, malaise, LAN, HA *Derm:* multiple EM lesions *Rheum* (~10%): migratory arthralgias & myalgias *Neurologic* (~15%): cranial neuropathies (esp. CN VII), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis *Cardiac* (~8%): heart block, myopericarditis
Late disseminated (mos to yrs)	*Derm* (rare in U.S.)*:* acrodermatitis chronica atrophicans, panniculitis *Rheum* (~60%, espec. if not Rx'd): recurrent mono- or oligoarthritis of large joints (classically knee), synovitis *Neurologic* (rare!)*:* subacute encephalomyelitis, polyneuropathy

(*NEJM* 2014;370:1724; CID 2020; 72:e1)

Diagnostic studies (*CID* 2020; 72:e1)

- Avoid testing without signs/symptoms
- *Early localized:* clinical dx if EM + possible exposure; no need for testing (often sero ⊖)
- *Early or late* d*isseminated:* 2-step testing
  - 1st step: ELISA screen (some false ⊕, false ⊖ w/ early abx or <6 wk after tick bite)
  - 2nd step: if ⊕ ELISA, confirm with IgM/IgG Western blot (↑ Sp) or 2nd ELISA
- Serum testing is sufficient for diagnosis of Lyme CNS infection or Lyme arthritis, though consider CSF (Ab testing in parallel with serum) or joint fluid sampling (PCR) to rule out other causes and provide a more definitive diagnosis

Treatment (*CID* 2020; 72:e1; IDSA 2021)

- **Prophylaxis**: doxycycline × 1 *only* if *all* of the following:
  1) *Ixodes scapularis* tick attached ≥36 h
  2) Local Lyme carriage in ticks ≥20%
  3) Abx can be given w/in ≤72 h of tick bite
  4) No contraindication to doxycycline (eg, preg, allergy, age <8 y)

  Regardless of Ppx, monitor for fever, flu-like sx, rash (erythema migrans) × 30 d
- **Treatment**

  Isolated EM: doxy × 10 d (alternative: cefurox or amox × 14 d or azithro × 7 d)

  Arthritis: doxy × 28 d (alternative: cefurox or amox × 28 d)

Carditis/meningitis: CTX IV or doxy PO (based on severity/response) × 14–21 d

- Consider coinfection if severe/refractory sx, persistent fever, cytopenias
- Recurrent sx after abx are likely re-infection, *not* relapse (*NEJM* 2012;367:1883)

BABESIOSIS

Microbiology & epidemiology (*MMWR* 2012;61:505)

- *Babesia microti* (U.S.) transmitted by *Ixodes* ticks; also risk from blood transfusion
- Peak incidence summer in NE U.S. (esp. near coast, "Nantucket fever"), north-central MW

Clinical manifestations

- Typically 1–4 wks after tick exposure; <9 wks if transfusion
- Range: asx/mild flu-like sx to severe DAT ⊖ **hemolytic anemia**/DIC, multiorgan failure
- Risk factors for severe dx: **asplenia**, ↓ cellular immunity, TNF inhib, ↑ age, pregnancy

Diagnosis (*CID* 2021;72:e49)

- Symptoms + blood smear w/ intraerythrocytic parasites (ring forms)
- Degree of parasitemia = % infected RBC on smear (correlates roughly w/ severity)
- Repeat smears (q12–24h) if sx persist despite negative initial smear
- PCR serum if smear ⊖ (or unavailable) and clinical suspicion

Treatment (*CID* 2021;72:e49)

- Atovaquone & azithro preferred; clinda/quinine (more adverse events); call ID if severe
- Duration depends on host; immunosupp often need longer Rx
- Consider exchange transfusion if parasitemia >10%, severe hemolysis/ end-organ failure

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EHRLICHIOSIS/ANAPLASMOSIS

Microbiology & epidemiology

- Gram ⊖ obligate intracellular bacterium; **human monocytic ehrlichiosis** (*E. chaffeensis*, HME); **human granulocytic anaplasmosis** (*A. phagocytophilum*, HGA)
- Transmission: HME by *Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (dog tick); HGA by *Ixodes;* **HGA** in NE, mid-Atl, MN; **HME** in SE and south-central U.S.
- Peak incidence spring and early summer; can be transmitted by blood transfusion

Clinical manifestations (typically w/in 3 wks of tick exposure)

- Asx or nonspecific: **fever**, **myalgias**, malaise, HA, delirium; onset often acute
- Laboratory: leukopenia, thrombocytopenia, ↑ aminotransferases, ↑ LDH, ↑ CK
- Severe disease can be complicated by bacterial superinfection

Diagnosis

- Intraleukocytic morulae on peripheral smear in acute infection; serum PCR ⊕ in acute infection and convalescence

Treatment (*JAMA* 2016;315:1767)

- Start Rx based on clinical suspicion; definitive dx requires PCR (but not 100% Se)
- Doxycycline × 10 d; if Pt does not defervesce in ≤48 h, consider co-infection/alt dx

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Rocky Mountain Spotted Fever (RMSF)

Microbiology & epidemiology

- Infection with *Rickettsia rickettsii* (Gram ⊖ obligate intracellular bacterium)
- Transmitted by *D. variabilis, D. andersoni* (wood tick); peak in spring/early summer
- Occurs in mid-Atl, SE/south central U.S., mountain west, Mexico, Central & S. America

Clinical manifestations (typically w/in 1–2 wks of tick exposure)

- Nonspecific: **fever**, **HA**, ΔMS, myalgias, N/V, occasionally abdominal pain

- Rash (2–5 d *after* onset of fever) = *centripetal:* starts on ankles and wrists → trunk, palms, & soles; progresses from macular to maculopapular to petechial
- Severe cases → vasculitis, multi-organ failure, meningoencephalitis; more likely in elderly

Diagnosis (*MMWR* 2016;65:1)

- Clinical dx (often w/o rash initially); *requires high suspicion* given risk of delayed Rx
- Acute illness: skin bx for rickettsiae (Se 70–90%), consider ✓serologies (may be ⊖)
- Confirm dx: re-check serology 14–21 d later, ⊕ if 4-fold ↑

Treatment (*MMWR* 2016;65:1)

- Doxy × 7–10 d, empiric Rx if suspicion; if does not defervesce in ≤48 h ? co-infection/alt dx

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TULAREMIA

Microbiology

- Infxn w/ *Francisella tularensis* bacteria via arthropod bites, animal contact (bite, scratch, lick), contaminated food or water, aresolized materials

Clinical manifestations (typically w/in 2–10 d of exposure)

- Fever, chills, malaise, HA, nausea, myalgias; ulcer w/ black eschar at site of entry; LAN; conjunctivitis; pharyngitis; PNA

Diagnosis & treatment

- Serology should be collected at presentation and 2 wks later, bacteria difficult to culture
- FLQ for mild infection, aminoglycoside for severe infection in consultation with ID

FEVER SYNDROMES

Temperature ≥100.4°F or ≥38°C

Diagnostic approach

- Thorough history including ROS, PMH/PSH, immunizations, including from childhood
- **Fever curve** (holding antipyretics); look at trend/pattern. Less likely to mount fever if: ESRD/ESLD, extremes of age, protein calorie malnutrition, immunosupp., steroid use.
- **Exposures**: travel, occupation/hobbies, animals, sexual contacts, TB. Consider geography, season, and incubation time in relation to exposures.
- **Physical exam**: look for thrush, dental caries; full eye exam; cardiac murmurs; HSM; abd tenderness; rash/skin lesions; LAN; synovitis; complete neuro exam

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FEVER OF UNKNOWN ORIGIN (FUO)

Definition & etiologies (*NEJM* 2022;386:463)

- **Fever** (as per above def) on >1 occasion during ≥3 wk & **no dx** despite 1 wk of evaluation
- More likely to be *unusual manifestation of common disease* than an uncommon disease
- In Pts with HIV: >75% causes are infectious, but *rarely due to HIV itself*
- *Frequent reassessment needed* to identify focal signs and progression of disease

Category	Etiologies of Classic FUO (*Medicine* 2007;86:26; *AJM* 2015;128:1138)
Infection ~30%	**Tuberculosis:** disseminated or extrapulm. disease can have normal CXR, PPD/IGRA, sputum AFB; bx (lung, liver, bone marrow) for granulomas has 80–90% yield in milliary disease **Endocarditis:** if blood cxs neg consider Bartonella, Coxiella, et al.

	Abscess: dental, paraspinal, hepatic, splenic, subphrenic, pancreatic, -perinephric, pelvic, prostatic abscess or prostatitis, appendicitis Osteomyelitis, sinusitis, typhoid, 1° CMV or EBV, malaria, *Babesia*
Connective tissue disease ~30%	**Giant cell arteritis/**PMR**:** headache, scalp pain, jaw claudication, visual disturbances, myalgias, arthralgias, ↑ ESR **Adult-onset Still's:** evanescent truncal rash, LAN, pharyngitis, ↑↑ ferritin PAN, ANCA ⊕, other vascul.; SLE, RA, psoriatic or reactive arthritis
Neoplasm ~20%	**Lymphoma:** LAN, HSM, ↓ Hct or plt, ↑ LDH; leukemia; myelodysplasia **Renal cell carcinoma:** microscopic hematuria, ↑ Hct HCC, pancreatic and colon cancers, sarcomas, mastocytosis Atrial myxomas: obstruction, embolism, constitutional symptoms
Misc ~20%	**Drug fever**, factitious, DVT/PE, hematoma Thyroiditis or thyroid storm, adrenal insufficiency, pheochromocytoma Granulomatous hepatitis (many causes), **sarcoidosis**, Kikuchi's, Behçet's Familial Mediterranean fever (peritonitis, episodic fever, pleuritis; ↑ WBC & ESR during attacks); other defects in innate immunity

More common causes boldfaced

Workup (*Archives* 2009;169:2018; *AJM* 2015;128:1138)

- Initial: CBC w/ diff, CMP, ESR, CRP, 3 sets BCx (off abx), U/A, UCx, CXR
- Additional workup based on sx: ANA, RF, cryoglobulin, LDH, CK/aldolase, SPEP, TFTs, PPD or IGRA, HIV Ag/Ab ± PCR, RPR, EBV serologies, CMV PCR, HBV/HCV serologies
- Consider imaging: chest & abd CT, tagged WBC scan, FDG-PET, TTE, LE duplex US
- Tissue dx: consider bx of LN (excisional preferred), liver (especially if ↑ Aϕ), TA (for GCA), BM, kidney (RPGN)

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic or critically ill)
- Empiric glucocorticoids not indicated unless strong suspicion for specific rheumatologic dx
- Stop unnecessary meds (only 20% with a med cause have eos or rash)
- Up to 30% of cases remain undiagnosed, most spontaneously defervesce (wks to mos)

Fever and Rash

Approach to diagnostic workup

- *Meningococcemia, endocarditis, RMSF, sepsis, & toxic shock need urgent dx & Rx*
- Workup: CBC w/diff, BMP, LFTs, LDH, CK, U/A, HIV Ag/Ab ± PCR, BCx (off abx)
- To narrow Ddx: characterize time course of rash, progression, & morphology
- **Erythema multiforme**: symmetric "target" lesions often of palms, soles, & mucous memb
  Infxn etiol: HSV, *Mycoplasma*, syphilis, VZV, EBV, CMV, adenovirus, etc.
  Non-infxn etiol: most likely meds (eg, NSAIDs, sulfa, AEDs), autoimmune disease
- **Erythema nodosum**: tender erythematous or violaceous nodules usually symmetric on LE
  Infxn etiol: Strep, TB, EBV, *Bartonella*, HBV, psittacosis, fungal, *L. venereum*, etc.
  Non-infxn etiol: sarcoidosis, IBD, Behçet's, other rheum, pregnancy/OCP use
- Pursue specific dx based on exposure hx & exam, including serologies, viral PCRs, possibly skin biopsy ± exam of vesicular or bullae fluid if present
- Immunosupp. Pts need broad w/u; higher risk of disseminated/rapidly progressive infxns

Variable	Possible Etiology
Summer/fall > other seasons	Enterovirus
Winter	Parvovirus, Meningococcemia
Spring/summer	Lyme, RMSF, Ehrlichiosis, Anaplasmosis
Year-round	Adenovirus, *Mycoplasma*
Cat and dog exposure	*Bartonella, Pasteurella, Toxoplasma, Capnocytophaga*
Tick exposure	Lyme, RMSF, Ehrlichiosis, Anaplasmosis
Adult <30 y	Mononucleosis (EBV or CMV)
Inadequate immunization	Measles, Rubella, VZV, influenza
Sexually active	HIV, syphilis, disseminated gonococcal infection,

	HSV
Consider noninfectious causes: allergy/DRESS, DVT, phlebitis, vasculitides, neutrophilic dermatoses, gout, connective tissues dis., malignancy, foreign body rxn	

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic or critically ill)
- Consider important empiric isolation precautions (ie, varicella → airborne/contact; measles → airborne; meningococcus → droplet) while workup pending

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FEVER IN A RETURNED TRAVELER

See CDC.gov/travel for up to date information on regional risks and recommendations

Region or Exposure	Common Etiologies (*NEJM* 2017;376:548)
Sub-Saharan Africa	**Malaria** >> dengue and other arboviruses, rickettsial disease, enteric fever
South/Southeast Asia	Dengue > malaria, enteric fever (*S. typhi/paratyphi*), Chikungunya and other arboviruses
Central & S. America	Dengue, enteric fever, malaria
Caribbean & Mexico	Dengue >> Chikungunya and other arbovirsuses > enteric fever, malaria
Middle East	Middle East Respiratory Syndrome, brucellosis
Freshwater swimming	Schistosomiasis, leptospirosis
Unpurified drinking water	Enteric disease (*E. coli* >> *S. typhi*, *Campylobacter*, hepatitis E > *Vibrio cholerae*), amoebic liver abscess
Lacking immunizations	HAV/HBV, *S. typhi*, influenza, measles, rubella, yellow fever

- Pts visiting friends and relatives abroad are most likely to contract illness during travel
- Also consider domestic infxns, influenza, STIs, & non-infxn causes

Select clinical manifestations

- **Ebola:** fever in traveler from area with active transmission of Ebola w/in 21 d
- **Malaria:** nonspecific sx including diarrhea, headache, myalgias, cough, Δ MS

- **Dengue:** nonspecific sx including headache, severe myalgias, rash/petechiae
- **Chikungunya:** nonspecific sx including joint pain, moderate myalgias
- **Typhoid** (*Lancet* 2015;385:1136): diarrhea/constipation, abd pain, ± rash, relative bradycardia
- **Rickettsial disease:** headache, myalgias, lymphadenopathy, ± rash/eschar
- **Zika:** rash, arthralgia, headache, conjunctivitis; often less severe than dengue, Chikungunya

Workup

- Routine testing: CBC w/ diff, BMP, LFTs, BCx, UA, rapid malaria test
- **Fever in a traveler from a malaria zone is malaria until proven otherwise; consider a medical emergency → hospitalization & empiric Rx.** One ⊖ smear does *not* r/o.
- Other tests based on s/s, labs, exposure, incubation period, geography, and seasonality. O&P exam, CXR, blood smears for filaria/Babesiosis/*Borrelia*, serologies, STI & HIV, PPD or IGRA, bone marrow aspirate, bx of lymph nodes or skin lesions, CSF studies.

PITUITARY DISORDERS

HYPOPITUITARY SYNDROMES (*Lancet* 2016;388:2403; *JCEM* 2016;11:3888)

Etiologies

- **Primary:** surgery, radiation (develops after avg 4–5 y), tumors (primary or metastatic), infection, infiltration (sarcoid, hemochromatosis), autoimmune, ischemia (including Sheehan's syndrome caused by pituitary infarction intrapartum), carotid aneurysms, cavernous sinus thrombosis, trauma, medications (eg, ipilimumab), apoplexy, empty sella, genetic
- **Secondary:** (hypothalamic dysfunction or stalk interruption): tumors (including craniopharyngioma), infection, infiltration, radiation, surgery, trauma

Clinical manifestations

- **Hormonal deficiencies:** ACTH, TSH, FSH and LH, GH, prolactin, and ADH
- **Panhypopituitarism:** deficiencies in multiple hormonal axes
- **Mass effect:** headache, visual field Δs, cranial nerve palsies

Central adrenal insufficiency: ↓ ACTH

- Sx similar to 1° adrenal insufficiency (see "Adrenal Disorders") *except:*
  no salt cravings or hyperkalemia (b/c aldo preserved)
  no hyperpigmentation (b/c ACTH/MSH is not ↑)

Central hypothyroidism: ↓ TSH

- Sx of central hypothyroidism similar to 1° (see "Thyroid Disorders") *except* absence of goiter
- Dx with free T_4 in addition to TSH, as TSH may be low or *inappropriately normal*

Hypoprolactinemia: ↓ prolactin

• Inability to lactate

Growth hormone deficiency: ↓ GH

• ↑ chronic risk for osteoporosis, fatigue, decreased lean body mass
• Dx with failure to ↑ GH w/ appropriate stimulus (eg, insulin tolerance test, glucagon stimulation, and macimorelin stimulation)
• GH replacement in adults controversial (*Annals* 2003;35:419; *NEJM* 2019;380:2551)

Central hypogonadism: ↓ FSH & LH

• Clinical manifestations: ↓ libido, impotence, oligomenorrhea or amenorrhea, infertility, ↓ muscle mass, osteoporosis
• Physical exam: ↓ testicular size; loss of axillary, pubic and body hair
• Dx with: ↓ a.m. testosterone or estradiol (also assess SHBG, esp. in obese) and ↓ or normal FSH/LH (all levels ↓ in acute illness, ∴ do not measure in hospitalized Pts)
• Treatment: testosterone or estrogen replacement vs. correction of the underlying cause

Central diabetes insipidus: ↓ ADH

• Typically from mass lesion extrinsic to sella; pituitary tumor does not typically present w/ DI
• Clinical manifestations: *severe* polyuria, thirst, nl to *mild* hyperNa (*severe* if ↓ access to H_2O)
• Diagnostic studies: see "Sodium and Water Homeostasis"

Pituitary apoplexy (*Endocr Rev* 2015;36:622)

• Rapid expansion of pituitary tumor (typically adenoma) due to hemorrhage or infarction
• Sx include excruciating headache, diplopia, hypopituitarism
• Rx: immediate high-dose glucocorticoids; prompt surgical decompression if severe neurologic impairment or Δ MS; conservative management if mild

Diagnostic evaluation

• **Hormonal studies**
  Chronic: ↓ target gland hormone + ↓ or (inappropriately) normal trophic pituitary hormone
  Acute: will develop defic. in target gland hormones, but cortisol normal w/ ACTH stim

Partial hypopituitarism is more common than panhypopituitarism

- **Pituitary MRI:** pituitary protocol (contrast enhanced) recommended

Treatment

- **Replace deficient target gland hormones**
- Most important deficiencies to recognize and treat in inpatients are *adrenal insufficiency* and *hypothyroidism*; if both present, treat with glucocorticoids first, then replace thyroid hormone so as not to precipitate adrenal crisis

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HYPERPITUITARY SYNDROMES

Pituitary tumors (*NEJM* 2020;382:937)

- **Pathophysiology: adenoma** → excess of trophic hormone (if tumor fxnal, but 30–40% not) and potentially *deficiencies* in other trophic hormones due to compression; cosecretion of PRL and growth hormone in 10% of prolactinomas
- Clinical manifestations: specific syndromes due to oversecretion of hormones (see below) ± non-specific mass effect: headache, visual Δs, diplopia, cranial neuropathies
- Workup: MRI brain pituitary protocol, hormone levels, ± visual field testing if <10 mm, no mass effect, no hormone overproduction, can f/up in 12 mos

Hyperprolactinemia (*NEJM* 2010;362:1219; *JCEM* 2011;96:273)

- Etiology
  - Prolactinoma (50% of pituitary adenomas)
  - Stalk compression due to nonprolactinoma → ↓ inhibitory dopamine → ↑ PRL (mild)
- Physiology: PRL induces lactation and inhibits GnRH → ↓ FSH & LH
- Clinical manifestations: **amenorrhea**, **galactorrhea**, **infertility**, ↓ libido, impotence
- Diagnostic studies
  - ↑ **PRL** (✓ *fasting* levels), but elevated in many situations, ∴ r/o pregnancy or exogenous estrogens, hypothyroidism, dopamine agonists (eg, psych meds, antiemetics), renal failure (↓ clearance), cirrhosis, stress, ↑ carb diet. Watch for *hook effect*: assay artifact yielding falsely low PRL if very high serum PRL levels; retest with sample dilution.

MRI brain pituitary protocol

- Treatment
  - If asx (no HA, galactorrhea, hypogonadal sx) & microadenoma (<**10 mm**), follow w/ MRI
  - If **sx** or macroadenoma (□**10 mm**) options include:
  - *Medical* with dopamine agonist such as cabergoline (70–100% success rate) or bromocriptine (not as well tol); side effects include N/V, orthostasis, mental fogginess
  - *Surgical:* transsphenoidal surgery (main indications: failed or cannot tolerate medical Rx, GH cosecretion or neurologic sx not improving); 10–20% recurrence rate
  - *Radiation:* if medical or surgical therapy have failed or are not tolerated

Acromegaly (↑ GH; 10% of adenomas; *Nat Rev Dis Primer* 2019;5:1)

- Physiology: stimulates secretion of insulin-like growth factor 1 (IGF-1)
- Clinical manifestations: ↑ soft tissue, arthralgias, jaw enlargement, headache, carpal tunnel syndrome, macroglossia, hoarseness, sleep apnea, amenorrhea, impotence, diabetes mellitus, acanthosis/skin tags, ↑ sweating, HTN/CMP, colonic polyps
- Diagnostic studies: *low utility in checking random GH levels because of pulsatile secretion*
  - ↑ **IGF-1** (somatomedin C); ± ↑ PRL; OGTT → GH *not* suppressed to <1 (<0.3 if newer assay) ng/mL; pituitary MRI to evaluate for tumor
- Treatment: **surgery**, octreotide (long- and short-acting preparations), dopamine agonists (if PRL cosecretion), pegvisomant (GH receptor antagonist), radiation
- Prognosis: w/ and w/o Rx ↑ mortality, risk of pituitary insufficiency, colon cancer

Cushing's disease (↑ ACTH): 5% of adenomas; see "Adrenal Disorders"

Central hyperthyroidism (↑ TSH, ↑ α-subunit): extremely rare; see "Thyroid Disorders"

↑ **FSH & LH:** often non-fxn, may present as *hypopituitarism* b/c compression effects

Multiple Endocrine Neoplasia (MEN) Syndromes	
Type	**Main Features**
1 (*MENIN* inactiv.)	Parathyroid hyperplasia/adenomas → hypercalcemia (~100% penetrance) Pancreatic islet cell neoplasia (gastrin, VIP, insulin, glucagon) Pituitary adenomas (fxn or non-fxn)
2A (*RET* proto- oncogene)	Medullary thyroid carcinoma (MTC) (~99%) Pheochromocytoma (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)
2B (*RET* proto- oncogene)	Medullary thyroid carcinoma (MTC) (~99%) Pheochromocytoma (~50%) Mucosal and gastrointestinal neuromas, marfanoid habitus
4 (*CDKN1B*)	Parathyroid hyperplasia/adenomas (~90%) Pituitary adenomas (fxnal or non-fxnal) Gastroenteropancreatic neuroendocrine tumors (~25%) Adrenal, kidney, reproductive organ tumors

Autoimmune Polyglandular Syndromes (APS) (*NEJM* 2018;378:1132)	
Type	**Features**
I (APECED)	Child onset, mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, AIRE mutation
II	Adult onset, adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1; polygenic

THYROID DISORDERS

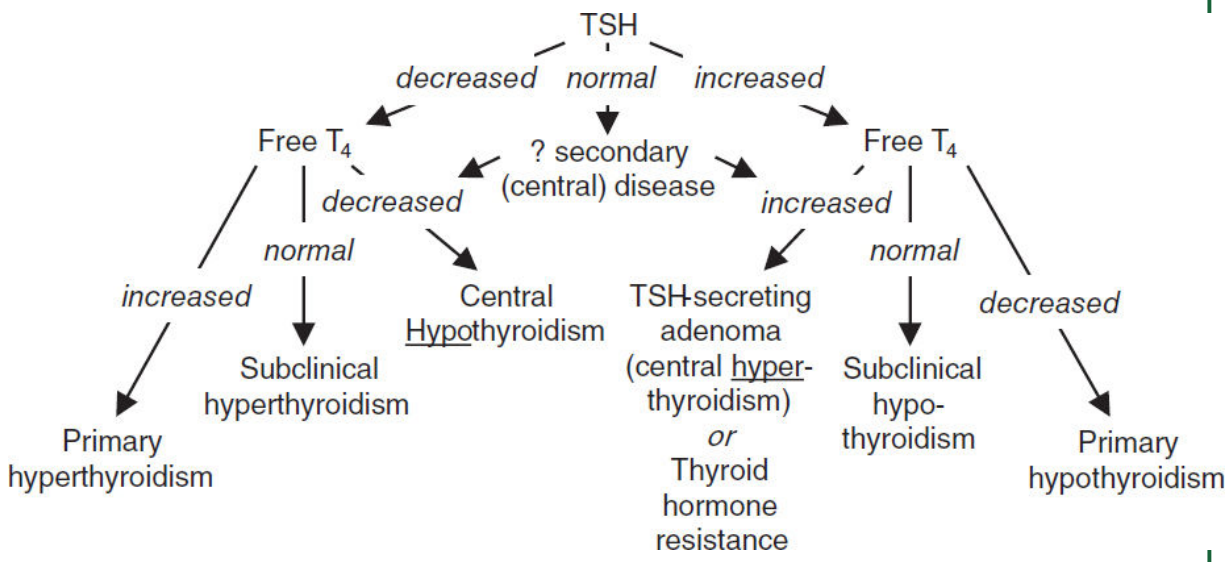
Common Diagnostic Tests in Thyroid Disorders	
Test	**Comments**
Thyroid-stimulating hormone (TSH)	*Most sensitive test* to detect 1° hypo- and hyperthyroidism. **Used as primary screening test for thyroid disease.** ↓'d by dopamine, glucocorticoids, severe illness, excessive biotin. May not be helpful in central hypothyroidism.
Free T_4 (fT_4)	Unbound T_4, not influenced by TBG. Checked in a variety of thyroid states including *hyperthyroidism & central hypothyroidism*
Total T_3	*Total* serum concentrations of T_3 (liothyronine). Useful when evaluating for *hyperthyroidism*.
Antithyroid peroxidase Ab (anti-TPO)	Antithyroid peroxidase (TPO) seen in Hashimoto's (high titer), painless subacute thyroiditis and Graves' disease (low titer)

(*Lancet* 2001;357:619 & *Thyroid* 2003;13:19)

Specialized Diagnostic Tests in Thyroid Disorders	
Test	**Comments**
Total T_4	*Total* serum concentrations (∴ influenced by TBG). Checked if concern that TSH and free T_4 are not accurate.
Free T_3	Unbound T_3, low clinical utility
Reverse T_3	Inactive, ↑'d in sick euthyroid syndrome. Rarely used clinically.
Thyroid stimulating Abs	Thyroid-stimulating Ig (TSI) and thyrotropin-binding inhibitory immunoglobulin (TBII) seen in Graves' disease. Diagnostic of Graves' disease in high titer.
Thyroglobulin	↑'d in goiter, hyperthyroidism and thyroiditis ↓'d in factitious ingestion of thyroid hormone Tumor marker for thyroid cancer only after total thyroidectomy and radioiodine therapy
Thyroxine-binding globulin (TBG)	↑ TBG (∴ ↑ T_4): estrogen (OCP, preg.), hepatitis, opioids, hereditary ↓ TBG (∴ ↓ T_4): androgens, glucocorticoids, nephrotic syndrome, cirrhosis, acromegaly, antiepileptics, hereditary

Specialized Diagnostic Tests in Thyroid Disorders	
Radioactive iodine uptake (RAIU) scan	Useful to differentiate causes of hyperthyroidism ↑ **uptake:** Graves' disease, toxic multinodular goiter or hot nodule **no uptake:** subacute painful (de Quervain's) or silent thyroiditis, exogenous thyroid hormone, recent iodine load, struma ovarii or antithyroid drugs

Figure 7-1 Approach to TSH levels



HYPOTHYROIDISM (*Annals* 2020;173:ITC1)

Etiologies

- Primary (>90% of cases of hypothyroidism; ↓ **free T_4,** ↑ TSH)
  - Goitrous: **Hashimoto's thyroiditis** (after hyperthyroid phase of thyroiditis), iodine deficiency, lithium, amiodarone
  - Nongoitrous: surgical destruction, s/p radioactive iodine or XRT, amiodarone
- Secondary (central): ↓ free T_4; TSH low, inappropriately nl, or slightly high (although functionally inactive due to abnormal glycosylation); due to hypothalamic or pituitary failure

Hashimoto's thyroiditis

- Autoimmune destruction with diffuse lymphocytic infiltration
- Associated with other autoimmune disease and may be part of APS Type II

- ⊕ antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) Abs in >90%

Clinical manifestations (*Annals* 2020;173:ITC1)

- **Early:** weakness, fatigue, arthralgias, myalgias, headache, depression, cold intolerance, weight gain, constipation, menorrhagia, dry skin, coarse brittle hair, brittle nails, carpal tunnel syndrome, delayed DTRs ("hung up" reflexes), diastolic HTN, hyperlipidemia
- **Late:** slow speech; hoarseness; loss of outer third of eyebrows; **myxedema** (nonpitting skin thickening due to ↑ glycosaminoglycans); periorbital puffiness; bradycardia; pleural, pericardial, & peritoneal effusions; atherosclerosis
- **Myxedema crisis:** vide infra

Diagnostic studies (*Lancet* 2017;390:1550)

- ↓ **free T_4;** ↑ **TSH** in 1° hypothyroidism; ⊕ antithyroid Ab (TPO) in Hashimoto's thyroiditis
- May see hyponatremia, hypoglycemia, anemia, ↑ LDL, ↓ HDL and ↑ CK
- Screening recommended for pregnant women

Treatment of overt hypothyroidism (*Endocrine* 2019;66:18)

- Levothyroxine (1.5–1.7 *μ*g/kg/d), re ✓ TSH q5–6wk, titrate q8-12 wks if TSH not in range
- *Lower starting dose* (0.3–0.5 *μ*g/kg/d) if at risk for ischemic heart disease or elderly
- ↑ dose typically needed if:
  poor GI absorption: meds that ↓ absorption (iron, calcium, cholestyramine, sucralfate, PPI), celiac disease, IBD
  meds that accelerate T_4 catabolism (eg, phenytoin, phenobarbital)
  initiation of estrogen replacement; pregnancy (~30% ↑ by wk 8): TSH goals change by trimester: 1st = 0.1–4.0 mIU/L, 2nd & 3rd = gradual return of TSH to nonpregnant nl range (*Thyroid* 2017;3:315)

Subclinical hypothyroidism (*NEJM* 2017;376:2556; *JAMA* 2019;322:153)

- Mild ↑ TSH and **normal free T_4** with only subtle or no sx
- If TSH <7 or ⊖ anti-TPO Ab, ~½ resolve after 2 y (*JCEM* 2012;97:1962) if ↑ titers of antithyroid Abs, progression to overt hypothyroidism is

~4%/y
- No clear benefit to Rx (*NEJM* 2017;376:2534). In practice, follow expectantly or Rx to improve mild sx or dyslipidemia. Experts often Rx if TSH >10 mU/L, goiter, pregnancy or infertility.

Myxedema coma (ie, profound hypothyroidism; *Thyroid* 2014;24:1670)
- Presentation: hypothermia, hypotension, hypoventilation, Δ MS (coma rare), hyponatremia, hypoglycemia; often precipitated by infxn or major cardiopulmonary or neurologic illness
- Treatment: supportive care most important. Slow metabolism of drugs can lead to coma. Correction of hypothyroidism takes time. Load 200-400 μg T_4 IV, then 50–100 μg IV qd; b/c peripheral conversion impaired, may also give 5–20 μg T_3 IV q8h if unstable w/ bradycardia and/or hypothermia (T_3 more arrhythmogenic); must give **empiric *adrenal replacement therapy*** first as ↓ adrenal reserves in myxedema coma.

HYPERTHYROIDISM (*Annals* 2020;172:ITC49)

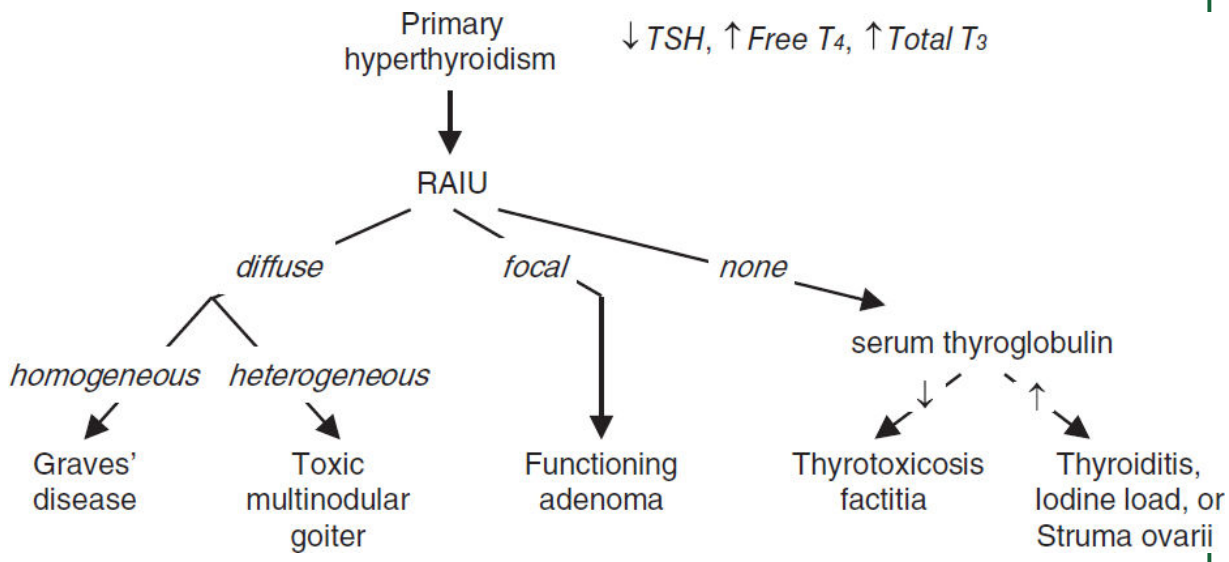
Etiologies (*Lancet* 2016;388:906)
- **Graves' disease** (60–80% of thyrotoxicosis)
- **Thyroiditis:** thyrotoxic phase of subacute (granulomatous) or painless (lymphocytic)
- **Toxic adenomas** (single or multinodular goiter)
- Extremely rare: TSH-secreting pituitary tumor or pituitary resistant to thyroid hormone (↑ TSH, ↑ free T_4)
- Misc: amiodarone, iodine-induced, thyrotoxicosis factitia, struma ovarii (3% of ovarian dermoid tumors and teratomas), tumors (eg, choriocarcinoma) secreting hCG (weak bioactivity against TSH-R), large deposits of metastatic follicular thyroid cancer

Clinical manifestations
- Restlessness, sweating, tremor, moist warm skin, fine hair, tachycardia, AF, weight loss, ↑ frequency of stools, menstrual irregularities, hyperreflexia, osteoporosis, stare and lid lag (due to sympathetic overactivity)
- **Apathetic thyrotoxicosis:** seen in elderly who can present with lethargy as only sx

Laboratory testing

- ↑ **free T_4** and **total T_3; ↓ TSH** (except in TSH-secreting tumors)
- **RAIU scan** is very useful study to differentiate causes (see table on page 7-3); cannot do if recent IV contrast or amio load b/c iodine blocks uptake, so ✓ autoantibodies instead
- Rarely need to ✓ for autoantibodies except in pregnancy (to assess risk of fetal Graves')
- May see hypercalciuria ± hypercalcemia, ↑ Aϕ, anemia

Figure 7-2 Workup of primary hyperthyroidism



Graves' disease (*NEJM* 2016;375:1552)

- ♀:♂ ratio is 5–10:1, most Pts between 40 and 60 y at dx
- ⊕ **thyroid antibodies:** TSI or TBII (⊕ in 80%), anti-TPO, antithyroglobulin; ANA
- Clinical manifestations in addition to those of hyperthyroidism (see above):
  Goiter: diffuse, nontender, w/ thyroid bruit
  Ophthalmopathy (*NEJM* 2010;362:726): seen in 50%; up to 90% if formally tested. Periorbital edema, lid retraction, proptosis, conjunctivitis, diplopia (EOM infiltration); associated w/ smoking. Stare and lid lag seen in any type of hyperthyroidism.
  Pretibial myxedema (3%): infiltrative dermopathy

Thyroiditis (*NEJM* 2003;348:2646; *Med Clin North Am* 2012;96:223)

- **Acute:** bacterial infection (very rare in U.S. except postsurgical), typically *Staph/Strep* spp.
- **Subacute:** transient thyrotoxicosis → transient hypothyroidism → normal thyroid fxn
  - **Painful** (viral, granulomatous or de Quervain's): fever, ↑ ESR; Rx = NSAIDs, ASA, steroids
  - **Silent** (postpartum, autoimmune including Hashimoto's, or lymphocytic): painless, ⊕ TPO Abs; if postpartum, can recur with subsequent pregnancies
  - **Other:** meds (amiodarone, lithium, TKIs, ICIs), palpation thyroiditis, post-radiation

Treatment (*Thyroid* 2016;26:1343; *JCEM* 2020;105:3704)

- β-blockers: control tachycardia (propranolol also ↓ T_4 → T_3 conversion)
- Graves' disease: either antithyroid drugs or radioactive iodine (*NEJM* 2016;375:1552)
  - **methimazole:** 60% chance of recurrence after 1 y; side effects include pruritus, rash, arthralgia, fever, N/V and *agranulocytosis* in 0.5%. PTU: 2nd line (risk of hepatocellular necrosis; TID dosing; slower effect; *JCEM* 2007;92:2157). For both, need to ✓ LFTs, WBC, TSH at baseline and in follow-up.
  - **radioactive iodine (RAI)** (*NEJM* 2011;364:542): typically done as outPt; preRx w/ antithyroid drugs in selected Pts w/ CV disease or elderly to prevent ↑ thyrotoxicosis, stop 3 d before to allow RAI uptake; >75% of treated Pts become hypothyroid
  - **surgery:** less commonly chosen for Graves', usually for Pts w/ obstructive goiter or ophthalmopathy. Adverse effects hypoparathyroidism, recurrent laryngeal nerve injury.
- Ophthalmopathy: can worsen after RAI; prophylax w/ prednisone in high-risk Pts; can be Rx'd w/ selenium, glucocorticoids, teprotumumab (IGF-1R inhibitor), radiation and/or surgical decompression of orbits (*NEJM* 2009;360:994)
- Toxic adenoma or toxic multinodular goiter: RAI or surgery (methimazole preRx for surgery, in selected patients before RAI)

Subclinical hyperthyroidism (*NEJM* 2018;378:2411)

- Mild ↓ TSH and **normal free T_4** with only subtle or no sx

- ~15% → overt hyperthyroidism in 2 y; ↑ risk of AF, CHD, fracture (*JAMA* 2015;313:2055)
- Rx controversial: consider if TSH <0.1 mU/L and ↑ risk for CV disease or osteopenic

Thyroid storm (extremely rare; *JCEM* 2015;2:451)

- Presentation: delirium, fever, tachycardia, systolic HTN w/ wide pulse pressure and ↓ MAP, GI symptoms; 20–30% mortality
- Diagnosis: no universally accepted criteria. Biochemical hyperthyroidism + severe sx, consider additional dx that may explain/contribute to sx.
- Treatment: β-blocker, PTU or methimazole, iopanoic acid or iodide (for Wolff-Chaikoff effect) >1 h after PTU, ± steroids (↓ T_4 → T_3)

Nonthyroidal Illness (Sick Euthyroid Syndrome) (*J Endocrinol* 2010;205:1)

- TFT abnormalities in Pts w/ severe nonthyroidal illness (∴ in acute illness, ✓ TFTs only if ↑ concern for thyroid disease); *may* have acquired transient central hypothyroidism
- If thyroid dysfxn suspected in critically ill Pt, TSH alone not reliable; must measure total T_4, free T_4, & T_3
- Mild illness: ↓ T_4 → T_3 conversion, ↑ rT_3 → ↓ T_3; in severe illness: ↓ TBG & albumin, ↑↑ rT_3 → ↓↓ T_3, ↑ degradation of T_4, central ↓ TSH → ↓↓ **T_3**, ↓↓ **T_4**, ↓ free **T_4**, ↓ **TSH**
- Recovery phase: ↑ TSH followed by recovery of T_4 and then T_3
- Replacement thyroxine not helpful or recommended for critically ill Pts w/ ↓ T_3 and T_4 unless other s/s of hypothyroidism

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Amiodarone and Thyroid Disease

Overview (*JCEM* 2021;106:226)

- 6 mg iodine per 200-mg tablet; risk of thyroid dysfunction lower with lower doses
- ✓ TSH prior to therapy, at 4-mo intervals on amio, and for 1 y after if amio d/c'd

Hypothyroidism (occurs in ~10%; more common in iodine-replete areas)

- Pathophysiology
  - (1) Wolff-Chaikoff effect: iodine load ↓ I^- uptake, organification and release of T_4 & T_3
  - (2) inhibits $T_4 \rightarrow T_3$ conversion
  - (3) ? direct/immune-mediated thyroid destruction
- Normal individuals: ↓ T_4; then escape Wolff-Chaikoff effect and have ↑ T_4, ↓ T_3, ↑ TSH; then TSH normalizes (after 1–3 mo)
- Susceptible individuals (eg, subclinical Hashimoto's, ∴ ✓ anti-TPO) do *not* escape effects
- Treatment: thyroxine to normalize TSH; may need larger than usual dose

Hyperthyroidism (3% of Pts on amio; ~10–20% of Pts *in iodine-deficient areas*)

- Type 1 = underlying multinodular goiter or autonomous thyroid tissue
  - Jod-Basedow effect: iodine load → ↑ **synthesis** of T_4 and T_3 in autonomous tissue
- Type 2 = destructive thyroiditis
  - ↑ **release** of preformed T_4 & T_3 → hyperthyroidism → hypothyroidism → recovery
- Doppler U/S: type 1 w/ ↑ thyroid blood flow; type 2 w/ ↓ flow
- Treatment: not absolutely necessary to d/c amio b/c amio ↓ $T_4 \rightarrow T_3$ conversion methimazole for type 1; steroids (eg, 40 mg prednisone qd) for type 2 often difficult to distinguish, so Rx for both typically initiated (*JCEM* 2001;86:3) consider thyroidectomy in severely ill patient

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THYROID CANCER (*Thyroid* 2016;26:1; *Endo Metab Clin NA* 2019;48:23)

Thyroid nodules (*JAMA* 2018;319:914)

- Prevalence 5–10% (50–60% if screen with U/S), ♀ > ♂, ~7–15% malignant
- Screening U/S recommended if FHx of MEN2 or medullary thyroid cancer, personal h/o neck XRT, palpable nodules or multinodular goiter

- Features a/w ↑ risk of malig: age <30 y, h/o neck XRT, family history of thyroid cancer
- U/S features a/w benign dx: cystic nodules, "spongiform" sonographic pattern
- Worrisome findings: hypoechoic, solid, irregular borders, microCa^{2+}, height>width, >20 mm
- Indications for FNA: >10-mm nodule w/ suspicious features

Papillary thyroid cancer

- Most common form (85% of differentiated thyroid cancers); peak incidence 30 to 50 y
- Risk factors: childhood radiation exposure, FHx in 1° relative, familial syndrome
- Low-risk, mort. 1–2% at 20 y; mets to neck LN common, but prognosis remains good
- Rx is surgery; after surgical resection, RAI in select intermediate-risk or high-risk

Follicular thyroid cancer

- Peak incidence 40 to 60 y, ♀:♂ 3:1; RFs: childhood radiation; FHx; familial syndrome
- Mortality 10–20% at 20 y; mets frequently distal due to hematogenous spread
- Hurthle cell carcinoma: pathologic dx; variant a/w poorer prognosis and ↑ recurrence rate

Anaplastic thyroid cancer (*Endo Metab Clin NA* 2019;48:269)

- ♀:♂ 1.5–2:1; poorly differentiated, extremely aggressive, mortality 90% at 5 y
- P/w rapidly growing fixed & hard neck mass, regional or distant spread in 90% at dx
- Rx options include surgery, radiation, trach, chemo, investigational clinical trials

Medullary thyroid cancer (*Endo Metab Clin NA* 2019;48:285)

- Neuroendocrine tumor of C cells, peak incidence 40 to 60 y, a/w MEN2A and MEN2B
- Most commonly solitary nodule; calcitonin production (presents with diarrhea, flushing) and level used to trend dz progression, dx w/

FNA (Se 50–80%); mortality 25–50% at 5 y

- Surgery first-line treatment

ADRENAL DISORDERS

Cushing's Syndrome (Hypercortisolism)

Cushing's syndrome = cortisol excess
Cushing's disease = Cushing's syndrome 2° to pituitary ACTH hypersecretion

Etiologies of hypercortisolism

- Most commonly iatrogenic caused by exogenous glucocorticoids (though underreported)
- **Cushing's disease** (60–70% of non-iatrogenic CS): ACTH-secreting pituitary adenoma (usually microadenoma) or hyperplasia
- **Adrenal tumor** (10–15%): adenoma or (rarely) carcinoma
- **Ectopic ACTH** (10–15%): SCLC, carcinoid, islet cell tumors, medullary thyroid ca, pheo

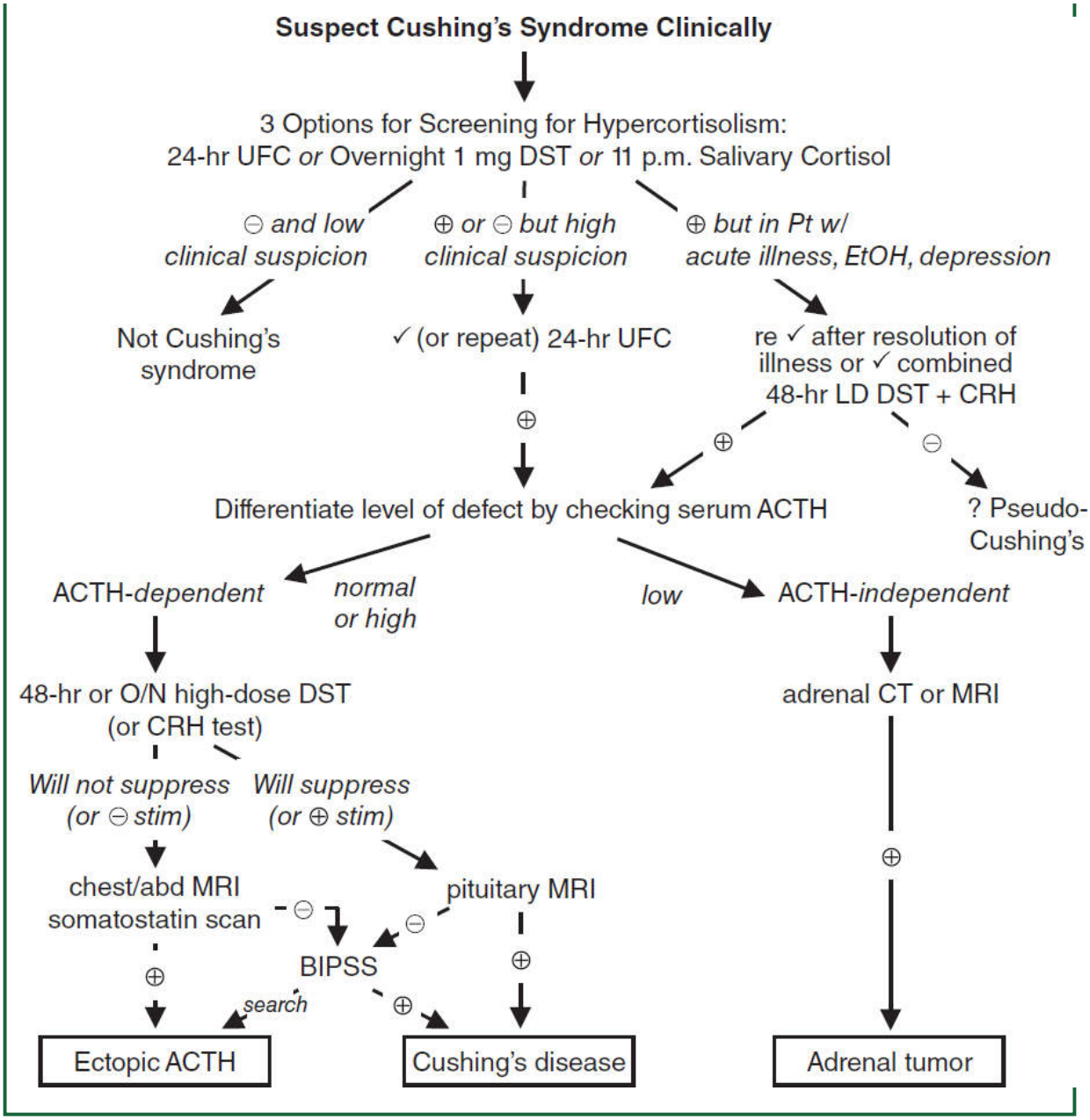
Clinical manifestations (*Lancet* 2006;367:1605)

- *Nonspecific:* glucose intolerance or DM, HTN, obesity, oligo- or amenorrhea, osteoporosis
- *More specific:* central obesity w/ extremity wasting, dorsocervical fat pads, spont. bruising
- *Most specific:* proximal myopathy, rounded facies, facial plethora, wide purple striae
- Other: depression, insomnia, psychosis, impaired cognition, hypokalemia, acne, hirsutism, hyperpigmentation (if ↑ ACTH), fungal skin infxns, nephrolithiasis, polyuria

Diagnosis

- Typically performed in *outPt* setting
- *Very difficult as inPt b/c hypercortisolism from acute illness and hosp.*

Figure 7-3 Approach to suspected Cushing's syndrome (*NEJM* 2017;376:1451)



CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; UFC, urinary free cortisol

Overnight 1 mg DST = give 1 mg at 11 p.m.; ✓ 8 a.m. serum cortisol (suppression if <1.8 μg/dL); <5% false ⊕ (primarily used to evaluate subclinical Cushing's in adrenal "incidentalomas")

11 p.m. salivary cortisol × 2 = abnl if level ↑; 24-h UFC × 2 = abnl if level ↑, >4× ULN virtually diagnostic

48-h LD DST + CRH = 0.5 mg q6h × 2 d, then IV CRH 2 h later; ✓ serum cortisol 15 min later (⊕ = >1.4 μg/dL)

48-h LD DST = 0.5 mg q6h × 2 d; ✓ 8 a.m. serum cortisol (suppression if <1.8 μg/dL);

48-h HD DST = 2 mg q6h × 2 d; ✓ 24-h UFC at baseline & during last 24 h of dex (suppressed if <80–90% of base)

O/N HD DST = 8 mg at 11 p.m.; ✓ 9 a.m. serum cortisol (suppression if <50% from day prior)
CRH stim test = 1 μg/kg IV; ✓ cortisol and ACTH (⊕ if > 35% ↑ in ACTH or >20% ↑ in cortisol above baseline)
BIPSS, bilat. Inferior petrosal sinus vein sampling; ✓ petrosal:peripheral ACTH ratio (⊕ ≥2 basal, ≥3 after CRH)

Treatment of Cushing's syndrome (*JCEM* 2015;100:2807. *J Intern Med* 2019;286:526)

- **Surgical:** resection of pituitary adenoma, adrenal tumor or ectopic ACTH-secreting tumor, or bilateral surgical adrenalectomy if unable to control source of ACTH
- **Medical:** ketoconazole, metyrapone, osilodrostat, cabergoline, pasireotide, or mitotane to ↓ cortisol, and/or mifepristone to block cortisol action at glucocorticoid receptor; frequently used as bridge to surgery or when surgery contraindicated
- **Radiation:** can do pituitary XRT, but not effective immediately (takes 6 mo to 2 y)
- Glucocorticoid replacement therapy × 6–36 mo after TSS (lifelong glucocorticoid + mineralocorticoid replacement if medical or surgical adrenalectomy)

HYPERALDOSTERONISM

Etiologies

- **Primary** (adrenal disorders, renin-independent increase in aldosterone; *JCEM* 2015;100:1) adrenal hyperplasia (60–70%), adenoma (**Conn's syndrome**, 30–40%), adrenocortical cancer, glucocorticoid-remediable aldosteronism (GRA; ACTH-dep. rearranged promoter)
- **Secondary** (extra-adrenal disorders, ↑ aldosterone is renin-dependent)
  Primary reninism: renin-secreting tumor (very rare)
  Secondary reninism: renovascular disease: RAS, malignant hypertension; edematous states w/ ↓ effective arterial volume: CHF, cirrhosis, nephrotic syndrome;
  hypovolemia, diuretics, T2D, Bartter's (defective Na/K/2Cl transporter ≈ receiving loop
  diuretic), Gitelman's (defective renal Na/Cl transporter ≈ receiving thiazide diuretic)

- **Nonaldosterone mineralocorticoid excess** mimics hyperaldosteronism
  - 11β-HSD defic. (→ lack of inactivation of cortisol, which binds to mineralocorticoid recept.)
  - Black licorice (glycyrrhizic acid inhibits 11β-HSD), extreme hypercortisolism (overwhelming 11β-HSD), exogenous mineralocorticoids
  - Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

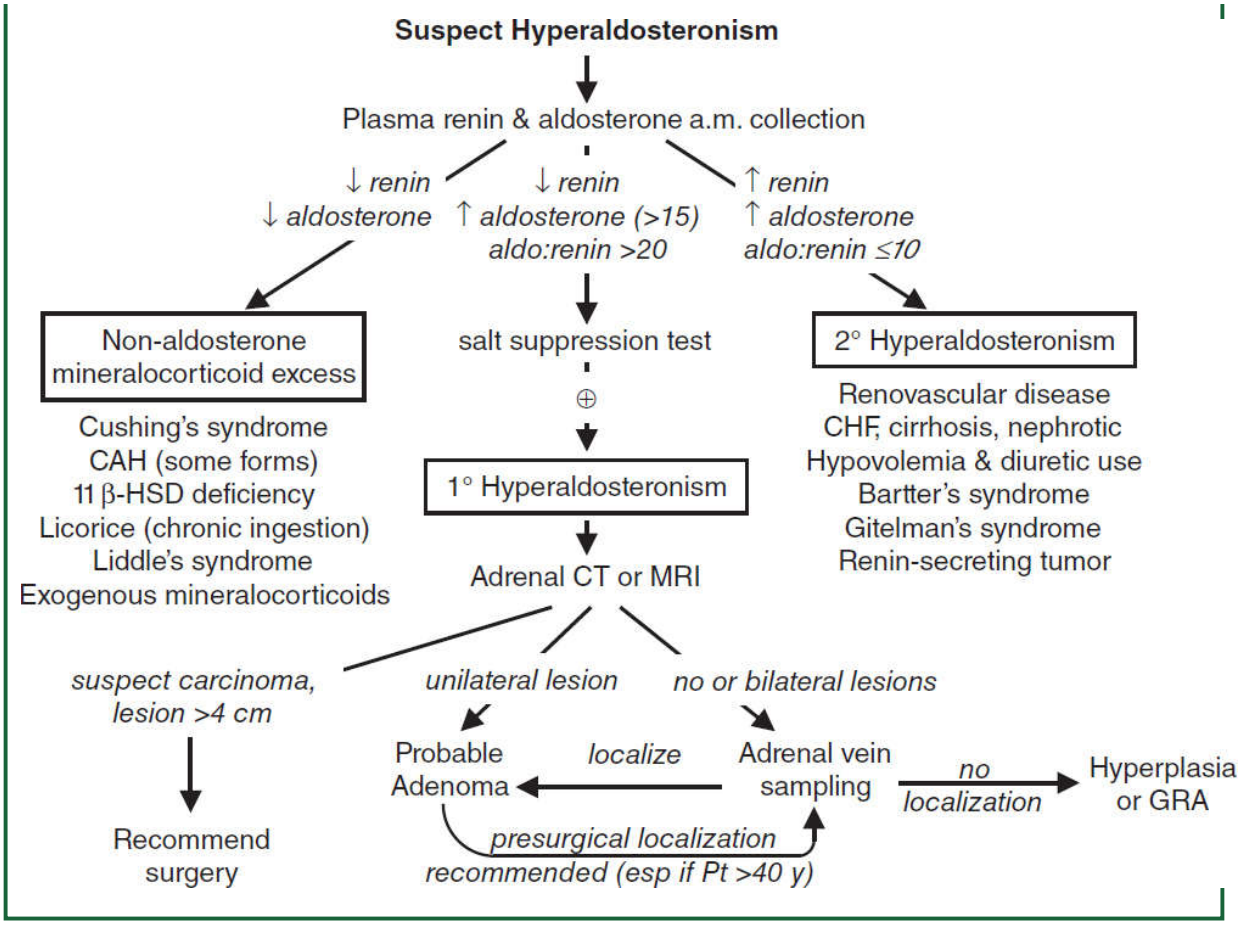
Clinical manifestations

- **Mild-to-moderate HTN**: 16-22% of all HTN, 11% of refractory cases (*Annals* 2020;173:10)
- Headache, muscle weakness, polyuria, polydipsia; no peripheral edema because of "escape" from Na retention; malignant HTN is rare
- Classically **hypokalemia** (but often normal), metabolic alkalosis, mild hypernatremia

Diagnosis (*JCEM* 2016;101:1889; *Endo Metab Clin* 2019;48:681; *J Clin Endo Met* 2021;106:2423)

- 5–10% of Pts w/ HTN; ∴ screen if HTN + hypoK, adrenal mass, refractory/early onset HTN
- Screening: ↓↓ renin, **aldo** >15–20 ng/dL, **plasma aldo:renin ratio** (>20 if 1°); obtain 8 a.m. paired values (*off* spirono & eplerenone for 6 wk); cut-offs arbitrary; Se var., Sp >70%
- ACEI/ARB, diuretics, CCB can ↑ renin activity → ↓ PAC/PRA ratio and βBs may ↑ PAC/PRA ratio; ∴ avoid. α-blockers generally best to control HTN during dx testing.
- Confirm with **sodium suppression test** (fail to suppress aldo after sodium load) oral salt load (+ KCl) × 3 d, ✓ 24-h urine (⊕ if urinary aldo >12 μg/d while urinary Na >200 mEq/d) or 2L NS over 4 h, measure plasma aldo at end of infusion (⊕ if aldo >5 ng/dL)

Figure 7-4 Approach to suspected hyperaldosteronism



Treatment (*SCNA* 2014;94:643)

- Adenoma → adrenalectomy vs. medical Rx w/ spironolactone or eplerenone
- Hyperplasia → spironolactone or eplerenone; GRA → glucocorticoids ± spironolactone
- Carcinoma → adrenalectomy

ADRENAL INSUFFICIENCY

Etiologies

- **Primary** = adrenocortical disease = ***Addison's disease***
  - **autoimmune:** isolated or in assoc w/ APS (see table on page 7-2)
  - **infection:** TB, CMV, histoplasmosis, paracoccidioidomycosis
  - **vascular:** hemorrhage (usually in setting of sepsis), adrenal vein thrombosis, HIT, trauma
  - **metastatic disease:** (90% of adrenals must be destroyed to cause insufficiency)

deposition diseases: hemochromatosis, amyloidosis, sarcoidosis
drugs: azole antifungals, etomidate (even after single dose), rifampin, anticonvulsants

- **Secondary** = pituitary failure of ACTH secretion (but adrenal **aldosterone intact** b/c RAA axis) any cause of primary or secondary hypopituitarism (see "Pituitary Disorders")
  glucocorticoid therapy (can occur after ≤2 wk of "suppressive doses"; dose effect variable; even <10 mg of prednisone daily chronically can be suppressive)
  megestrol (a progestin with some glucocorticoid activity)

Clinical manifestations (*Lancet* 2021;397:613)

- **Primary or secondary: weakness and fatigability** (95%), **weight loss** (70%), **orthostatic hypotension** (60%), nausea (50%), vomiting (50%), hyponatremia (75%)
- **Primary only** (extra s/s due to lack of aldosterone and ↑ ACTH): marked **orthostatic hypotension** (because volume depleted), salt craving, **hyperpigmentation** (seen in creases, mucous membranes, pressure areas, nipples), **hyperkalemia**
- **Secondary only:** ± other manifestations of hypopituitarism (see "Pituitary Disorders")

Diagnostic studies (*JCEM* 2016;101:364)

- Early a.m. serum cortisol: <3 μg/dL virtually diagnostic; ≥18 μg/dL generally consistent with intact adrenal function, lower cutoff w/ modern specific assays (see Appendix)
- Standard (250 μg) **cosyntropin stimulation test** (testing ability of ACTH → ↑ cortisol)
  normal = 60-min (or 30-min) post-ACTH cortisol ≥18 μg/dL
  abnormal in *primary* b/c adrenal gland diseased and unable to give adequate output
  abnormal in *chronic* secondary b/c adrenals atrophied and unable to respond
  (very rarely, may be *normal* in *acute pituitary injury* b/c adrenals still able to respond → use early a.m. cortisol instead)
  All glucocorticoids (incl creams, inh. & drops) affect test. Must know exposure to interpret.
- Other tests (w/ guidance by endocrinologist): renin, aldosterone, insulin-induced hypoglycemia (measure serum cortisol response);

metyrapone (blocks cortisol synthesis and therefore stimulates ACTH, measure plasma 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels)
- Other lab abnormalities: hypoglycemia, eosinophilia, lymphocytosis, ± neutropenia
- ACTH: ↑ in 1°, ↓ or low-normal in 2°
- Imaging studies to consider
  pituitary MRI to detect anatomical abnormalities
  adrenal CT: small, noncalcified adrenals in autoimmune, enlarged in metastatic disease, hemorrhage, infection or deposition (although they may be normal-appearing)

Treatment

- *Acute* insufficiency: volume resusc. w/ normal saline + **hydrocortisone IV** (see below)
- *Chronic* insufficiency: (1) prednisone ~4–5 mg PO qam or hydrocortisone 15–25 mg PO qd ($^2/_3$ a.m., $^1/_3$ early p.m.); (2) fludrocortisone (*not* needed in 2° adrenal insufficiency) 0.05–0.2 mg PO qam (*JCEM* 2018;103:376); (3) backup dexamethasone 4-mg IM prefilled syringe given to Pt for emergency situations

Adrenal insufficiency & critical illness (*NEJM* 2003;348:727; *JAMA* 2009;301:2362)

- Low cortisol binding proteins; ∴ dx of adrenal insufficiency problematic (*NEJM* 2013;368:1477)
- Adrenal insufficiency rare in most cases of shock unless adrenal infarction or bleed, Waterhouse-Friderichson, CNS or pituitary bleed
- Reasonable to collect cortisol level in HoTN Pt w/ suspicion for adrenal insufficiency
- Can consider above dx criteria, but decision for Rx should also be based on clinical assessment due to risk of false ⊖ and ⊕ results in context of altered physiology
- If concerned, initiate corticosteroids early: use hydrocortisone 100 mg IV followed by 50 mg IV q6h
- Controversial data for empiric steroids in all critically ill Pts (see "Sepsis")

Adrenal crisis in adrenal insufficiency (*NEJM* 2019;381;852)

- Precipitants: preexisting adrenal insufficiency + serious infection or GI illness, bilateral adrenal hemorrhage or infarction, pituitary infarction
- Presentation: shock + anorexia, N/V, abd pain, weakness, fatigue, confusion, coma, fever
- Lab findings: hyponatremia, hyperkalemia (1°)
- Rx: hydrocortisone 100 mg IV followed by 50 mg IV q6 + IVF; do not delay for dx tests

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PHEOCHROMOCYTOMA & PARAGANGLIOMA

Clinical manifestations (*NEJM* 2019;381:552)

- Neuroendocrine neoplasm leads to inappropriate and paroxysmal release of adrenergic agents including epinephrine, norepinephrine, and rarely dopamine
- **Classic triad**: episodic headaches, palpitations and profuse sweating; only 50% have paroxysmal hypertension and most Pts do *not* have three classic sx
- Paroxysms can be triggered by meds (eg, β-blockers), abdominal manipulation
- Up to 40% of pheos/paragangliomas thought to have underlying genetic etiology; genetic testing frequently recommended
- Associated with MEN2A/2B, von Hippel Lindau, NF1, familial paraganglioma (mutations in succinate dehydrogenase gene B, C and D), *MAX* or *TMEM127* mutations

Diagnostic studies (*JCEM* 2014;99:1915)

- 24° urinary fractionated metanephrines: 98% Se, 98% Sp. Screening test of choice if low-risk (b/c false ⊕ with severe illness, renal failure, OSA, labetalol due to assay interference, acetaminophen, TCAs, medications containing sympathomimetics).
- Plasma fractionated metanephrines: 97% Se, 91% Sp. Screening test of choice if high risk, but ↑ rate of false ⊕ in low-prevalence population. False ⊕ rate lower if patient supine for 30 min (estimated 2.8× ↑ false ⊕ if seated).
- Adrenal CT or T2-weighted MRI; PET for known metastatic disease or to localize nonadrenal mass but usually easy to find; consider MIBG scintigraphy if CT/MRI ⊖

• Consider genetic testing in all Pts (*J Intern Med* 2019;285:187)

Treatment

• α-blockade first (usually phenoxybenzamine) ± β-blockade (often propranolol) → surgery
• Preoperative volume expansion is critical due to possible hypotension after tumor excision

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ADRENAL INCIDENTALOMAS

Epidemiology

• 4% of Pts undergoing abdominal CT scan have incidentally discovered adrenal mass; prevalence ↑ with age

Differential diagnosis

• **Nonfunctioning mass:** adenoma, cysts, abscesses, granuloma, hemorrhage, lipoma, myelolipoma, primary or metastatic malignancy
• **Functioning mass:** pheochromocytoma, adenoma (cortisol, aldosterone, sex hormones), other endocrine tumor, carcinoma

Hormonal workup (*EJE* 2016;175:G1; *NEJM* 2021;384:1542)

• **Rule out subclinical Cushing's syndrome** *in all Pts* using 1 mg overnight DST (Sp 91%). Abnormal results require confirmatory testing.
• **Rule out hyperaldosteronism** *if hypertensive* w/ plasma aldo & renin (see above)
• **Rule out pheochromocytoma** *in ALL Pts* (b/c of morbidity unRx'd pheo) using 24-h urine fractionated metanephrines or plasma fractionated metanephrines

Malignancy workup

• CT and MRI characteristics may suggest adenoma vs. carcinoma
  Benign features: unenhanced CT <10 Hounsfield units or CT contrast-medium washout >50% at 10 min; size <4 cm; smooth margins, homogenous and hypodense appearance; can follow such incidentalomas w/ periodic scans
  Suspicious features: size ≥4 cm or ↑ size on repeat scan; >10 Hounsfield units on CT, irregular margins, heterogeneous, dense or vascular appearance; h/o malignancy or young age.

Such incidentalomas warrant resection or repeat scan at short interval.

- Rule out metastatic cancer (and infection) in Pts w/ h/o cancer; ~50% of adrenal incidentalomas are malignant

Follow-up

- If hormonal workup ⊖ and appearance benign, no further follow-up imaging needed, but controversial (*Annals* 2019;171:107)

CALCIUM DISORDERS

Laboratory Findings in Calcium Disorders					
Ca	**PTH**	**Disease**	**PO_4**	**25-(OH)D**	**1,25-$(OH)_2$D**
↑	↑↑	Hyperparathyroidism (1° and 3°)	↓	↓ to nl	nl to ↑
	↑ or nl	Familial hypocalciuric hypercalcemia	↓	var.	nl
	↓	Malignancy	var.	var.	var.
		Vitamin D excess	↑	↑	nl to ↑
		Milk-alkali syndrome, thiazides	var.	var.	var.
		↑ Bone turnover	nl to ↑	var.	nl
↓	↑↑	Pseudohypoparathyroidism	↑	var.	↓
	↑	Vitamin D deficiency	↓	↓↓	nl / ↓
		Chronic renal failure (2° hyperpara)	nl to↑	var.	↓
	var.	Acute calcium sequestration	var.	var.	var.
	↓	Hypoparathyroidism	↑	var.	↓ to nl

Pitfalls in measuring calcium

- Physiologically active Ca is free or ionized (ICa). Serum Ca reflects total calcium (bound + unbound) and ∴ influenced by albumin (main Ca-binding protein).
- Corrected Ca (mg/dL) = measured Ca (mg/dL) + {0.8 × [4 – albumin (g/dL)]}
- Alkalosis will cause more Ca to be bound to albumin (∴ total Ca may be normal but ↓ ICa)
- Best to measure **ionized Ca directly** (*but accuracy is lab dependent*)

HYPERCALCEMIA

Etiologies of Hypercalcemia	
Category	**Etiologies**
Hyperparathyroidism (HPT) (*NEJM* 2018;379:1050; *Lancet* 2018;391:168)	**1°: adenoma** (85%), hyperplasia (15–20%; spont. vs. MEN1/2A), carcinoma (<1%), meds (Lithium → ↑ PTH) **3°:** after long-standing 2° hyperparathyroidism (as in renal failure) → autonomous nodule develops, requires surgery

Etiologies of Hypercalcemia	
Familial hypocalciuric hypercalcemia (FHH)	Inact. mut. in Ca-sensing receptor (FHH1), Gα11 (FHH2), AP2S1 (FHH3) → ↑ Ca set point; ± mild ↑ PTH Acquired form due to autoAb vs. Ca-sensing receptor (rare) FE_{Ca} [(24-h U_{Ca}/serum Ca) / (24-h U_{Cr}/serum Cr)] <0.01
Malignancy (*NEJM* 2022;386:1443)	PTH-related peptide (PTHrP) → humoral ↑ Ca of malignancy (eg, squamous cell cancers, renal, breast, bladder) Cytokines → ↑ osteoclast activity (eg, hematologic malig) ↑ 1,25-$(OH)_2$D (eg, rare lymphomas) Local osteolysis (eg, breast cancer, myeloma)
Vitamin D excess	Granulomas (sarcoid, TB, histo, GPA) → ↑ 1-OHase → ↑ 1,25-$(OH)_2$D. Vitamin D intoxication.
↑ **Bone turnover**	Hyperthyroidism, immobilization + Paget's disease, vitamin A
Miscellaneous	Thiazides; Ca-based antacids or massive dairy consumption (milk-alkali syndrome); adrenal insufficiency
Among inPts w/ hypercalcemia: 45% have cancer, 25% 1° *HPT, 10% CKD → 3° HPT*	

(*JCEM* 2005;90:6316; *NEJM* 2013;368:644)

Clinical manifestations ("bones, stones, abdominal groans, and psychic moans")

- **Hypercalcemic crisis** (usually when Ca >13–15): polyuria, dehydration, ΔMS
  Ca toxic to renal tubules → blocks ADH activity, causes vasoconstriction and ↓ GFR → polyuria but Ca reabsorption → ↑ serum Ca → ↑ nephrotoxicity and CNS sx
- Osteopenia, fractures, and osteitis fibrosa cystica (latter seen in severe hyperpara. only → ↑ osteoclast activity → cysts, fibrous nodules, salt & pepper appearance on X-ray)
- Nephrolithiasis, nephrocalcinosis, nephrogenic DI
- Abdominal pain, anorexia, nausea, vomiting, constipation, pancreatitis, PUD
- Fatigue, weakness, depression, confusion, coma, ↓ DTRs, short QT interval
- 1° HPT: 80% asx, 20% nephrolithiasis, osteoporosis, etc.

Diagnostic studies

- Hyperparathyroidism (HPT) and malignancy account for 90% of cases of ↑ Ca; HPT more likely if asx or chronic; malignancy (usually overt) more likely if acute or sx

- Ca, alb, ICa, PTH (may be inapprop. normal in 1° HPT & FHH; *JAMA* 2014;312:2680), PO_4
  ↑ or high nl PTH: Ca/Cr clearance ratio <0.01 → FHH
  ↓ PTH: ✓ PTHrP, Aϕ, & search for malig (eg, CT, mammogram, SPEP/UPEP) and ✓ vit D: ↑ 25-(OH)D → meds; ↑ 1,25-(OH)2D → granuloma (✓ CXR, ACE, r/o lymph)

Acute Treatment of Hypercalcemia (*BMJ* 2015;350:h2723)			
Treatment	**Onset**	**Duration**	**Comments**
Normal saline (4–6 L/d)	h	during Rx	Natriuresis → ↑ renal Ca excretion
· **Furosemide**	h	during Rx	Use cautiously, only if volume overloaded
Bisphosphonates	1–2 d	var.	Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis; monitor for hypocalcemia
Calcitonin	h	~48 hrs	Bridging Rx, quickly develop tachyphylaxis
Glucocorticoids	days	days	Useful in some malig, granulomatous disorders & vitamin D intox.
Denosumab (*JCEM* 2014;99:3144)	days	months	Monoclonal Ab against RANKL; typically used in hyperCa of malignancy; not renally cleared
Hemodialysis	min	during Rx	If other measures ineffective or contraindicated

Treatment of asymptomatic 1° HPT (*JCEM* 2014;99:3561; *JAMA* 2020;323:1186)

- Surgery if: age <50 y; serum Ca >1 mg/dL >ULN; CrCl <60 mL/min, DEXA T score <–2.5
- If surgery declined/deferred, can Rx with cinacalcet (↓ Ca & PTH but may not ↑ BMD)
- If not yet candidate for surgery: ✓ serum Ca & Cr annually and BMD q2y

HYPOCALCEMIA

Etiologies of Hypocalcemia	
Category	**Etiologies**

Etiologies of Hypocalcemia	
Hypoparathyroidism (*NEJM* 2019;380:1738; *JCEM* 2020;105:1722)	Iatrogenic (s/p thyroidectomy, rarely after parathyroidectomy); sporadic; familial (APS1, activating Ca-sensing receptor mutations; see page 7-2); Wilson's, hemochromatosis; hypoMg (↓ secretion and effect); activating Ca-sensing receptor autoAb
Pseudo-hypoparathyroidism (*Endo Metab Clin North Am* 2018;47:865)	1a, 1b, & 1c: PTH end-organ resistance (∴ ↑ serum PTH) 1a & 1c: + skeletal abnormalities, short stature & developmental delay 1b: w/o extra features Pseudopseudohypoparathyroidism = 1a mutation inherited from father, no hormonal abnormalities
Vit D defic. or resist (*NEJM* 2011;364:248; *JCEM* 2012;97:1153)	Nutritional/sunlight deprivation; GI disease/fat malabs.; drugs (anticonvulsants, rifampin, ketoconazole, 5-FU/leucovorin); genetic (1α-hydroxylase, VDR mutations). Deficiency more common.
Chronic renal failure	↓ 1,25-$(OH)_2$D production from elevated FGF23, ↑ PO_4 from ↓ clearance
Accelerated net bone formation	Postparathyroidectomy, Paget's disease (*JBMR* 2019;34:579), osteoblastic metastases
Calcium sequestration	Pancreatitis, citrate excess (after blood transfusions), acute ↑↑ PO_4 (ARF, rhabdomyolysis, tumor lysis), bisphosphonates

Clinical manifestations

- **Neuromuscular irritability:** perioral paresthesias, cramps, ⊕ **Trousseau's** (inflation of BP cuff ≥**3** min → carpal spasm), ⊕ **Chvostek's** (tapping facial nerve → contraction of facial muscles), laryngospasm; irritability, depression, psychosis, seizures, ↑ QT
- Rickets and/or osteomalacia: chronic ↓ vit D → ↓ Ca, ↓ PO_4 → ↓ bone/cartilage mineralization, growth failure, bone pain, muscle weakness
- **Renal osteodystrophy**: osteomalacia [↓ mineralization of bone due to ↓ Ca and 1,25-$(OH)_2$D] & osteitis fibrosa cystica (due to ↑ PTH), adynamic bone disease or mixed uremic osteodystrophy; dx by bone biopsy

Diagnostic studies

- Ca, alb, ICa, PTH, 25-(OH)D, 1,25-$(OH)_2$D (if renal failure or rickets), Cr, Mg, PO_4, Aϕ, U_{Ca}

Treatment (also treat concomitant vitamin D deficiency; *Endocrine* 2020;69:485)

- Severely symptomatic: Ca gluconate (1–2 g IV over 20 min) + oral Ca + calcitriol (but takes hrs to work) ± Mg (50–100 mEq/d); 10% $CaCl_2$ in codes or via CVL
- Consider Ca gtt or PO to follow b/c effect of IV bolus typically lasts only a few hours
- Chronic (depends on etiol.): oral Ca (1–3 g/d; citrate better absorbed than carbonate, esp. if achlorhydria or on PPI) and typically calcitriol (0.25–2 mcg/d), and replete vit. D defic. Consider thiazide to ↓ urinary Ca or recombinant PTH 1-84 (if hypopara).
- Chronic renal failure: phosphate binder(s), oral Ca, calcitriol or analogue

DIABETES MELLITUS

Definition (*Diabetes Care* 2022;45:S256)

- Either Hb_{A1c} ≥6.5, fasting glc ≥126 mg/dL, or glc 2 h after OGTT ≥200 mg/dL × 2 (for any test) or single random glc ≥200 mg/dL w/ classic sx of hyperglycemia; all tests equally reasonable (nb, may be ⊕ on one test but not another); OGTT preferred during preg
- Blood glc higher than normal, but not frank DM ("prediabetics," ~40% U.S. population)
  Hb_{A1c} 5.7–6.4%, impaired fasting glc (IFG) 100–125 mg/dL, or 2 h prandial glc 140–199.
  Preventing progression to DM: diet/exercise (58% ↓), metformin (31% ↓; *NEJM* 2002;346:393)

Categories

- **Type 1** (*Lancet* 2018;391:2449): islet cell destruction; absolute insulin deficiency; ketosis in absence of insulin; prevalence 0.4%; usual onset in childhood but can occur throughout adulthood; ↑ risk if ⊕ FHx; HLA associations; anti-GAD, anti-islet cell & anti-insulin autoAb
- **Type 2** (*Lancet* 2017;389:2239): insulin resistance + relative insulin ↓; prevalence 6%; onset generally later in life; no HLA assoc.; risk factors: age, ⊕ FHx, obesity, sedentary lifestyle
- **Type 2 DM p/w DKA** ("ketosis-prone diabetes" or "Flatbush diabetes"): most often seen in nonwhite, ± anti-GAD Ab, eventually may not require insulin (*Endo Rev* 2008;29:292)
- **M**ature-**O**nset **D**iabetes of the **Y**oung (**MODY**): autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*JCEM* 2021;106:237)
- **Secondary causes of diabetes:** exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), endocrino-pathies (Cushing's, acromegaly), gestational, drugs (protease inhibitors, atypical antiψ)

Clinical manifestations

- Polyuria, polydipsia, polyphagia with unexplained weight loss; may be asymptomatic

Diabetes Treatment Approach for Pt w/ ASCVD, HF, or CKD	
Med (↓ Hb_{A1C})	**Comments**
GLP-1 receptor agonists (~1–2%)	↑ glc-depend. insulin secretion. Delay gastric emptying. Wt ↓, N/V. ↓ CVD/MI/stroke, esp. if ASCVD. ↓ prog of albuminuria. *1st line* if est. ASCVD or high ASCVD risk (age >55, LVH, arterial stenosis >50%), *regardless of A1c*.
SGLT-2 inhibitors (~0.5–1%)	↑ glucosuria. Wt ↓. ↑ genital infxn. ? caution if PAD. ↓ CVD/HHF. ↓ prog. of renal disease. ± ↓ MI if ASCVD. *1st line* if HF, proteinuric CKD, *regardless of A1c*.
Metformin (~1–1.5%)	↓ hepatic gluconeogenesis. Mild wt ↓. Rare lactic acidosis. Caution if GFR 30–45; contra. if <30. Poss CV benefit. Historically 1st line Rx, although some debate given benefit of GLP1RA & SGLT2i.
Additional Diabetes Treatment Options	
DPP-4 inhibitors (~0.5–1%)	Block degrad. GLP-1 & GIP → ↑ insulin. ↑ risk of HF w/ saxagliptin (*NEJM* 2013;369:1317), not w/ others.
Sulfonylureas (SU) (~1.5%)	↑ insulin secretion. Hypoglycemia; wt gain.
Thiazolidinediones (TZD) (~1%)	↑ insulin sens. in adipose & muscle. Wt ↑, fluid retention & CHF. Hepatox. ↑ MI w/ rosiglitazone? Contraindic. in HF & liver dysfxn.
Glinides (~1%)	↑ insulin secretion; hypoglycemia; wt gain
α-gluc. inhib (~0.5%)	↓ intestinal CHO absorption. Abd pain, flatulence.
Pramlintide (~0.5%)	Delays gastric emptying & ↓ glucagon. N/V
Insulin (variable)	↓↓ glc; wt gain. Mandatory in T1D; consider in T2D if oral Rx inadeq. Weekly vs. daily w/ similar glycemic ctrl (*NEJM* 2020;383:2107).
Tirzepatide (~2–2.5%)	Dual glucose-dependent insulinotropic polypeptide-GLP-1 receptor agonist. Greater ↓ in A1C & wt vs. semaglutide (*NEJM* 2021;385:503). Not yet FDA approved.
Gastric bypass	Wt ↓↓↓; can cause remission DM (*NEJM* 2014;370:2002)

Lifestyle changes including weight management are foundational. *Diabetes Care* 2022;45:S256; *NEJM* 2021; 385:896. *NEJM* 2019;381:1995; *Lancet* 2019;393:31; *Circ* 2019;139:2022; *NEJM* 2019;380:2295.

Insulin Preparations (*Diabetes Care* 2019;42:S90)				
Type (example)	**Onset**	**Peak**	**Duration**	**Comments**
Rapid (lispro, aspart)	Immed	1-2 h	<4 h	Give immediately before meal
Short (regular)	~30 min	2–3 h	5–8 h	Give ~30 min before meal
Intermed. (NPH)	2–3 h	4–8 h	10–14 h	Can cause protamine Ab prod
Long (glargine, detemir)	1–2 h	n/a	12–24 h	Once-daily basal insulin

Complications (*NEJM* 2004;350:48; 2016;374:1455; *CJASN* 2017;12:1366)

- **Retinopathy**
  nonproliferative: "dot & blot" and retinal hemorrhages, cotton-wool/protein exudates
  proliferative: neovascularization, vitreous hemorrhage, retinal detachment, blindness
  treatment: photocoagulation, surgery, intravitreal bevacizumab injections
- **Nephropathy:** microalbuminuria → proteinuria ± nephrotic syndrome → renal failure. Strict BP control using ACEI or ARB; SGLT-2 inhib (*NEJM* 2016;375:323 & 2019;380:2295); finerenone (*NEJM* 2020;383:2219); low-protein diet; dialysis or transplant.
- **Neuropathy:** *peripheral:* symmetric distal sensory loss, paresthesias, ± motor loss
  autonomic: gastroparesis, constipation, neurogenic bladder, erectile dysfxn, orthostasis
  mononeuropathy: sudden-onset peripheral or CN deficit (footdrop, CN III >VI >IV)
- **Accelerated atherosclerosis:** coronary, cerebral and peripheral arterial beds
- **Infections:** UTI, osteomyelitis of foot, candidiasis, mucormycosis, necrotizing external otitis
- **Dermatologic:** necrobiosis lipoidica diabeticorum, lipodystrophy, acanthosis nigricans

Outpatient screening and treatment goals (*Diabetes Care* 2022;45;S83 & S144)

- ✓ Hb_{A1C} q3–6mo, goal <7% for most Pts. Goal <6.5% if low-risk hypoglycemia; ≤8% if h/o severe hypoglycemia, elderly or other comorbid.

- Microvascular complications (nephropathy, retinopathy, neuropathy) ↓↓ by strict glycemic control (*NEJM* 1993;329:977).
- Effect of strict glycemic control on macrovascular complications (ASCVD) more nuanced. Benefit in T1D (*NEJM* 2005;353:2643) & T2D, but emerged after a decade (*NEJM* 2015;372:2197). In shorter-term trials (~5 yrs), modest ↓ in risk of MI, but no effect on death and even ↑ in some studies, potentially because of hypoglycemia (*Lancet* 2009;373:1765).
- Microalbuminuria screening yearly with spot microalbumin/Cr ratio, goal <30 mg/g
- Wt loss (dietary/drugs) can regress or resolve DM (*Endo Rev* 2018;39:79; *NEJM* 2018;379:1107)
- **BP** ≤130/80 if high CV risk, ≤140/90 if lower risk; benefit of ACEI/ARB
- **Lipids:** statin initiation in all diabetics age 40–75 if LDL-C >70 (see "Lipid Disorders")
- ASA in 2° prevention; ? role in 1°, balancing ↓ MACE & ↑ bleeding (*NEJM* 2018;379:1529)
- Dilated retinal exam and comprehensive foot exam

Management of hyperglycemia in inPts (for ICU: see "Sepsis") (*Clin Ther* 2013;35:724)

- Identify reversible causes/precipitants (dextrose IVF, glucocorticoids, postop, ↑ carb diet)
- Dx studies: BG fingersticks (fasting, qAC, qHS; or q6h if NPO), Hb_{A1C}
- Treatment goals: avoid hypoglycemia, extreme hyperglycemia (>180 mg/dL)
- Transition to inPt:
  T1D: do not stop basal insulin (can → DKA)
  T2D: stopping oral DM meds generally preferred to avoid hypoglycemia or med interaction (except if short stay, excellent outPt cntl, no plan for IV contrast, nl diet). *If Pt on insulin as outpt do not rely on sliding scale alone* (*Diabetes Care* 2022;45:S244).
- Starting new insulin regimen
  Basal = 0.2–0.4 U/kg/d NPH Q12h or detemir or glargine + correction insulin for BG >150 mg/dL + prandial insulin if eating: 0.05–0.1 U/kg/meal lispro, aspart, or regular
- *When NPO*

T1D: continue basal insulin at current dose or 75% depending on BG control

T2D: continue basal insulin at 25–75% depending on BG control and level of insulin resistance. Hold all prandial insulin.

- Discharge regimen: similar to admission regimen unless poor outPt cntl or strong reason for Δ. Arrange early insulin and glucometer teaching, prompt outPt follow-up.

DIABETIC KETOACIDOSIS (DKA)

Precipitants (the I's)

- **Insulin defic.** (ie, failure to take enough insulin); **Iatrogenesis** (glucocorticoids; SGLT2 inhibitors—can be w/o marked hyperglycemia; *Diabetes Care* 2016;39:532)
- **Infection** (pneumonia, UTI) or **Inflammation** (pancreatitis, cholecystitis)
- **Ischemia** or **Infarction** (myocardial, cerebral, gut); **Intoxication** (alcohol, drugs)

Pathophysiology (*NEJM* 2015;372:546)

- Occurs in **T1D** (and in ketosis-prone T2D); ↑ glucagon and ↓ insulin
- Hyperglycemia due to: ↑ gluconeogenesis, ↑ glycogenolysis, ↓ glucose uptake into cells
- Ketosis due to: insulin deficiency → mobilization and oxidation of fatty acids,
  ↑ substrate for ketogenesis, ↑ ketogenic state of the liver, ↓ ketone clearance

Clinical manifestations (*Diabetes Care* 2009;32:1335 & 2016;39:S99)

- Polyuria, polydipsia, & dehydration → ↑ HR, HoTN, dry mucous membranes, ↓ skin turgor
- N/V, abdominal pain (either due to intra-abdominal process or DKA), ileus
- Kussmaul's respirations (deep) to compensate for metabolic acidosis with odor of acetone
- Δ MS → somnolence, stupor, coma; mortality ~1% even at tertiary care centers

Diagnostic studies

- ↑ **Anion gap metabolic acidosis** (pH <7.3 & HCO_3 <18): can later develop nonanion gap acidosis due to urinary loss of ketones (HCO_3 equiv.) & fluid resuscitation w/ chloride
- **Ketosis: ⊕ urine and serum ketones** (predominant ketone is β-OH-butyrate, but acetoacetate measured by assay; urine ketones may be ⊕ in fasting normal Pts)
- ↑ Serum glc usually >250 mg/dL (but can be euglycemic if on SGLT-2i);↑ BUN & Cr
- Hyponatremia: corrected Na = measured Na + [2.4 × (measured glc – 100)/100]
- ↓ or ↑ K (but even if serum K is elevated, *usually total body K depleted*); ↓ total body phos
- Leukocytosis & ↑ amylase (even if no pancreatitis)

Treatment of DKA (*BMJ* 2019;365:1114)	
R/o possible precipitants	Infection, intra-abdominal process, MI, etc. (see above)
Aggressive hydration	1L NS then ~250 cc/hr, tailor to dehydration & CV status
Insulin	0.1 U/kg bolus followed by 0.1 U/kg/h IV Continue insulin drip until AG normal If glc <250 and AG still high → add dextrose to IVF and ↓ insulin drip to 0.02—0.05 U/kg/hr AG nl & can eat → SC insulin (overlap IV & SC 2–3 h)
Electrolyte repletion	K: add 20–40 mEq/L IVF if serum K <5.4; insulin promotes K entry into cells → hold insulin if K <3.3. Careful K repletion in Pts with renal failure. HCO_3: consider repletion if pH <6.9 or if cardiac instability

HYPEROSMOLAR HYPERGLYCEMIC STATE

Definition, precipitants, pathophysiology (*Med Clin North Am* 2017;101:587)

- Extreme hyperglycemia (w/o ketoacidosis) + hyperosm. + Δ MS in T2D (typically elderly)
- Precip same as for DKA, but also include dehydration and renal failure
- Hyperglycemia → osmotic diuresis → vol depletion → prerenal azotemia → ↑ glc, etc.

Clinical manifestations & dx studies (*Diabetes Care* 2014;37:3124)

- Volume depletion and Δ MS

- ↑ **serum glc** (usually >600 mg/dL) and ↑ **meas. serum osmolality** (>320 mOsm/L) effective Osm = 2 × Na (mEq/L) + glc (mg/dL)/18
- pH >7.3, no ketoacidosis; usually ↑ BUN & Cr; [Na] depends on glucose & dehydration

Treatment

- Rule-out possible precipitants; ~15% mortality due to precipitating factors
- **Aggressive hydration:** initially NS, then ½ NS, average fluid loss up to 8–10 L
- **Insulin** (eg, 10 U IV followed by 0.05–0.1 U/kg/h), target glucose ~250 until Pt alert

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HYPOGLYCEMIA

Clinical manifestations (glucose <~55 mg/dL)

- **CNS:** headache, visual Δs, Δ MS, weakness, seizure, LOC (neuroglycopenic sx)
- **Autonomic:** diaphoresis, palpitations, tremor (adrenergic sx)

Etiologies

- **Pts w/ diabetes**: excess insulin, oral hypoglycemics, missed meals, renal failure (↓ insulin & SU clearance); β-blockers can mask adrenergic symptoms of hypoglycemia
- **Pt without diabetes**: low fasting glucose w/o sx can be normal
- ↑ **insulin:** exogenous insulin, sulfonylureas, insulinoma, anti-insulin antibodies
- ↓ **glucose production:** hypopituitarism, adrenal insufficiency, glucagon deficiency, hepatic failure, renal failure, CHF, alcoholism, sepsis, severe malnutrition
  Postprandial, esp. postgastrectomy or gastric bypass: excessive response to glc load
  ↑ **IGF-II:** non-islet tumor (rare)

Evaluation in patients without diabetes (*JCEM* 2009;94:709)

- If clinically ill: take measures to avoid recurrent hypoglycemia; ✓ BUN, Cr, LFTs, TFTs, prealbumin; IGF-I/IGF-II ratio when appropriate

- If otherwise healthy: 72-h fast w/ monitored blood glc; stop for neuroglycopenic sx
- *At time of hypoglycemia:* insulin, C peptide (↑ w/ insulinoma and sulfonylureas, ↓ w/ exogenous insulin), β-OH-butyrate, sulfonylurea levels
- At end of fast, give 1 mg glucagon IV and measure response of plasma glc before feeding

Treatment

- Glucose tablets, paste, & fruit juice are first-line Rx for Pts who can take POs
- 25–50 g of D_{50} IV; if no access, glucagon 0.5–1 mg IM or SC (side effect: N/V)

LIPID DISORDERS

Measurements

- Lipoproteins = lipid core (cholesteryl esters & triglycerides) + phospholipid surface + proteins. Include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a)
- Measure after 12-h fast; LDL typically calculated: LDL-C = TC – HDL-C – (TG/5) underestim. if TG >400 or LDL-C <70 mg/dL; ∴ directly measure LDL-C levels stable up to 24 h after ACS, then ↓ and may take 6 wk to return to nl
- PEx clues: tendon xanthomas (eg, Achilles), imply LDL >300 mg/dL; eruptive xanthomas on extensor surfaces imply TG >1500 mg/dL; xanthelasma (yellowish streaks on eyelids)
- Metabolic syndrome (≥3 of following): waist ≥40″ (♂) or ≥35″ (♀); TG ≥150 mg/dL; HDL<40 (♂) or <50 mg/dL (♀); BP ≥130/85 mmHg; fasting glc ≥100 mg/dL (*Circ* 2009;120:1640)
- Lp(a) = LDL particle + apo(a); concentration genetically determined; a/w CAD & AS

Dyslipidemias

- 1° (inherited causes): *familial hyperchol.* (1:250): defective LDL receptor; ↑↑ chol; ↑ CAD; *familial hyperTG*: ↑ TG & pancreatitis; *familial combined hyperlipid.:* ↑ chol & TG; etc.
- 2°: DM (↑ TG, ↓ HDL), hypothyroidism (↑ LDL, ↑ TG), nephrotic syndrome (↑ LDL, ↑ TG), liver failure (↓ LDL), alcohol (↑ TG, ↑ HDL), thiazides (↑ LDL, ↑ TG), protease inhib (↑ TG)

Drug Treatment			
Drug	**↓ LDL**	**↓ TG**	**Side Effects/Comments**
Statins	30–60%	10–25%	↑ ALT in 0.5–3%; ✓ before starting and then prn Myalgias <10%, rhabdo <0.1%, dose-dependent ↑ risk of DM; screen if risk factors (*ATVB* 2019;39:e38)

Drug Treatment			
Ezetimibe	~24%	—	Well tolerated
Bempedoic acid	~16%	—	Hyperuricemia/gout; ↓ eGFR. CVOT under way.
PCSK9i	50–60%	15–25%	mAb inj SC q2-4w or siRNA inj SC q6mo
Fibrates	5–15%	35–50%	Myopathy risk ↑ w/ statin. ↑ Cr; ✓ renal fxn q6mo.
Ω-3 FA	5% ↑	25–50%	EPA & DHA at doses of up to 4 g/d No benefit to low-dose supplementation

Resins ↓ LDL-C by ~20%, but not well tolerated; niacin ↑ HDL-C and ↓ TG & LDL-C; no effect on CV outcomes.

Treatment of LDL-C (*Lancet* 2014;384:607)

- **Statins:** every 1 mmol (39 mg/dL) ↓ LDL-C → 22% ↓ major vascular events (CV death, MI, stroke, revasc) in individuals w/ & w/o CAD (*Lancet* 2010;376:1670)
- **Ezetimibe:** ↓ major vascular events incl MI & stroke when added to statin post-ACS, w/ magnitude of benefit consistent w/ LDL-statin relationship (IMPROVE-IT, *NEJM* 2015;372:2387)
- **PCSK9 inhibitors:** ~60% ↓ LDL-C on top of statin, as monoRx, and in FH (*EHJ* 2014;35:2249); ↓ CV outcomes (*NEJM* 2017;376:1713 & 2018;379:2097)
- In homozygous FH: apheresis; evinacumab (ANGPTL3 inhib) ↓ LDL-C by ~50% (*NEJM* 2020;383:711)

Treatment of other lipid fractions (*Lancet* 2014;384:618 & 626)

- **HDL-C:** low levels a/w ↑ risk of MI, but no clinical benefit shown by raising
- **Triglycerides:** reasonable to treat levels >500 mg/dL w/ fibrates or Ω-3 FA to ↓ risk of pancreatitis. May be a/w CAD (*NEJM* 2014;371:22). 4 g/d of EPA ↓ CV risk, but 2 g/d EPA + 2 g/d DHA did not despite similar ↓ TG (*NEJM* 2019;380:11; *JAMA* 2020;324:2268)
- **Lp(a):** PCKS9i ↓ ~25%. siRNA that ↓ ≥75% under study (*NEJM* 2020;382:244).

2018 ACC/AHA Cholesterol Guidelines (*Circ* 2019;139:e1082)	
Population	**Recommendation**
Very high-risk ASCVD*	High-intensity statin; add EZE then PCSK9i if LDL-C ≥70

2018 ACC/AHA Cholesterol Guidelines (*Circ* 2019;139:e1082)		
Clinical ASCVD		High-intensity statin (? mod if >75 y), add EZE if LDL-C ≥70
LDL-C ≥190 mg/dL		High-intensity statin; add EZE or PCKS9i if LDL-C ≥100
DM, age 40–75 y		High-intensity statin (? moderate if no CV RFs)
Age 40–75 y (and none of above); *calc 10-y risk*	≥20%	High-intensity statin
	7.5%–<20%	Moderate-intensity statin; if uncertain consider CAC
	5–<7.5%	Moderate-intensity statin reasonable
	<5%	Emphasize lifestyle

ASCVD incl h/o ACS, stable angina, art. revasc, stroke, TIA, PAD. *Multiple major ASCVD events (MI, stroke, sx PAD) or 1 major event + multiple high-risk conditions (age ≥65, DM, HTN, CKD, smoking, FH, prior PCI/CABG). 10-y CV Risk Score: http://my.americanheart.org/cvriskcalculator. Additional risk factors to consider: LDL-C ≥160 mg/dL, met. synd.,CKD, FHx premature ASCVD, hsCRP ≥2 mg/l, Lp(a) ≥50 mg/dL, ABI <0.9, high-risk ethnic groups.

Statin Doses & LDL-C Reduction (doubling of dose → 6% further ↓ LDL-C)								
Intensity	**↓ LDL-C**	**Rosuva**	**Atorva**	**Simva**	**Prava**	**Lova**	**Fluva**	**Pitava**
High	**≥50%**	20–40	40–80	(80)				
Mod	**30–50%**	5–10	10–20	20–40	40–80	40	80	2–4

APPROACH TO RHEUMATIC DISEASE

Major categories of inflammatory rheumatic disease

- **Inflammatory arthritis**: crystalline (gout, CPPD), RA, spondyloarthritis, adult-onset Still's
- **Connective tissue disease**: SLE, Sjögren's, scleroderma, myositides (DM, PM), MCTD
- **Vasculitis**: large (GCA, Takayasu's); medium (PAN); small (ANCA, IgA, cryo); Behçet's
- **Other**: IgG4-related disease, autoinflammatory disease (familial Mediterranean fever, TNF receptor-associated periodic syndrome, VEXAS = vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), sarcoid (see "ILD"), HLH/MAS, relapsing polychondritis

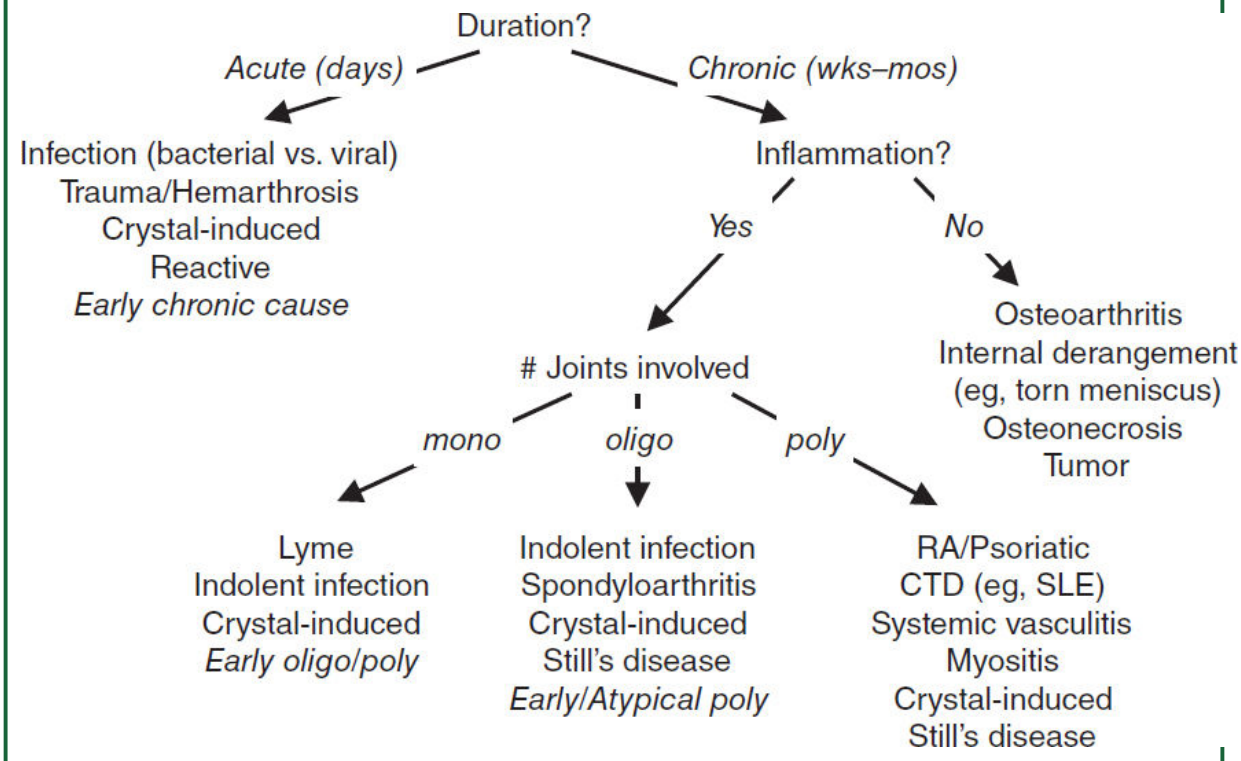
Approach to patient with joint pain

- **Articular** vs. **periarticular** (bursitis, tendinitis) source of pain: typically active ROM more painful than passive ROM in periarticular process
- **Inflammatory** vs. **noninflammatory** pain: *features of inflammatory arthropathy* include joint swelling, warmth or redness, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise. Assess for extra-articular features.
- Physical exam: localize complaint, identify signs of inflammation, and assess number and pattern of affected joints.

Key Physical Exam Findings in Joint Pain					
	Articular (Joint) Disease			*Periarticular/Soft Tissue*	
Physical Exam	**OA**	**Inflammatory Arthritis[a]**	**Arthralgia**	**Bursitis or Tendinitis**	**Myofascial**
Swelling	Varies	Yes	No	Yes	No
Erythema	No	Varies	No	Yes	No
Warmth	No	Yes	No	Yes	No
Tenderness	Joint line	Yes	Varies	Periarticular	Yes
ROM[b]	Limited	Limited	Full or limited	Full, often limited by pain	Full
Pain w/ active or passive	Both	Both	Usually both	Active > passive	Usually both

[a]May initially present as arthralgia w/o overt arthritis. [b]Range of motion of joint or joint a/w bursa or tendon.

Figure 8-1 Approach to arthritis



Analysis of Joint Fluid				
Test	**Normal**	**Noninflamm**	**Inflammatory**	**Septic**
Appearance	Clear	Clear, yellow	Clear to opaque yellow-white	Opaque
WBC/mm^3	<200	<2000	>2000	>2000 *(usually >50k*)*
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Intracellular crystals	⊖	⊖	⊕ in some (eg, gout)	May be ⊖ or ⊕ if concurrent gout/CPPD

*WBC count of aspirated fluid in septic bursitis often < WBC count in septic arthritis.

Imaging features of major arthritides

- **OA:** plain films: asym joint space narrowing (JSN), **osteophytes**, subchondral sclerosis & cysts; subchondral "gull-wing" erosions may be seen in less-common erosive OA; MRI may show early disease not seen on plain films; U/S ≈ MRI for structural damage ⊖
- **RA:** plain films: symmetric JSN, early = periarticular **osteopenia;** late = marginal **erosions**; subluxations; MRI & U/S can detect early and subclinical disease; MRI ≈ U/S for erosions
- **Gout:** plain films: early = nonspec swelling; late = **tophus**, joint erosions w/ overhanging edges; U/S for detection of microtophi (double-contour sign); dual-energy CT (DECT): identify articular/periarticular UrA deposits vs. calcium deposits; MRI ≈ U/S for erosions
- **Spondyloarthritis:** e/o **sacroiliitis**: plain films: early = pseudo-widening SI joint space, late = sclerosis, erosions, **ankylosis;** SI MRI ↑ Se for early Δ; U/S ≈ MRI to detect enthesitis

Comparison of Major Arthritides				
Feature	**Primary OA**	**RA**	**Gout/CPPD**	**Spondyloarthritis**
Onset	Gradual	Gradual	Acute	Variable
Inflamm.	⊖	⊕	⊕	⊕
Pathology	Degeneration	Pannus	Crystals, tophi	Enthesitis
# of joints	Poly	Poly	Mono to poly	Oligo or poly
Typical joints	Hips, knees, spine, 1st CMC, DIP, PIP	MCP, PIP, wrists, feet, ankles, knees	Gout: foot/ankle CPPD: knee, wrist	Sacroiliac, spine, large peripheral joints
Joints often *spared*	MCP, shoulder, elbow, wrist	L & T spine, DIPs	Spine	*Any joint can be involved*
Special articular findings	Bouchard's & Heberden's nodes	Ulnar dev., swan neck & boutonnière deformities	Monosodium urate/CPPD crystals; tophi	Dactylitis, enthesitis (eg, Achilles), bamboo spine, syndesmophytes
Extra-articular	None	SC nodules, pulm sx, sicca	Olec. bursitis, renal stones	Psoriasis, IBD, uveitis, urethritis, conjunctivitis
Lab data	Normal	Often ⊕ RF & anti-CCP	↑ UrA (may be nl during flare)	± HLA-B27

INFLAMMATORY MARKER & AUTOANTIBODY TESTING

Inflammatory markers (*Mod Rheumatol* 2009;19:469; *NEJM* 1999;340:448)

- **ESR:** *indirect* measure of inflammation [↑ RBC aggregation due to acute-phase proteins (fibrinogen, Ig)]; slow to rise; may ↑ w/ age, preg., anemia, obesity, ESRD. Ddx for >100: malig. esp. MM, lymphoma; GCA or other vasculitis; endocarditis, TB, osteomyelitis.
- **CRP:** *direct* measure of inflammation (protein produced by liver, part of innate immune system); *typically rises and falls before the ESR* w/ treatment/resolution of process

Autoantibody testing (*Best Pract Res Clin Rheumatol* 2014;28:907)

- ANA (anti-nuclear Ab): *screening test* for Ab directed against nuclear proteins.
- Order ANA only when *clinical suspicion for CTD* b/c nonspecific: 1:40 (very low ⊕, 25–30% of healthy Pts); 1:80 (low ⊕, 10–15% of healthy Pts); ≥1:160 (⊕, 5% of healthy Pts). May be ⊕ in Pts prior to clin manifest (*NEJM* 2003;349:1526; *Arthritis Res Ther* 2011;13:1).
- If ANA ⊕ and high clinical suspicion for CTD, consider testing for Ab against dsDNA, Smith, Ro/La, RNP, Scl-70 and myositis-specific

Abs (*highly specific* for various CTD)
- ANA does *not* correlate well w/ disease activity, ∴ no clinical value in serial testing
- ANA also ⊕ in: AIH, PBC, thyroid disease, certain infxns and malignancies, IBD, IPF
- RF and anti-CCP (see "Rheumatoid Arthritis")

DDX & APPROACH TO COMMON INPATIENT RHEUM PRESENTATIONS

Feature	Rheum Ddx	Rheum Lab w/up (+ ANA)
FUO	GCA/PMR, AOSD, SLE, inflamm arthr, Taka- yasu, PAN, ANCA ⊕ vasc, cryo, HSP, VEXAS	ESR, CRP, RF, ANCA, ± cryo
Pulm HTN	Scleroderma (limited >diffuse), MCTD, SLE, PM/DM (less common)	Scl-70, centromere, RNA Pol III, RNP
DAH	ANCA ⊕ vasc, Goodpasture's, SLE, APS	ANCA, GBM, C3/C4, APLA
ILD	Scleroderma (diffuse >limited), sarcoid, RA, DM, PM, antisynthetase syndrome, Sjögren's, MCTD, SLE (esp. pleura), ANCA ⊕ vasc (esp. MPA)	Scl-70, RF/CCP, CK, aldolase, ± myositis specific Abs, Jo-1, Ro/La, ANCA
Pleuro-pericarditis	SLE, scleroderma, RA, MCTD, DM/PM, ANCA ⊕ vasc, Sjögren's, AOSD, PAN	dsDNA, RF/CCP, Sm, Ro/La, Scl-70, RNP, ANCA
AKI + active sed. or CTD s/s	SLE (GN or nephrotic), ANCA ⊕ vasc (GN), scleroderma renal crisis, Sjögren's (RTA/TIN), PAN (infarct), HSP, Goodpasture's, cryo, APS	dsDNA, Sm, Ro/La, RNP, C3/C4, Scl-70, RNA Pol III, ANCA, GBM, cryos, APLA
Neuropathy	ANCA ⊕ vasc, SLE, Sjögren's, cryo, sarcoid, RA, PAN	Ro/La, ANCA, cryo RF/CCP, HCV, HBV

RHEUMATOID ARTHRITIS (RA)

Definition & epidemiology (*Lancet* 2016;388:2023)

- Chronic, symmetric, and potentially destructive inflammatory polyarthritis characterized by proliferative synovial tissue (pannus) formation in affected joints
- Pathogenesis involves overproduction of TNF, IL-1, and IL-6 (∴ used as drug targets)
- Risk stems from combination of genetics (~50% of risk), environmental influences (eg, smoking, silica dust), and Pt factors (periodontal disease, Δs in gut microbiome)
- HLA-DRB1 haplotype a/w disease suscept., severity, & response to Rx (*JAMA* 2015;313:1645)
- Prevalence = 1/100 adults and 1/20 ♀ >70 y; ♀ to ♂ ratio = 3:1; peak incidence 50–75 y

Clinical manifestations (*JAMA* 2018;320:1360)

- Usually insidious onset **pain**, **swelling**, & impaired function of joints w/ prolonged **morning stiffness** for ≥6 wk (typically PIPs, MCPs, wrists, knees, ankles, MTPs, cervical spine)
- Typically polyarticular (60% small joints, 30% large joints, 10% both), may be monoarticular (knee, shoulder, wrist) early in course; rheumatoid joints more susceptible to infection
- Joint deformities: **ulnar deviation**, **swan neck** (MCP flexion, PIP hyperextension, DIP flexion), **boutonnière** (PIP flexion, DIP hyperextension), **cock-up deformities** (toes)
- **C1–C2 instability** → myelopathy, ∴✓ C-spine flex/ext films prior to elective intubation
- Constitutional symptoms: *low-grade* fever, weight loss, malaise
- **Extra-articular manifestations** (18–41% of Pts) can occur at any time; ↑ frequency in seropositive (⊕ RF or anti-CCP) and w/ active disease (*Autoimmun Rev* 2021;20:102776)

Extra-Articular Manifestations

Extra-Articular Manifestations	
Skin	**Rheumatoid nodules** (20–30%, usually sero ⊕): extensor surface, bursae; can be in lung, heart, sclera Raynaud's, pyoderma gangrenosum, cutan. vasculitis (ulcers, purpura, etc.)
Pulm	**ILD** (a/w *MUC5B* mutations), airway disease, pleuritis, effusions (low glc), nodules, pulm HTN; precedes joint sx in 20% of cases; RA med toxicity (MTX, ? anti-TNF, & anti-CD20) (*Semin Arthritis Rheum* 2014;43:613)
CV	Accel. athero w/ ↑ **risk of MI & CV death**, AF, pericarditis (effusions in ⅓ of sero ⊕), myocarditis, coronary/systemic vasculitis (*Nat Rev Rheum* 2020;16:361)
Nervous	Nerve entrapment (eg, carpal tunnel), stroke, mononeuritis multiplex, CNS vasculitis
Ocular	Scleritis, episcleritis, keratoconjunctivitis sicca (2° Sjögren's)
Heme	Anemia of chronic disease, neutropenia (Felty's syndrome: 1%, typically long- standing RA + splenomegaly; large granular lymphocyte leukemia: bone marrow infiltrated w/ lymphocytes ± myeloid hypoplasia), NHL, amyloidosis
Renal	Glomerulonephritis (usually mesangial), nephrotic syndrome (2° amyloidosis), nephrotoxicity from RA meds
Vasculitis	Small & medium vessels (usually ↑ RF titer, long-standing RA); pericarditis, ulcers, scleritis, & neuropathy most common

Laboratory & radiologic studies

- **RF** (IgM/IgA/IgG anti-IgGAb) ⊕ in ~70%; also seen in other rheumatic diseases (SLE, Sjögren's), cryoglobulinemia, infection (SBE, hepatitis, TB), ~5% of healthy pop.
- **Anti-CCP** (Ab to cyclic citrullinated peptide): ⊕ in ~70% of Pts w/ RA, similar Se, but more Sp (>90%) than RF particularly for early RA (*Arth Rheum* 2009;61:1472); a/w increased joint damage and low remission rates
- ~20% are seronegative (RF *and* anti-CCP negative)
- ↑ ESR/CRP but nl in ~30%; ⊕ ANA in ~40%; ↑ globulin during periods of active disease
- Radiographs of hands and wrists: periarticular osteopenia, bone erosions, joint subluxation
- Increasing use of MSK U/S to diagnose synovitis, tenosynovitis, and erosive disease

ACR/EULAR classification criteria (*Arth Rheum* 2010;62:2569)

- Used in clinical research, but not in clinical practice

- Relevant for Pts with ≥1 joint with synovitis not better explained by another disease
- Likelihood of RA ↑ w/ higher # (espec. ≥4) of small joints involved, ⊕ RF or anti-CCP (espec. high titer), ↑ ESR or CRP, and duration ≥6 wk

Management (*Lancet* 2017;389:2328 & 2338; *JAMA* 2018;320:1360)

- Early dx and Rx (esp DMARD) w/ frequent follow-up and escalation of Rx as needed with **goal to achieve clinical remission** or low disease activity
- ↓ time to remission ≈ ↑ length of sustained remission (*Arthritis Res Ther* 2010;12:R97)
- Sero ⊕ (eg, RF or anti-CCP) a/w aggressive joint disease & extraarticular disease
- At dx, start *both* rapid-acting agent (to acutely ↓ inflammation) and **D**isease**-M**odifying **A**nti**- R**heumatic **D**rug **(DMARD)** (typically take 1–3 mo to have max effect)
- *Rapid-acting drugs:*
  - **NSAIDs** or COX-2 inhibitors: ↑ CV risk, GI adverse events, AKI; consider starting w/ PPI
  - **glucocorticoids**: low dose (<20 mg/d oral) or joint injection
  - NSAIDs + glucocorticoids: ↑↑ GI events; give PPI and minimize long-term concurrent use
- *DMARDs (see RA therapeutics below):*
  - **Methotrexate** (1st line unless CKD, hepatitis, EtOH, or lung disease), alternatives include sulfasalazine (SSZ) or leflunomide; consider HCQ if mild disease
  - If inadequate response after 3 mo (despite DMARD dose escalation) consider:
    - **combination Rx** w/ other DMARDs (eg, "triple therapy" w/ MTX, SSZ, and HCQ) *or*
    - **adding biologic** (anti-TNF typically 1st line unless contraindication)
    - MTX/SSZ/HCQ non-inferior to etanercept/MTX (*NEJM* 2013;369:307)
    - JAKi: if fail biologics vs. initial DMARD, but ↑ serious side effect risk over abatacept or TNFi (see below) (*Lancet* 2018;391:2503 & 2513; *NEJM* 2020;383:1511; *NEJM* 2022;386:316)

• Given a/w CV morbidity/mortality, try to ↓ risk w/ lifestyle mgmt, lipid & DM screening

RA Therapeutics (*Arth Care Res* 2021;73:924)		
Class	**Drug**	**Side Effects**
Traditional DMARDs	Methotrexate (MTX) Leflunomide Sulfasalazine (SSZ)	MTX: GI distress, stomatitis, ILD, myelosuppression, hepatotoxicity Supplement MTX ± SSZ w/ folate ✓ *G6PD prior to SSZ*
Biologic DMARDs (all anti-TNF ≈ efficacy; if inadequate resp to anti-TNF try non-TNF)	Anti-TNF: etanercept, infliximab, adali- mumab, certolizumab, golimumab CTLA4-Ig: abatacept Anti-IL-6R Ab: tocilizumab (studied as mono-Rx w/o MTX); sarilumab Anti-CD20: rituximab Anti-IL-1R: anakinra ***Never use 2 biologics together***	↑ risk bacterial/fungal/viral infxn ✓ TB, Hep B/C before starting Immunize against Zoster + Pneumococcus Anti-TNF: ? risk for CHF & CNS demyelinating disease Anti-IL-6R: risk of GI perf. Rituximab: infusion reaction
Other	Hydroxychloroquine (HCQ) JAKi: tofacitinib, baricitinib; upadacitinib (JAK1 selective) Rare: cyclosporine, azathioprine, gold	HCQ: retinopathy, rash JAKi: infxn, ↑ LFTs, HTN, VTE, CV events, malignancy, death CsA: ↑ Cr, HTN, gum hyperplasia

ADULT-ONSET STILL'S DISEASE (AOSD) & RELAPSING POLYCHONDRITIS

Adult-onset Still's disease (*J Autoimmun* 2018;93:24)

- **Rare autoinflammatory syndrome**, <4/million per y incidence; ♂ = ♀ w/ bimodal typical onset 15–25 or 36–46 y; sx evolve over wks to mos
- Dx if 5 criteria are present & ≥2 major; exclude infxn, malig, other rheumatic, drug rxn
  - **Major:** fever ≥39°C for ≥1 wk (usually daily or twice daily high-spiking fever); arthralgias/ arthritis ≥2 wk; Still's rash (qv); ↑ WBC w/ 80% PMN
  - **Minor:** sore throat; LAN; HSM; ↑ AST/ALT/LDH; negative ANA & RF
- Still's rash (>85%): nonpruritic macular or maculopapular salmon-colored rash; usually trunk or extremities; may be precipitated by trauma (Koebner phenomenon), warm water
- Plain films: soft tissue swelling (*early*) → cartilage loss, erosions, carpal ankylosis (*late*)
- Treatment: NSAIDs; steroids; steroid-sparing (MTX, **anakinra**, anti-TNF, **tocilizumab**)
- Variable clinical course: 20% w/ long-term remission; 30% remit-relapse; ~50% chronic (esp. arthritis); ↑ risk of macrophage activation syndrome (life threatening)

Relapsing polychondritis (*Rheumatology* 2018;57:1525)

- Inflammatory destruction of cartilaginous structures; typical onset age 40–60, ♂ = ♀, <1/million per y incidence
- Subacute onset of **red**, **painful**, and **swollen cartilage;** ultimately atrophic & deformed

- Multiple sites of cartilaginous inflammation: bilateral auricular chondritis, nonerosive inflammatory arthritis, nasal chondritis, laryngeal or tracheal chondritis, valvulopathy. Ocular inflammation and cochlear/vestibular dysfxn also common.
- 40% of cases a/w immunologic disorder (eg, RA, SLE, vasc., Sjögren's), cancer or MDS (including VEXAS; *NEJM* 2020;383:2628)
- Labs: ↑ ESR & CRP, leukocytosis, eosinophilia, anemia of chronic inflammation
- Bx (not req for dx): proteoglycan depletion, perichondrial inflammation and replacement with granulation tissue and fibrosis; immunofluorescence with Ig and C3 deposits
- Screen for pulm (PFTs, CXR/CT, ± bronch) and cardiac (ECG, TTE) involvement
- Rx guided by disease activity/severity: steroids 1st line; NSAIDs/dapsone for arthralgias, mild disease; MTX, AZA, or biologics steroid-sparing; cyclophosph if organ-threatening

CRYSTAL DEPOSITION ARTHRITIDES

Comparison of Gout and Pseudogout		
	Gout (*Rheumatology* 2018;58:27)	**Pseudogout** (*NEJM* 2016;374:2575)
Acute clinical	*S*udden onset painful *mono-articular* arthritis (classically **podagra** [MTP of great toe]) or bursitis; frequently nocturnal May be *polyarticular* in subseq flares Can mimic cellulitis (esp in foot)	Mono- or asymmetric oligoarthritis (esp knees, wrists, and MCP joints); rare axial involvement (eg, crowned dens syndrome)
Chronic clinical	Solid crystal deposition (**tophus**) in joints (esp. toes, fingers, wrists, knees) & tissue (esp. olecranon bursa, pinna, Achilles)	"Pseudo-RA" w/ polyarticular arthritis w/ morning stiffness or "Pseudo-OA"
Assoc. conditions	Metabolic syndrome; CKD; CHF	**3 H's:** Hyper-PTH, Hypo-Mg, Hemochromatosis
Crystal	Monosodium urate (MSU)	Calcium pyrophosphate dihydrate
Polarized microscopy*	Needle-shaped, **negatively birefringent**	Rhomboid-shaped, weakly **positively birefringent**
Radio- graphic findings	Early = nonspecific tissue swelling Late = tophus, joint erosions w/ overhanging edges "Double contour sign" on MSK US DECT: UrA vs. Ca deposits	**Chondrocalcinosis:** linear densities within articular cartilage; often found in menisci, fibrocartilage of wrist, hands, symphysis pubis
Other	a/w uric acid stones; urate nephropathy	✓ Ca, Mg, Fe, ferritin, TIBC, UrA, PTH in young or severe cases

*Crystals should be intracellular; infection can coexist with acute attacks, ∴ always ✓ Gram stain & Cx

GOUT

Definition & epidemiology (*Rheumatology* 2018;58:27; *Lancet* 2021;397:1843)

- Humans lack enzyme (uricase) to metabolize urate (end-product of purine metabolism)
- MSU crystal deposition promotes inflammation in joints and peri-articular tissue;
- Prev >1/30 American adults, ♂ >♀; peak incidence 5th decade; most common inflamm arthritis in ♂ over 30 y; *rare* in premenopausal ♀ (estrogens ↑ renal urate excretion)

Etiologies

- UrA underexcretion (85–90%): meds (eg, diuretics); idiopathic; ↓ renal function; obesity
- Uric acid (UrA) overproduction (10–15%): ↑ meat, seafood, EtOH, psoriasis, idiopathic, myelo- and lymphoproliferative disease, chronic hemolytic anemia, cytotoxic drugs, rare inherited enzyme defic, genetic variants (*Nature Rev Rheumatol* 2018;14:341)

Diagnosis

- ↑ **UrA is not diagnostic;** 25% of measurements nl during flare; ± ↑ WBC & ESR
- **Arthrocentesis is gold standard:** intracellular negatively birefringent needle-shaped MSU crystal. U/S w/ double-contour sign or dual-energy CT can aid non-invasive dx.
- 2015 ACR/EULAR Classification Criteria (*Ann Rheum Dis* 2015;74:1789) used 1° in research

Acute treatment (*Arthritis Care Res* 2020;72:744)

- Colchinine, NSAIDs, & steroids all 1st-line; choice guided by side effect profile/comorbidities. IL-1i (*J Rheum* 2019;46:1345) or ACTH if these contraindicated. Start Rx ASAP; continue until acute flare resolves; consider combo Rx if severe; rest/ice; self-limited w/in 3–21+ d w/o Rx.
- Continue urate-lowering therapy during attack if already taking

Acute Treatment for Gout		
Drug	**Initial Dose**	**Comments**
NSAIDs (nonsel or COX-2 inhib)	Full anti-inflammatory dose → tapering	Gastritis & GIB risk. Avoid in CKD & CVD. ≈ efficacy among NSAIDs.

Acute Treatment for Gout		
Colchicine (PO; IV no longer available in U.S.)	1.2 mg then 0.6 mg 1 h later → 0.6 mg bid	N/V/diarrhea (w/ ↑ dose), marrow suppression, myopathy, neuropathy. ↓ dose in CKD (however, not nephrotoxic).
Corticosteroids (PO, IA, IV, IM)	eg, prednisone 0.5 mg/kg/d × 5–10 d ± taper	Rule out joint infection 1st. Corticosteroid injection if <3 joints.
ACTH (IM)	eg, 100 IU IM ×1–2 doses	↑ cost, ↓ s/e, limited data (*Semin Arthritis Rheum* 2014;43:648)
IL-1 inhibitors (*J Rheumatol* 2019;46:1345)	anakinra (100 mg SC qd × 3 d); canakinumab (150 mg SC × 1)	↑↑ cost; anakinra a/w injection site pain Canakinumab approved in EU (*Ann Rheum Dis* 2012;71:1839; *Arth Rheum* 2010;62:3064)

Chronic treatment (*Arthritis Care Res* 2020;72:744)

- **Approach:** if ≥2 attacks/y, polyarticular attack, tophus, joint erosions, GFR <60, or urolithiasis → start urate-lowering therapy + pharmacologic Ppx to ↓ risk of acute attacks
- **Urate-lowering therapy (ULT):** goal UrA <6 mg/dL; when starting ULT, always give with pharm Ppx as below; *do NOT d/c during acute attack or due to AKI*
- **Pharmacologic prophylaxis:** continue 6 mos w/ above Rx or longer if frequent attacks:
  low-dose **colchicine** (~50% ↓ risk of acute flare; *J Rheum* 2004;31:2429), **NSAIDs** (less evidence; *Ann Rheum Dis* 2006;65:1312), low-dose **steroids**, **IL-1 inhibitors**
- **Lifestyle** Δs: ↓ intake of meat, EtOH, & seafood, ↑ low-fat dairy, wt loss, avoid dehydration

Urate-Lowering Therapy (Chronic Treatment for Gout)		
Drug (route)	**Mechanism**	**Comments**
Allopurinol (PO)	Xanthine oxidase inhibitor	1st line; adjust starting dose in CKD; titrate ↑ q2–5wk; a/w rash, hypersensitivity syndrome (see below), BM suppression **(avoid w/ AZA/6-MP)**, diarrhea, N/V, hepatitis; monitor CBC, LFT's; *not nephrotoxic* max dose = 800 mg/d
Febuxostat (PO)	Nonpurine xanthine oxidase inhib	2nd line; use if allopurinol intolerant; a/w ↑ LFT, rash, arthralgias, N/V; **avoid w/ AZA/6-MP** (BM suppress); start 40 mg, max dose = 120 mg/d

Urate-Lowering Therapy (Chronic Treatment for Gout)		
Pegloticase (IV)	Recombinant uricase	For refractory tophaceous gout; infusion reactions (including anaphylaxis); Ab formation may limit use (*JAMA* 2011;306:711); **avoid w/ G6PD deficiency**
Probenecid (PO)	Uricosuric	Rarely used; risk of urolithiasis

- **Allopurinol hypersensitivity syndrome:** 10–25% mortality; incidence ~5/1000. ↓ risk w/ *starting* dose 100 mg/d if eGFR >40 or 50 mg/d if eGFR ≤40. Titrate by 100 mg/d (eGFR >40) or 50 mg/d (eGFR ≤40) q2–5 wk until UrA <6 mg/dL (dose can be >300 mg/d even in CKD). A/w *HLA-B5801*, esp. Han Chinese, Koreans, Thai; screen in these high-risk populations prior to initiating (*Arthritis Care Res* 2020;72:744; *JAMA Intern Med* 2015;175:1550).

Calcium Pyrophosphate Dihydrate (CPPD) Deposition Disease/Pseudogout

Definition (*NEJM* 2016;374:2575)

- Deposition of CPPD crystals w/in tendons, ligaments, articular capsules, synovium, cartilage; frequently asymptomatic

Etiologies (*Nat Rev Rheumatol* 2018;14:592)

- Most cases ***idiopathic*;** consider further metabolic eval in young (<50 y) and florid forms
- Metabolic (*3 H's*): hemochromatosis; hyperparathyroidism; hypomagnesemia (esp. in Gitelman's or Bartter's syndromes)
- Joint trauma (incl. previous surgery); intra-articular hyaluronate can precipitate attacks
- Familial chondrocalcinosis (autosomal dominant disorder); early-onset, polyarticular dis.

Clinical manifestations

- **Chondrocalcinosis:** calcification of cartilage, resulting from CPPD crystal deposition in articular cartilage, fibrocartilage, or menisci
  - ↑ incidence w/ age; can be asymptomatic; chondrocalcinosis in 20% >60 y at autopsy

- **Pseudogout:** acute CPPD crystal-induced mono- or asymmetric oligoarticular arthritis, *indistinguishable from gout except through synovial fluid exam for crystals*
  location: **knees**, **wrists**, and MCP joints; rarely, axial (eg, crowned dens syndrome due to CPPD deposition at C1–C2)
  precipitants: surgery, trauma, or severe illness
- Chronic forms: "pseudo-RA" and pyrophosphate arthropathy (resembles OA, can involve axial skeleton)

Diagnostic studies

- Arthrocentesis is gold standard: **rhomboid shaped, weakly *positively* birefringent crystals** (yellow *perpendicular* & blue *parallel* to axis on polarizer; see table above)
- Radiographs: see table above

Treatment (*NEJM* 2016;374:2575)

- Asymptomatic chondrocalcinosis requires no treatment
- Acute therapy for pseudogout: no RCTs, extrapolated from practice in gout; ∴ same as for gout, though colchicine not as effective
- If associated metabolic disease, Rx of underlying disorder *may* improve arthritis sx
- Low-dose daily colchicine or NSAID may be effective for prophylaxis or chronic arthropathy

SERONEGATIVE SPONDYLOARTHRITIS

Definition and classification system (*NEJM* 2016;374:2563)

- Spondyloarthritis (SpA): group of inflammatory disorders that share common clinical manifestations: inflammatory spine disease, peripheral arthritis, enthesitis (see below), and extra-articular manifestations (primarily ocular and skin disease)
- Seronegative = absence of autoantibodies
- Subtypes: ankylosing spondylitis (AS), psoriatic (PsA), reactive (ReA), IBD-assoc, juvenille SpA, and undifferentiated. Distinguished by *axial* vs. *peripheral* predominant involvement.

Epidemiology & pathogenesis (*Nat Rev Rheumatol* 2015;11:110)

- Prevalence 1/200 to 1/50 worldwide; AS and non-radiographic axial SpA most common
- HLA-B27 accounts for ~30% of attributable genetic risk but not required for diagnosis
- Environmental factors likely critical for disease, esp reactive arthritis (ie, infection)

Spondyloarthritis (SpA) Epidemiology and Key Presentation Features

Disease	Epidemiology	Key Features
Ankylosing spondylitis (AS)	♂:♀ = 3:1; onset in teens to mid-20s (rare after 40 y)	Progressive limitation of spinal motion, a.m. stiffness, buttock pain, "bamboo spine," ⊕ Schober test
Psoriatic arthritis (PsA)	♂ = ♀; peak incidence 45–54 y; seen in 20–30% of Pts w/ psoriasis	In 13–17% arthritis precedes skin findings by yrs; does not correlate with psoriasis activity; a/w HIV
Reactive arthritis (ReA)	♂ >> ♀; 20–40 y; 10–30 d after **GI or GU infxn*** in genetically susceptible host	Arthritis, urethritis, and conjunctivitis. Most resolve w/in 12 mo.

Spondyloarthritis (SpA) Epidemiology and Key Presentation Features		
IBD- associated arthritis	♂ = ♀; seen in 20% of IBD Pts; Crohn's >UC	Type I <5 joints: correlates w/ IBD activ. Type II >5 joints or axial disease: does not correlate w/ IBD activity

*GU: Chlamydia, Ureaplasma urealyticum; GI: Shigella, Salmonella, Yersinia, Campylobacter, *C. diff*.

Major clinical manifestations (*Lancet* 2017;390:73)

- **Inflammatory back pain:** SI joints (**sacroiliitis**), apophyseal joints of spine
  characterized by **IPAIN** (Insidious onset, Pain at night, Age of onset <40 y, Improves w/ exercise/hot water, No improvement w/ rest), a.m. stiffness, *responsive to NSAIDs*
- **Peripheral arthritis:** typically asymmetric, oligoarticular, large joints, lower >upper limbs; however, can be symmetric & polyarticular (thus, mimic RA), espec. in psoriatic arthritis
- **Enthesitis:** inflammation at site of tendon/ligament insertion into bone, esp Achilles, plantar fascia (calcaneal insertion), pre-patellar, elbow epicondyles
- **Rigidity of spine:** bamboo spine by X-ray, ankylosis due to progressive growth of bony spurs that bridge intervertebral disc
- **Dactylitis:** "sausage digit," inflammation of entire digit (joint + tenosynovial inflamm)
- **Uveitis:** anterior uveitis *most common extra-articular manifestation* in seronegative SpA*;* usually unilateral and p/w pain, red eye, blurry vision, photophobia

Distinguishing Features				
	Axial Predom	*Peripheral Predominant*		
Feature	**Ankylosing Spondylitis**	**Psoriatic**	**Reactive**	**IBD Assoc**
Axial involv.	100%	20–40%	40–60%	5–20%
Sacroiliitis	Symmetric	Asymm	Asymm	Symmetric
Periph involv.	Less common ~50%	Frequent	Frequent	Frequent
Peripheral distribution	Lower >upper	Upper >lower (see below)	Lower >upper	Lower >upper
HLA-B27	80–90%	20%	50–80%	5–30%
Enthesitis	Frequent	Frequent	Frequent	Rare
Dactylitis	Uncommon	Common	Common	Uncommon
Ocular	Uveitis in 25–40%	Conjunctivitis, uveitis, episcleritis	**Conjunctivitis** (noninfectious), uveitis, keratitis	Uveitis
Skin	None	**Psoriasis;** nail pitting and onycholysis	Circinate balanitis, keratoderma blennorrhagica	*E. nodosum*, pyoderma-gangrenosum
Imaging	Bamboo spine (symm syndes.)	"Pencil-in-cup" DIP deformity	*Asymmetric* syndesmophytes	Periph dis. rarely erosive

Clinical assessment (*Nat Rev Rheumatol* 2021;17:109)

- **Seronegative:** rheumatoid factor and other autoantibodies usually ⊖; ± ↑ ESR/CRP
- **HLA-B27:** nonspecific, b/c common in general population (6–8%); most useful when high clinical suspicion but nl imaging; ⊕ 90% of Pts w/ AS, but only 20–80% in other SpA
- **Axial disease physical exam**

  The following are not specific PEx findings but useful in monitoring disease during Rx:

  Lumbar flexion deformity assessed by **modified Schober's test** (⊕ if <5 cm ↑ in distance between a point 5 cm below the lumbosacral jxn and another point 10 cm above, when going from standing to maximum forward flexion)

  T-spine mobility (extension) and kyphosis severity measured by **occiput-to-wall distance** (although occiput-to-wall distance also increased in osteoporotic kyphosis)
- **Infectious evaluation for reactive arthritis** (⊖ studies do not r/o)

GU: U/A, PCR of urine and/or genital swab for *Chlamydia;* urethritis usually due to *Chlamydia* infxn preceding arthritis, but can also see sterile urethritis post dysentery

GI: stool Cx, *C. diff* toxin. Consider HIV in workup for reactive or psoriatic arthritis.

- **Radiology**

  MRI preferred for *early* detection of inflammation (sacroiliitis)

  Plain films detect late structural changes (SI erosions/sclerosis)

  Calcification of spinal ligaments w/ bridging symm syndesmophytes ("bamboo spine")

  Squaring and generalized demineralization of vertebral bodies ("shiny corners")

Descriptions of skin manifestations

- **Psoriasis:** erythematous plaques with sharply defined margins often w/ thick silvery scale
- **Circinate balanitis:** shallow, painless ulcers of glans penis and urethral meatus
- **Keratoderma blennorrhagica:** hyperkeratosis of palms/soles, scrotum, trunk, scalp
- **Erythema nodosum:** red tender nodules in subcutan. fat (panniculitis), typically on shins Ddx includes idiopathic, infxn, sarcoid, drug rxn, vasculitis, IBD, lymphoma
- **Pyoderma gangrenosum:** neutrophilic dermatosis → painful ulcers w/ violaceous border Ddx incl. idiopathic, IBD, RA, heme and solid malignancies, MGUS, MDS, polycyth. vera

Psoriatic arthritis subtypes (*Lancet* 2018;391:2273 & 2285; *Nat Rev Dis Primers* 2021;7:59)

- **Mono/oligoarticular** (large or DIP joint, dactylitic digit): most common initial manifestation
- **Polyarthritis** (small joints of the hands/feet, wrists, ankles, knees, elbows): indistinguishable from RA, but often asymmetric
- **Arthritis mutilans:** severe destructive arthritis with bone resorption, esp. hands
- **Axial disease:** unilateral/asymmetric sacroiliitis
- **DIP-limited:** good correlation with nail pitting and onycholysis

Treatment approach (*Arthritis Care Res* 2019;71:2 & 2019;71:1285; *NEJM* 2021;385:628)

- Untreated disease may lead to irreversible structural damage and associated ↓ function
- Early physiotherapy beneficial
- Tight control of inflammation may improve outcomes (eg, in PsA; *Lancet* 2015;386:2489)
- **NSAIDs:** 1st line; rapidly ↓ stiffness and pain; prolonged, continuous administration may modify disease course but associated w/ GI and CV toxicity (*Cochrane Database Syst Rev* 2015;17:CD010952); may exacerbate IBD
- **Intra-articular corticosteroids** in mono- or oligoarthritis; limited role for systemic steroids, esp. for axial disease
- **Conventional DMARDs** (eg, MTX, SSZ, leflunomide): no efficacy for axial disease or enthesitis; may have role in peripheral arthritis, uveitis, and extra-articular manifestations
- **Anti-TNFs:** effective for both axial and peripheral SpA, improves function and may slow progression of structural changes; adalimumab or infliximab preferred if eyes involved
- **Anti-IL17A** (secukinumab, ixekizumab): for both AS and axial and peripheral PsA (*NEJM* 2015;373:1329 & 2534; *Lancet* 2015;386:1137)
- **Anti-IL12/23** (ustekinumab) and anti-IL23 (guselkumab) for both axial & peripheral PsA (*Lancet* 2020;395:1115) but not axial SpA (*Arthritis Rheumatol* 2019;71:258)
- **PDE-4 inhibitor** (apremilast): effective in PsA refractory to conventional DMARD or as first-line (*Rheumatology* 2018;7:1253); a/w GI side effects and wt loss
- **JAK inhibitor:** for conventional DMARD- or anti-TNF-resistant peripheral and/or axial SpA (*NEJM* 2017;377:1525 & 1537; 2021;384:1227)
- **Other:**
  - Abx indicated in ReA if active GU infxn but not typically needed for uncomplicated enteric infx. Can consider prolonged abx for refractory *Chlamydia* ReA (*Arthritis Rheum* 2010;62:1298), but controversial.
  - Involve ophtho if suspect eyes affected (may need steroid drops or intravitreal injection)
  - Treat underlying IBD when appropriate

INFECTIOUS ARTHRITIS & BURSITIS

ETIOLOGIES & DIAGNOSIS OF INFECTIOUS ARTHRITIS

Etiologies (*Curr Rheumatol Rep* 2013;15:332)

- **Bacterial** (nongonococcal): early diagnosis and treatment essential
- **Gonococcal** (*N. gonorrhea*): consider in sexually active young adults
- Viral: parvovirus, HCV, HBV, acute HIV, Chikungunya; mainly polyarticular, may mimic RA
- Mycobacterial: monoarticular or axial (Pott's disease)
- Fungal: *Candida* (esp. prosthetic joints), coccidiomycosis (valley fever), histoplasmosis
- Other: Lyme, *Mycoplasma*, *Salmonella*, Brucellosis, *T. whipplei*

Diagnosis (*JAMA* 2007;297:1478)

- H&P w/ poor sensitivity and specificity for septic arthritis
- **Arthrocentesis in acute onset inflammatory monoarthritis** to r/o septic arthritis; if possible, obtain fluid sample prior to starting antibiotics
- Do not tap through overlying infected area to prevent introducing infxn into joint space
- ✓ Fluid cell count w/ diff, Gram stain, bacterial culture, crystal analysis; **WBC >50k**
  w/ PMN predominance suspicious for bact. infxn; *crystals do not r/o septic arthritis!*

BACTERIAL (NONGONOCOCCAL) ARTHRITIS

Epidemiology & risk factors (*Infect Dis Clin North Am* 2017;31:203)

- 1/50,000 incidence per year
- **Immunocompromised host:** DM, EtOH use, HIV, age >80, SLE, cancer, steroid use, etc.
- **Damaged joints:** RA, OA, gout, trauma, prior surgery/prosthetic, prior arthrocentesis (rare)

- **Bacterial seeding:** bacteremia especially secondary to IVDU or endocarditis; direct inoculation or spread from contiguous focus (eg, cellulitis, septic bursitis, osteomyelitis)

Clinical manifestations (*JAMA* 2007;297:1478; *Lancet* 2010;375:846)

- Acute onset **monoarticular arthritis** (>80%) w/ pain (Se 85%), swelling (Se 78%), warmth
- Location: **knee** (most common), hip, wrist, shoulder, ankle. In IVDU, tends to involve other areas including axial joints (eg, SI, symphysis pubis, sternoclavicular, manubrial joints).
- **Constit. sx:** fevers (Se 57%), rigors (Se 19%), sweats (Se 27%), malaise, myalgias
- Infection can track from initial site to form fistulae, abscesses, or osteomyelitis
- *Septic bursitis must be differentiated from septic arthritis (intra-articular infection)*

Additional diagnostic studies (*JAMA* 2007;297:1478)

- **Synovial fluid: WBC usually >50k** (Se 62%, Sp 92%) but can be <10k, >**90% polys;** Gram stain ⊕ in ~75% of *Staph*, ~50% of GNR; Cx ⊕ in >90%; synovial bx most sens.
- **Leukocytosis** (Se 90%, Sp 36%); **elevated ESR/CRP** (Se >90%)
- **Blood cultures** ⊕ in >50% of cases, ~80% when more than 1 joint involved
- X-rays of joints should be obtained but usually normal until after ~2 wk of infection when may see bony erosions, joint space narrowing, osteomyelitis, and periostitis
- **CT & MRI** useful esp. for suspected hip infection or epidural abscess

Treatment for native joints (*IDCNA* 2017;31:203)

- Prompt empiric antibiotics guided by Gram stain after surgical drainage. If Gram stain ⊖, empiric Rx w/ vancomycin; add anti-pseudomonal agent if IVDU or immunocompromised.

Common Microbes (by Gram stain)		**Population**	**Initial Antibiotic Regimen** (tailor based on Gram stain, cx, clin course)
GPC clusters	*S. aureus* (most common)	Normal joints Prosthetic joints Damaged joints	Vancomycin. Can later Δ to antistaphylococcal penicillin or cefazolin based on sensitivities.
	S. epidermidis	Prosthetic joints	

		Postprocedure	
GPC chains	Streptococci	Healthy adults Splenic dysfunction	PCN-G or ampicillin
GN	Diplococci: *N. gonorrhea*	Sexually active young adults	Ceftriaxone or cefotaxime
	Rods: *E. coli*, *Pseudomonas*, *Serratia*	IVDU, GI infection immunosupp, trauma elderly	Cefepime or piperacillin/tazobactam + antipseudomonal aminoglycoside in IVDU

- **IV antibiotics** × ≥2 wk followed by oral antibiotics; varies by clinical course & microbiology
- Joint must be **drained**, often serially w/ arthroscopy (larger joints, initial Rx) or arthrocentesis. Serial synovial fluid analyses should demonstrate ↓ in WBC and sterility.
- 10–15% mortality (up to 50% w/ polyarticular); depends on virulence, time to Rx, host

Prosthetic joint infections (*Infect Dis Clin North Am* 2012;26:29; *CID* 2013;56:e1)

- ↑ risk in first 2 y s/p procedure; rate generally low (0.5–2.4%); risk factors include obesity, RA, immunocompromised state, steroids, & superficial surgical site infxn
- Staphylococci (coag negative & *S. aureus*) in >50%; polymicrobial in 10–20%
- Early (<3 mo s/p surgery) or delayed (3–24 mo) onset of sx from microbe typically acquired during implantation; early w/ virulent (eg, MRSA) and delayed w/ less virulent organisms (eg, *P. acnes*, coag negative *Staph*) & more indolent presentation
- Late (>24 mo) onset typically related to secondary hematogenous seeding
- Diagnosis requires arthrocentesis; ESR & CRP (CRP Se 73–91%, Sp 81– 86%; *NEJM* 2009;361:787) can be helpful
- Requires prolonged abx (initial empiric regimen: vanc + 3rd/4th gen cephalosporin) for 6 wks (*NEJM* 2021;384:1991) & 2-stage joint replacement (retention a/w ~40% failure; *CID* 2013;56:182) or life-long suppressive abx. *Consult ID & orthopedics.*

Disseminated Gonococcal Infection (DGI)

Epidemiology (*Infect Dis Clin North Am* 2005;19:853)

- *N. gonorrhea;* most frequent type of infectious arthritis in sexually active young adults
- **Normal host** as well as Pts w/ deficiencies of terminal components of complement
- ♀:♂ = 4:1 historically, but now ↑ in ♂. Occurs in <3% of *N. gonorrhea* infxn; ↑ incidence w/ menses, pregnancy, postpartum, SLE; ↑ incidence in MSM.

Clinical manifestations

- Preceded by **mucosal infection** (eg, cervix, urethra, anus, or pharynx) that is often asx
- Two distinct syndromes, although Pts can have both:
  - **Joint-localized:** purulent arthritis (40%), usually 1–2 joints (knees >wrists >ankles)
  - **Arthritis-dermatitis syndrome:** triad of **polyarthralgias, tenosynovitis, skin lesions**
    1) *polyarthralgias*: migratory joint pain, can affect small or large joints
    2) *tenosynovitis*: pain/inflammation of tendon and its sheath in wrists, fingers, ankles, toes
    3) *skin lesions*: gunmetal gray pustules with erythematous base on extremities & trunk
- Rare complications: Fitz-Hugh-Curtis syndrome (perihepatitis), pericarditis, meningitis, myocarditis, osteomyelitis from direct extension of joint-localized infection

Additional diagnostic studies

- Synovial fluid: **WBC >50k** (but can be <10k), **poly predominant**
  Gram stain ⊕ in ~25%; culture ⊕ in up to 50% if done w/ Thayer-Martin media
- Blood culture: more likely ⊕ in arthritis-dermatitis syndrome; rarely in joint-localized disease
- Gram stain and culture of skin lesions occasionally ⊕
- Cervical, urethral, pharyngeal, rectal PCR or cx on Thayer-Martin media; ✓ *Chlamydia*

Treatment

- **Ceftriaxone × 7–14 d w/ empiric doxycycline × 7 d** for *Chlamydia* if co-infection has not been excluded (see STI)
- Joint arthroscopy/lavage may be required for purulent arthritis; rarely >1 time

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OLECRANON & PREPATELLAR BURSITIS

Epidemiology & risk factors (*Joint Bone Spine* 2019;86:583)

- >150 bursae in the body; 2 most commonly infected are **olecranon** and **prepatellar**
- Most commonly (esp. superficial bursae) due to direct trauma, percutaneous inoculation, or contiguous spread from adjacent infection (eg, cellulitis)
- Other risk factors: recurrent noninfectious inflammation (eg, gout, RA), diabetes
- *S. aureus* (80%) most common, followed by streptococci

Diagnosis

- Physical exam: discrete bursal swelling, erythema, maximal tenderness at center of bursa with preserved joint range of motion
- Aspirate bursa if concern for infxn, ✓ cell count, Gram stain, bacterial cx, crystals
  WBC >20k w/ poly predominance suspicious for bacterial infection, but lower counts very common (crystals do *not* rule out septic bursitis!)
- Assess for adjacent joint effusion, which can also be septic
- Do *not* tap through infected skin to avoid introducing infxn into bursa

Initial therapy

- Prompt empiric coverage for staphylococci and streptococci: PO abx acceptable for mild presentation; **vancomycin** if ill appearing; broaden spectrum based on risk factors
- Modify antibiotics based on Gram stain, culture results, & clinical course. Duration of Rx is 1–3 wks. **Serial aspirations** every 1–3 d until sterile or no reaccumulation of fluid.
- Surgery if unable to drain bursa through aspiration, evidence of foreign body or necrosis, recurrent/refractory bursitis w/ concern for infxn of adjacent structures

CONNECTIVE TISSUE DISEASES

Approx Prev of Autoantibodies in Rheumatic Diseases											
Disease	**ANA**	**dsDNA**	**Sm**	**Ro/La**	**Scl- 70**	**RNA PIII**	**Centr**	**Jo-1**	**U1-RNP**	**RF**	**CCP**
SLE	≥95	75	20	25	⊖	⊖	⊖	⊖	45	35	15
Sjögren's	≥95	rare	⊖	45	⊖	⊖	⊖	⊖	rare	>75	10
dcSSc	>90	⊖	⊖	rare	40	20	rare	⊖	rare	30	10
lcSSc	>90	⊖	⊖	rare	10	rare	60	⊖	rare	30	15
IM	75–95	⊖	⊖	⊖	rare	⊖	⊖	25	⊖	15	15
MCTD	≥95	⊖	⊖	rare	⊖	⊖	⊖	⊖	100	50	10
RA	40	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	70	70

Centr, centromere; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cSSc; IM, inflammatory myopathies; RF, rheumatoid factor; Sm, Smith (*Primer on the Rheumatic Diseases*, 12th ed., 2001; *Lancet* 2013;382:797; *J Rheumatol* 2015;42:558)

- Only order auto-Ab testing if clinical suspicion for CTD, the presence of auto-Ab without characteristic clinical findings ≠ diagnosis, and auto-Ab do not define a particular CTD
- Overlap syndromes may be reflected by multiple autoantibodies

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see "Systemic Lupus Erythematosus" and "Rheumatoid Arthritis" for those diseases

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SYSTEMIC SCLEROSIS AND SCLERODERMA DISORDERS

Definition & epidemiology (*Best Pract Res Clin Rheumatol* 2018;32:223)

- **Scleroderma** refers to the presence of tight, thickened skin
- **Localized scleroderma:** *morphea* (plaques of fibrotic skin), *linear* (fibrotic bands), "*en coup de sabre*" (linear scleroderma on one side of scalp and forehead ≈ saber scar)
- **Systemic sclerosis (SSc)** = scleroderma + internal organ involvement. High-mortality.
  SSc w/ *limited cutaneous disease (lcSSc):* formerly CREST syndrome (see below)

SSc w/ *diffuse cutaneous disease (dcSSc):* often rapidly progressive skin thickening
SSc *sine scleroderma* (visceral disease without skin involvement, rare)

- Peak onset **age 30–50;** ♀ > ♂ (8:1). Earlier/more severe disease in African Americans
- <6/100,000 annual SSc incidence wordwide; lcSSc incidence ~2× that of dcSSc
- Pathogenesis: unclear. Endothelial injury → ROS/oxidative stress → perivascular inflammation → fibrosis. Cytokines, growth factors, genetics, environ. factors + antibodies (against PDGFR, endo. cells, fibroblasts) may contribute (*NEJM* 2009;360:1989).

ACR/EULAR SSc classification criteria (*Ann Rheum Dis* 2013;72:1747)

- Sufficient for dx: skin thickening of fingers of both hands extending proximal to MCPs
- Other items considered in criteria: Raynaud's, SSc-related auto-Ab, pulm hypertension (PHT) and/or ILD, abnormal nailfold capillaries, telangiectasia, fingertip lesions (ulcers, scars), skin thickening distal to MCPs
- **Rule out other causes** of thickened skin: diabetes (scleredema), scleromyxedema, toxin, hypothyroidism, nephrogenic systemic fibrosis, eosinophilic fasciitis, amyloidosis, GVHD

Clinical Manifestations of Systemic Sclerosis (*Lancet* 2017;390:1685)	
Skin	Tightening and thickening of extremities, face, trunk (bx not req for dx) "Puffy" hands, carpal tunnel syndrome, sclerodactyly Nailfold capillary dilatation & dropout Immobile, pinched, "mouse-like" facies and "purse-string" mouth Calcinosis cutis (subcutaneous calcification), telangiectasias
Arteries	**Raynaud's phenomenon** (80%); digital or visceral ischemia
Renal	**Scleroderma renal crisis (SRC)** = abrupt onset of HTN (*relative to Pt's baseline*), MAHA. Urine sediment typically bland. Renal bx not required but would show "onion-skin" hypertrophy of arteries & arterioles. Affects 5–10%. ACEI effective (see below) but 40% still progress to ESRD and 5y-mortality is 40% (*QJM* 2007;100:485). Risks: dcSSc, early disease (⅔ of cases in 1st yr), >15 mg/d prednisone, RNA Pol III Ab.

Clinical Manifestations of Systemic Sclerosis (*Lancet* 2017;390:1685)	
GI (>80% of Pts)	GERD and erosive esophagitis, esophageal dysmotility (dysphagia, odynophagia, aspiration), gastric dysmotility, small intestinal dysmotility (malabsorption, bact overgrowth, bloating)
Musculoskel	Arthralgias/arthritis; myositis; joint contractures; tendon friction rubs
Cardiac	Myocardial fibrosis; pericardial effusion; conduction abnormalities; CAD
Pulmonary	**Pulmonary fibrosis** (typically develops w/in 4 y); **pulmonary arterial hypertension** (typically develops after many yrs); #1 cause of mortality
Endocrine	Amenorrhea and infertility common; thyroid fibrosis ± hypothyroidism

SSc Subgroup Comparison		
	Limited (lcSSc)	**Diffuse (dcSSc)**
General		Fatigue, weight loss
Skin	Thickening on extremities *distal* to elbows/knees and *face* only	Thickening of distal *and proximal* ext, face *and trunk*
Pulmonary	PAH (rapidly progressive) >fibrosis	Fibrosis >PAH
GI	Primary biliary cirrhosis	
Renal	SRC later in disease course	SRC earlier & more common
Cardiac		Restrictive cardiomyopathy
Other	**CREST syndrome** = **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias	Raynaud's
Antibodies	Centromere (10–40%)	Scl 70, RNA-Pol III (40%)
Prognosis	Survival >70% at 10 y	Survival 40–60% at 10 y

Diagnostic studies & monitoring (*Lancet* 2017;390:1685)

- **Autoantibodies:** >95% Pts w/ auto-Ab; generally mutually exclusive
  - ⊕ **anti-Scl-70** (anti-topoisomerase 1): a/w diffuse SSc; ↑ risk pulm fibrosis
  - ⊕ **anticentromere:** a/w limited SSc; ↑ risk of severe digit ischemia and PHT
  - ⊕ **anti-RNA-Pol III:** a/w diffuse SSc; ↑ risk renal crisis; a/w cancer
  - ⊕ ANA (>90%), ⊕ RF (30%), ⊕ anti-U1-RNP a/w overlap syndrome
  - Other: anti-Th/To (a/w limited SSc), U3-RNP (a/w ILD), PmScl (polymyositis-SSc overlap)

- CXCL4 levels reported to correlate w/ degree of fibrosis (*NEJM* 2014;370:433)
- At baseline: ✓ BUN/Cr & UA for proteinuria, PFTs (spirometry, lung volumes, D_LCO), high- res chest CT (if diffuse disease), TTE (RVSP for PHT), RHC if ↑ RVSP or suspect PHT
- Annual PFTs; TTE q1–2y
- Skin bx not routine, but helpful to assess other possible causes for skin thickening
- ↑ risk of malignancy (esp. lung cancer) compared to general population
- Frequent (eg, daily) BP ✓ to monitor for HTN suggestive of scleroderma renal crisis

Treatment (*Ann Rheum Dis* 2017;76:1327; *Arthritis Rheumatol* 2018;70:1820)
- *Minimize steroid exposure to reduce risk of renal crisis*
- Interstitial lung disease: tocilizumab (*Lancet Respir Med* 2020;8:963), MMF (↓ toxicity vs. cyclophosphamide; *Lancet Respir Med* 2020;8:304); nintedanib (multikinase inhibitor/antifibrotic) a/w ↓ FVC decline (*NEJM* 2019; 380:2518).
  PAH: pulmonary vasodilators (see "Pulm Hypertension"); early Rx a/w better outcomes
- Renal crisis: **ACEI** (not ARB) for Rx, not prophylaxis (*Semin Arthritis Rheum* 2015;44:687)
- GI: PPI/H2-blockers for GERD; promotility agents & antibx for bacterial overgrowth
- Cardiac: NSAIDs ± colchicine superior to steroids for pericarditis
- Arthritis: acetaminophen, NSAIDs, hydroxychloroquine, MTX
- Myositis: MTX, AZA, steroids
- Skin: PUVA for morphea. Pruritus: emollients, topical/oral steroids. Fibrosis: MTX; MMF? (*Ann Rheum Dis* 2017;76:1207; *Int J Rheum Dis* 2017;20:481). CYC if severe (*NEJM* 2006;354:2655).
- Auto-HSCT promising for severe disease (*NEJM* 2018;378:35)

RAYNAUD'S PHENOMENON

Clinical manifestations & diagnosis (*NEJM* 2016;375:556; *Nat Rev Rheum* 2020;16:208)
- Episodic, reversible digital ischemia, triggered by cold temp, or stress, classically: **blanching** (white, ischemia) → **cyanosis** (blue,

hypoxia) → **rubor** (red, reperfusion); color Δ usually well demarcated; affects fingers, toes, ears, nose

Primary vs. Secondary Raynaud's Phenomenon		
	Primary (80–90%)	**Secondary (10–20%)**
Vessel wall	*Functionally* abnl	*Structurally* abnl
Etiologies	Idiopathic; however, can be exacerbated by comorbid conditions, including HTN, athero, CAD, DM	SSc, SLE, PM-DM, MCTD, Sjögren's, RA Arterial disease (athero, Buerger's), trauma Heme (cyro, Waldenström's, APS) Drugs (ergopeptides, estrogens, cocaine)
Epidem.	20–40 y; ♀ > ♂ (5:1)	>35 y
Clinical	Mild, *symm.* episodic attacks. *No tissue injury,* PVD, or systemic sx*; spares thumb.*	Severe, *asymm.* attacks; **tissue ischemia & injury** (eg, digital ulcers); can be assoc w/ systemic sx; may affect thumb or prox limbs
Auto Ab	⊖ CTD antibodies	Depends on etiology, CTD Ab often ⊕
Nailfold	Normal capillaroscopy	**Dropout and enlarged or distorted loops**

Treatment (*Curr Opin Rheumatol* 2021;33:453; *Clin Rheumatol* 2019;38:3317)

- All: avoid cold, maintain warmth of digits & body; avoid cigarettes, sympathomimetics, caffeine, & trauma; abx for infected ulceration
- **Mild–mod: long-acting CCB**, topical nitrates, SSRI, ARB, α-blockers, ASA/clopidogrel
- Severe: PDE inhibitors, anti-ET-1 receptor (if ulcers esp. w/ PHT), digital sympathectomy
- Digit-threatening: IV prostaglandins, digital sympathectomy, ± anticoagulation

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Inflammatory Myopathies

Definition & epidemiology (*NEJM* 2015;372:1734; *Lancet Neurol* 2018;17:816)

- All lead to skeletal muscle inflammation & weakness, variable extramuscular involvement
- **Polymyositis** (PM): incidence <1/million/y; onset typically 40s–50s; ♀ > ♂

- **Dermatomyositis** (DM): similar to PM but w/ skin manifestations; incidence ~1/million/y; also occurs in childhood; **malignancy *a/w* PM** (10%) **and DM** (24%)
- **Necrotizing autoimmune myositis** (NM): usually adults; risk factors: statin exposure (⊕ anti-HMGCR; *NEJM* 2016;374:664), CTD, cancer, rarely viral infection; incidence unclear
- **Inclusion body myositis** (IBM): age >50; ♂ > ♀; incidence ~5/million/y; often *misdiagnosed as PM*
- Ddx: drug-induced toxic myopathy (statins, cocaine, steroids, colchicine); infxn (HIV, EBV, CMV); metabolic (hypothyroid, hypo-K, hypo-Ca); neuromuscular dis. (eg, myasthenia gravis); glycogen storage disease; mitochondrial cytopathy; muscular dystrophy

Clinical manifestations

- **Muscle weakness:** typically gradual onset (wks to mos) but often accelerated in NM (days to wks) and more insidious (yrs) in IBM; progressive and painless
  - DM/PM/NM: **proximal and symmetric***;* difficulty climbing stairs, arising from chairs, brushing hair; fine motor skills (eg, buttoning) lost late
  - IBM: weakness may be asymmetric, distal, and involve facial muscles
- **Skin findings in dermatomyositis:** may precede myositis by mos to yrs
  - *Gottron's papules*: seen in >80% of Pts & pathognomonic; violaceous, often scaly, areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli
  - *Heliotrope rash*: purplish discoloration over upper eyelids ± periorbital edema
  - *Poikiloderma*: red or purple rash w/ areas of hyper and hypopigmentation mostly on sun- exposed areas; upper back (shawl sign), neck & chest (V sign), and hips (Holster sign)
  - *Mechanic's hands*: cracking, fissuring radial side of digits and can include pigmentation along palmar crease; a/w antisynthetase syndrome; also seen in PM
- **Pulmonary:** acute alveolitis, **interstitial lung disease**; resp muscle weakness; aspiration

Antisynthetase syndrome: acute onset DM or PM w/ **rapidly progressive ILD**, fever, weight loss, Raynaud's, mechanic's hands, arthritis; most commonly **anti-Jo-1** ⊕

MDA5-assoc. DM: ↑ amyopathic, ↑ rapidly progressive ILD, palmar papules, skin ulcers

- **Cardiac:** (33%): often asx; conduction abnl; myo/pericarditis; HF uncommon; ↑ CK-MB/Tn
- **GI:** dysphagia, aspiration
- **Polyarthralgias or polyarthritis:** usually early, nonerosive; small joints >large joints
- **Raynaud's** (30%, DM and overlap CTD) w/ dilatation & dropout of nail bed capillaries

Diagnostic studies (*Ann Rheum Dis* 2017;76:1955)

- ↑ **CK** (rarely >100,000 U/L, can be ↑↑↑ in NM), aldolase, SGOT, LDH; ± ↑ ESR & CRP
- Autoantibodies: ⊕ ANA (>75%)
  - ⊕ **anti-Jo-1** (25%): most common specific Ab; a/w antisynthetase syndrome
  - ⊕ anti-Mi-2 (DM >PM 15–20%) is a/w disease that responds well to steroids
  - ⊕ anti-SRP is a/w NM, poor Rx response; ⊕ anti-HMGCR in NM a/w statin exposure
  - Multiple others (*Best Pract Res Clin Rheumatol* 2018;32:887). Often ordered as an Ab panel.
- Consider **EMG** (↑ spontaneous activity, ↓ amplitude, polyphasic potentials w/ contraction) or **MRI** (muscle edema, inflammation, atrophy) for evaluation; may guide biopsy
- **Pathology and muscle biopsy:** all with interstitial mononuclear infiltrates, muscle fiber necrosis, degeneration, & regeneration (required for definitive diagnosis)
  - PM: CD8 *T cell-mediated muscle injury;* perivascular and endomysial inflammation surrounds MHC class I-expressing non-necrotic fibers
  - DM: *immune complex deposition in blood vessels* with complement activation; *perifascicular atrophy* w/ interfascicular and perivascular inflam (B & CD4 T cells)
  - NM: necrotic fibers w/ macrophages

IBM: *T cell-mediated injury, vacuole formation;* same as PM w/ eosinophilic inclusions and rimmed vacuoles and chronic myopathic changes (variable fiber size)

Treatment (*Nat Rev Rheum* 2018;14:279)

- Immunosuppression not effective for IBM. For all others:
- **Steroids** (prednisone 1 mg/kg); MTX or AZA early if mod/severe or taper fails (2–3 mo)
- For resistant (30–40%) or severe disease: AZA/MTX combo, IVIg (NM, DM ± PM), rituximab, MMF, cyclophosphamide (esp. if ILD or vasculitis)
- IVIg w/ pulse steroids acutely for life-threatening esophageal or resp muscle involvement
- ✓ **for occult malignancy** (esp. if DM); monitor respiratory muscle strength with spirometry
- NM: stop statin; steroids + MTX, RTX, or IVIg

Myositides, Myopathies, and Myalgias					
Disease	**Weakness**	**Pain**	**↑ CK**	**↑ ESR**	**Biopsy**
DM/PM/NM	⊕	⊖	⊕	±	as above
IBM	⊕	⊖	⊕	⊖	as above
Hypothyroidism	⊕	±	⊕	⊖	mild necrosis inflam, atrophy
Steroid-induced	⊕	⊖	⊖	⊖	atrophy
PMR	⊖	⊕	⊖	⊕	normal
Fibromyalgia	⊖	⊕	⊖	⊖	normal

SJÖGREN'S SYNDROME (*NEJM* 2018;378:931)

Definition & epidemiology

- Chronic dysfxn of **exocrine glands** (eg, salivary/lacrimal) due to lymphoplasmacytic infiltration, extraglandular manifestations common in primary form
- Can be primary or secondary (a/w RA, scleroderma, SLE, PM, hypothyroidism, HIV)
- ~1/1000 prevelance with 9:1 ♀:♂ ratio; typically presents between age 40 & 60

Clinical manifestations

- **Dry eyes** (keratoconjunctivitis sicca): ↓ tear production; burning, scratchy sensation
- **Dry mouth** (xerostomia): difficulty speaking/swallowing, **dental caries**, xerotrachea, thrush
- **Parotid gland enlargement:** intermittent, painless, typically bilateral
- **Vaginal dryness** and **dyspareunia**
- **Recurrent nonallergic rhinitis/sinusitis** due to upper airway gland involvement
- **Extraglandular manifestations:** arthritis, interstitial nephritis (40%), type I RTA (20%), cutaneous vasculitis (25%), PNS >CNS neurological disease (20%), ILD, PBC
- ↑ risk of lymphoproliferative disorders (~50× ↑ risk of lymphoma and WM in 1° Sjögren's)
- Neonatal lupus, including fetal skin rash or heart block (a/w SSA and/or SSB antibodies)

Diagnostic studies

- Autoantibodies: ⊕ ANA (95%), ⊕ RF (75%)
  Primary Sjögren's: ⊕ **anti-Ro** (anti-SSA, ~50%) ± **anti-La** (anti-SSB, ~30%)
- **Schirmer test:** filter paper in palpebral fissures to assess tear production
- **Rose-Bengal** staining: dye that reveals devitalized epithelium of cornea/conjunctiva
- **Ocular staining score:** substitute for Rose-Bengal staining to determine degree of keratoconjunctivitis sicca using fluorescein and lissamine green
- **Biopsy** (minor salivary, labial, lacrimal, or parotid gland): lymphocytic infiltration

Classification criteria (≥4 points 96% Se & 95% Sp; *Arthritis Rheumatol* 2017;69:35)

- 3 points: ⊕ anti-Ro; labial saliv. gland bx w/ lymphocytic sialadenitis & score ≥1 foci/4 mm^2
- 1 point: abnormal ocular staining score ≥5; Schirmer's test ≤5 mm/5 min; unstimulated salivary flow rate of ≤0.1 mL/min

Treatment (*Ann Rheum Dis* 2020;79:3)

- Ocular: artificial tears, cyclosporine eyedrops, autologous tears

- Oral: sugar-free gum, lemon drops, saliva substitute, hydration, pilocarpine, cevimeline
- Systemic: depends on extraglandular manifest.; NSAIDs, steroids, DMARDs, rituximab

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MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Definition (*Best Pract Res Clin Rheumatol* 2016;30:95)

- Features of **SLE**, **systemic sclerosis**, and/or **polymyositis** that appear gradually over years and often evolve to a dominant phenotype of SLE or systemic sclerosis
- Different from undifferentiated CTD (UCTD): nonspecific symptoms that fail to meet criteria for any CTD; 30% go on to develop CTD over 3–5 y (usually SLE)

Clinical & laboratory manifestations (*Rheumatology* 2018;57:255)

- **Raynaud's phenomenon** (qv) typical presenting symptom (75–90%)
- Hand edema ("puffy hands"), sclerodactyly, RA-like **arthritis** w/o erosions, polyarthralgias
- Pulmonary involvement (85%) with **pulmonary hypertension**, fibrosis
- Pericarditis most frequent cardiovascular manifestation; GI: dysmotility (70%)
- Membranous & mesangial GN common (25%); low risk for renal HTN crisis or severe GN
- ⊕ ANA (>95%); ⊕ RF (50%); requires ⊕ **anti-U1-RNP** but *not* specific (seen in ~50% SLE)

Treatment: as per specific rheumatic diseases detailed above

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Definition and epidemiology (*Nat Rev Rheumatol* 2021;17:515)

- Multisystem inflammatory autoimmune disease with a broad spectrum of clinical manifestations in association with antinuclear antibody (ANA) production
- Prevalence 5–35/10,000 in U.S.; predominantly affects women 2nd to 4th decade
- ♀:♂ ratio = 8:1; African Americans affected 2–4× as often as Caucasians
- Complex genetics; some HLA association; rarely C1q & C2 deficiency

Classification Criteria (*Ann Rheum Dis* 2019;78:1151) for *research/classification* not dx

Required criteria: **ANA titer** ≥1**:80** AND ≥1**0** points (at least one clinical):

Clinical domains (points*)

Renal • proteinuria >0.5 g/d (4) • class II or V nephritis (8) • class III or IV nephritis (10)	**Hematologic** • leukopenia (3) • thrombocytopenia (4) • autoimm. hemolytic anemia (4)	**Neuropsychiatric** • delirium (2) • psychosis (3) • seizure (5)
Mucutaneous • non-sclarring alopecia (2) • oral ulcers (2) • discoid lupus (4); subacute (4) or acute (6) cutaneous lupus	**Serosal** • pleural/pericardial effusion (5) • acute pericarditis (6)	**Musculoskeletal** • joint involvement (6) **Constitutional** • fever (2)

Immunology domains (points*)

Antiphospholipid antibodies • anti-CL, anti-B2GP1, or a lupus anticoagulant (2)	**Complement proteins** • low C3 or C4 (3) • low C3 and C4 (4)	**SLE-specific Abs** • anti-dsDNA or anti- Smith (6)

*Within each domain, only the highest weighted criterion is counted toward the total score.

Autoantibodies in SLE (*Nat Rev Rheumatol* 2020;16:565)

Autoantibodies in SLE (*Nat Rev Rheumatol* 2020;16:565)			
Auto-Ab	**Frequency (approx)**	**Clinical Associations**	**Timeline**
ANA	95–99% if active disease 90% if in remission Homogeneous or speckled	Any or all of broad spectrum of clinical manifestations Sensitive but not specific	May appear yrs before overt disease
Ro **La**	15–35% ⊕ anti-Ro may be seen w/ ⊖ or low titer ANA	Sjögren's/SLE overlap Neonatal lupus; photosens.; subacute cutaneous lupus	
ds-DNA	70%; ~95% Sp; titers may parallel dis. activity, esp. renal	Lupus nephritis Vasculitis	Appears mos before or at dx, but may become ⊕ after dx
Sm	30%; very specific for SLE	Lupus nephritis	
U1-RNP	40%	MCTD; Raynaud's; Tend *not* to have nephritis	
Histone	90% in DLE; 60–80% in SLE	Mild arthritis and serositis	At diagnosis

Workup

- Autoantibodies: ANA, if ⊕ → ✓ anti-ds-DNA, anti-Sm, anti-Ro, anti-La, anti-U1-RNP
- CBC, APLA (⊕ in 20–40%; ACL, B2GP1, lupus anticoagulant), total complement, C3 & C4
- Lytes, BUN, Cr, U/A, urine sed, spot microalb:Cr ratio or 24-h urine for CrCl and protein
- If ↓ GFR, active sediment, hematuria, or proteinuria (>0.5 g/dL) → renal bx to guide Rx

Treatment (*Ann Rheum Dis.* 2019;78:736; *Lancet* 2019;393:2332; *Nat Rev Rheumatol* 2019;15:30)		
Drug	**Indication**	**Adverse Effects**
Hydroxychloroquine (HCQ)	**All Pts b/c ↓ flares** (*NEJM* 1991;324:150); monoRx for arthritis, serositis, skin disease	Retinal tox (<1%), Stevens-Johnson; myopathy. *Not immunosuppressive.*
NSAIDs	Arthritis, myalgias, serositis	Gastritis, UGIB, renal failure
Corticosteroids	Low dose for arthritis, serositis; high-dose (1 mg/kg) ± pulse (1 g × 3 d) for major dis. (eg, renal, CNS, heme). Minimize as able.	Adrenal suppression, diabetes, cataracts, osteopenia, avascular necrosis of bone, myopathy

Treatment (*Ann Rheum Dis.* 2019;78:736; *Lancet* 2019;393:2332; *Nat Rev Rheumatol* 2019;15:30)		
Mycophenolate (MMF)	**Nephritis** (induction/maint); nonrenal refractory to HCQ	Cytopenias, ↑ LFTs, diarrhea, teratogen
Cyclophosphamide (CYC)	**Severe organ-threatening nephritis or CNS disease** (induction, minimize exposure)	Cytopenias, infertility/teratogen, myeloprolif. dis., hemorrhagic cystitis, bladder cancer
Azathioprine (AZA)	Nephritis (maintenance) Non-renal dis. refractory to HCQ	Myelosuppr. (✓TPMT), ↑ LFTs, teratogen, lymphoprolif. dis.
Methotrexate (MTX)	Arthritis (preferred over MMF/AZA) Skin disease & serositis	Myelosuppression, alopecia, hepatotoxicity, stomatitis, pneumonitis, teratogen
Cyclosporine (CsA)	Renal disease	Hyperplastic gums, HTN, hirsutism, CKD, anemia
Voclosporin (calcineurin inhibitor *Lancet* 2021;397:2070)	Nephritis (induction). Added to MMF+steroids; ↑ complete renal response w/ ↓ steroid.	HTN, ↓ GFR, diarrhea. (Stable PK, ∴ does not require levels like other calcineurin inhibitors)
Belimumab (*NEJM* 2013;368:1528 & 2020;383:1117)	Arthritis, serositis, skin disease (esp. if ⊕ ds-DNA or ↓ C3/C4). Nephritis (induction). ↑ renal response when added.	B-cell depletion by binding BLyS (less immunosuppressive than RTX)
Rituximab (RTX)	ITP, AIHA, refractory SLE	Infusion reaction / serum sickness, PML, infection
Baricitinib (*Lancet* 2018;392:222)	Prelim data: 4 mg w/ efficacy in arthritis, skin disease	Infections (zoster), ↑ LFTs, cytopenias, dyslipidemia
Anifrolumab (anti- IFN receptor)	Moderate to severe disease (*NEJM* 2020;382:211)	Infection (PNA, zoster), hypersensitivity reaction

Lupus Nephritis – 40% affected (*Nat Rev Rheumatol* 2020;16:255)		
Class	**Presentation**	**Treatment (all benefit from HCQ)**
I: Min. mesangial	Normal U/A & eGFR	No specific treatment
II: Mesangial prolif	Micro hematuria/proteinuria	No specific treatment ± ACEI
III: Focal prolif	Hematuria/proteinuria, ± HTN, ↓ GFR, ± nephrotic	Induce: MMF *or* CYC + steroids Maintenance: MMF >AZA (*NEJM* 2004;350:971 & 2005;353:2219 & 2011;365:1886)
IV: Diffuse prolif	Hematuria/proteinuria and HTN, ↓ GFR, ± nephrotic	

Lupus Nephritis – 40% affected (*Nat Rev Rheumatol* 2020;16:255)		
V: Membranous (can coexist with class III or IV)	Proteinuria, nephrotic	ACEI If nephrotic-range proteinuria, induce w/ MMF + steroids Maintenance: MMF superior to AZA
VI: Adv. Sclerotic	ESRD	Renal replacement therapy

Prognosis (*Nat Rev Rheumatol* 2021;17:515)

- Overall mortality 2–3× higher than general population, higher in Blacks.
- Leading causes of morbidity/mortality: **infection**, CV events, **renal failure** (nephritis remission achieved in <50%; >10% end up w/ ESRD), neurologic events, thrombosis

Drug-induced lupus (DLE) (*Drug Saf* 2017;16:1255; *Autoimmun Rev* 2018;17:912)

- Many drugs: **procainamide**, **hydralazine**, penicillamine, minocycline, INH, methyldopa, quinidine, chlorpromazine, diltiazem, **anti-TNF** (esp. infliximab), interferons
- Abrupt onset; generally mild disease with arthritis, serositis, skin disease; renal dx, malar and discoid rash rare; prevalence ♀:♂ = 1:1
- ⊕ Anti-histone (95%) (may be ⊖ in anti-TNF); ⊖ anti-ds-DNA (often ⊕ in anti-TNF cases, even w/o manifestations of DLE) & ⊖ anti-Sm; normal complement levels
- Usually reversible w/in 4–6 wk after stopping medication

IGG4-RELATED DISEASE

Definition & etiology (*NEJM* 2012;366:539; *Nat Rev Rheumatol* 2020;16:702)

- Characterized by tumor-like inflammatory lesions that can affect nearly any organ
- Etiology: ? autoimmune; unclear role of IgG4; may have h/o atopy
- ♂ > ♀, mean age ~ 60. Incidence ~1/100,000 per y in Japan, but elsewhere unknown.

Clinical manifestations (*Arthritis Rheumatol* 2015;67:2466 & 2020;72:7)

- Commonly pancreatitis, aortitis, cholangitis, sialadenitis, thyroiditis, dacroadenitis, orbital myositis ± pseudotumor, retroperitoneal fibrosis, renal and lung involvement
- Insidious progression; multiple lesions may be present synchronously or metachronously

Diagnosis and management (*Lancet Rheumatol* 2019;1:e55)

- **Biopsy** w/ specific findings: lymphoplasmacytic infiltrate w/ significant IgG4+ plasma cell infiltrate, storiform fibrosis, obliterative phlebitis
- ↑ serum IgG4 (Se 90%, Sp 60%); may have low C3, C4
- Highly responsive to steroids but relapse common. Efficacy of DMARDs in maintenance remains unclear but B-cell depleting agents appear promising (*Eur J Intern Med* 2020;74:92).

VASCULITIS

OVERVIEW

- Inflammation w/in blood vessel walls causing end-organ damage often a/w systemic sx; may be primary or secondary (eg, infection, malignancy) in etiology
- Classified by size of *predominant* vessel affected (*Arthritis Rheum* 2013;65:1); overlap of vessel size affected is common
- Clinical manifestations based on size of vessels involved; constitutional sx (low-grade fever, fatigue, weight loss, myalgias, anorexia) common to all

Distinguishing Characteristics of Vasculitis Subtypes

	Large Vessel		*Medium Vessel*	*Small Vessel*	
	TAK	**GCA**	**PAN**	**ANCA-Assoc.**	**IC**
Epidem	Young, ♀ >♂	Elderly, ♀ >♂	Middle-aged to older	Variable	Variable
Renal	Arteries	None	Microaneurysms	GN	GN
Pulm	Rare	None	Rare	Frequent	Cryo >IgA
Periph Neurop	No		Yes	Yes	Yes
GI	Rare	Rare	Yes	No	IgA >Cryo
Skin	Rare	None	Common	Common	Common
Granul.	Yes		No	Yes, except MPA	No
Other		Assoc w PMR	Mesenteric aneurysms, testicular involv.	GPA: upper airway EGPA: asthma	Cryo a/w HCV

TAK, Takayasu's arteritis; GCA, giant cell arteritis; PAN, polyarteritis nodosa; ANCA-assoc. is GPA, EGPA, & MPA; IC, immune complex small-vessel vasculitis (eg, IgA, cryoglobulinemia); GN, glomerulonephritis.

LARGE-VESSEL VASCULITIS

Takayasu's arteritis ("pulseless disease")

- **Arteritis of aorta and its branches → stenosis/aneurysm →** claudication. Most often **subclavian** & **innominate arteries** (>90%); carotid, coronary, renal, or pulm a. (~50%)
- Epidemiology: most common in **Asia;** ♀:♂ ~9:1 in Japan but lower elsewhere; **age <50 y**. Prev 8/million in U.S. w/ ~4:1 ♀:♂ (*J Rheumatol* 2021;48:952).
- Clinical manifestations: systemic inflamm with **fever**, **arthralgias**, wt loss
  Vessel inflamm w/ pain & tenderness, ↓ **& unequal pulses/BPs in extremities**, **bruits**, limb claudication, renovascular HTN (>50%), neurogenic syncope, Ao aneurysm ± AI
  "Burnt out" or fibrotic period (eg, vascular stenosis)
- Dx studies: ↑ ESR (75%), CRP; **arteriography** (MRA, CTA) → occlusion, stenosis, irregularity, and aneurysms; carotid U/S Doppler studies; PET-CT; **pathology** → focal panarteritis, cellular infiltrate with *granulomas* and giant cells (bx not required for dx)
- Rx: **steroids** ± MTX, AZA, or anti-TNF; tocilizumab 2nd line (*Ann Rheum Dis.* 2020;79:19); ASA if critical cerebral stenosis; if surgical/endovascular revasc, preferably done in remission
- Monitoring: MRA, CTA, or PET-CT; ESR/CRP

Giant cell arteritis (GCA) (*JAMA* 2016;315:2442)

- **Granulomatous arteritis** typically involving **aorta/branches**; predilection for **extracranial branches of carotid a.**, particularly temporal a. (thus also called **temporal arteritis**).
- Epidemiology: 90% >60 y, peak incidence at 70–80 y, extremely rare <50 y; ♀:♂ = 3:1. Prev 2/1000 of those age ≥50 (*Semin Arthritis Rheum* 2017;47:253).
- Clinical manifestations (*NEJM* 2014;371:50): constitutional sx: **fevers**, fatigue, wt loss
  Temporal artery (TA) → headache, tender TAs and scalp, absent TA pulse
  Ophthalmic artery (20%) → optic neuropathy, diplopia, amaurosis fugax, blindness
  Facial arteries → **jaw claudication**
  Large vessel vasculitis → intermittent claudication of extremities; thoracic aorta aneurysm

Strong association w/ PMR; ~50% of Pts w/ GCA ultimately received PMR diagnosis

- Dx: ↑ **ESR** (Se 84%, Sp 30%), ↑ CRP (Se 86%, Sp 30%), anemia. **Temporal artery bx** (shows vasculitis & granulomas) whenever *GCA suspected* (Se ≤85%); consider bilat to ↑ yield (3–7% discordant). If bx ⊖ or suspect aortitis/large vessel involvement: U/S (halo sign) or MRA of temporal/cranial arteries, or CTA, MRA, or PET of aorta/large arteries (*Arthritis Rheumatol* 2021;73:1349). Some advocate imaging upfront to r/o, but requires imaging expertise (*Ann Rheum Dis* 2018;77:636 & 2020;79:19).
- Rx: **steroids**: *do not await bx/path!* Have >2 wks to bx w/o Δ. Pred 40–60 mg/d w/ *slow* taper; ASA if critical cerebral narrowing; consider IV steroids if vision threatened (*Arthritis Rheumatol* 2021;73:1349). Adding tocilizumab ↑ sustained remission (*NEJM* 2017;377:317).
- **Polymyalgia rheumatica** (*JAMA* 2016;315:2442; *Lancet* 2017;390:1700)
  Prev 7/1000 of age ≥50. In 50% of GCA Pts; 15% of PMR Pts develop GCA. ♀:♂ ≈ 2.
  ESR >40 mm/h (and/or ↑ CRP); *bilateral* ***pain & morning stiffness*** (>30 min), involving 2 of 3 areas: neck or torso, shoulders or prox. arms, hips or prox. thighs; nighttime pain; ± subdeltoid bursitis on U/S; exclude other causes of sx (eg, RA); nl CK
  Rx: pred 12.5–25 mg/d; if clinical response, initiate slow taper. If not, consider alternate dx or ↑ dose. Consider MTX if at ↑ risk of steroid side effects (*Ann Rheum Dis* 2015;74:1799).
- Follow clinical status & ESR/CRP; ~⅓relapse over 2 y (*J Rheum* 2015;42:1213)

MEDIUM-VESSEL VASCULITIS

Polyarteritis nodosa (“classic” PAN) (*Nat Rev Rheumatol* 2017;13:381)

- **Necrotizing nongranulomatous vasculitis of medium & small arteries** (w/in muscular media) w/o glomerulonephritis or capillary involvement (ie, no DAH), not a/w ANCA
- Incidence ~2/million/y; ↑ in HBV-endemic areas; ♂ >♀; av. age ~50; 10% **HBV-assoc**
- Clinical manifestations (*Arth Rheum* 2010;62:616): const. sx (80%): wt loss, **fever**, fatigue

Neuro (79%): **mononeuritis multiplex**, peripheral neuropathies, stroke
Musculoskeletal (64%): **extremity pain**, **myalgias**, arthralgias, arthritis
Renal (51%): **HTN**, hematuria, proteinuria, renal failure; *glomerulonephritis unusual*
GI (38%): **abd pain**, GIB/infarction, cholecystitis; GU (25%): ovarian or testicular pain
Skin (50%): **livedo reticularis**, purpura, nodules, ulcers, Raynaud's
Ophthalmic (9%): retinal vasculitis, retinal exudates, conjunctivitis, uveitis
Cardiac (22%): coronary arteritis, cardiomyopathy, pericarditis
Pulmonary: rare; *if lung involvement, suspect other vasculitis*

- Dx (*Arthritis Care Res* 2021;73:1061): ↑ ESR/CRP; r/o ANCA, HBV; ↓ C3/C4 if HBV-assoc.
  Angiogram (mesenteric or renal vessels) → **microaneurysms** & focal vessel narrowing
  CTA or MRA may be adequate for dx, but conventional angiogram is most sensitive
  Biopsy (nerve, deep-skin, or affected organ) → vasculitis of small and medium a. w/ fibrinoid necrosis *w/o granulomas*
- Rx: based on severity; **steroids** ± DMARD (MTX, AZA; CYC if severe); antivirals if HBV. Most dis. monophasic so consider stopping DMARD if in steroid-free remission at 18 m.

ANCA-Associated Small-Vessel Vasculitis

Microvascular vasculitis (eg, capillaries, postcapillary venules, & arterioles)

Disease	Granul.	Renal	Pulm	Asthma	ANCA Type[a]	ANCA ⊕
Granulomatosis with polyangiitis[b]	⊕	80%	90% (+ ENT)	—	anti-PR3	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO	70%
Eosinophilic granulomatosis with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO	50%

[a]Predominant type, can see either type (*NEJM* 2012;367:214). [b]GPA is formerly Wegener's granulomatosis, EGPA is formerly Churg-Strauss. Microscopic polyangiitis (MPA).

Differential diagnosis of ANCA (*Nat Rev Dis Primers* 2020;6:71)

- **anti-PR3:** GPA, EGPA, microscopic polyangiitis (rarely), levamisole (contam. in cocaine)
- **anti-MPO:** microscopic polyangiitis, EGPA, GPA, drug-induced vasculitis, nonvasculitic rheumatic dis., levamisole (contaminant in cocaine)
- **Atypical ANCA patterns:** drug-induced vasculitis, nonvasculitic rheumatic diseases, ulcerative colitis, primary sclerosing cholangitis, endocarditis, cystic fibrosis

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis)

- **Necrotizing granulomatous systemic vasculitis** frequently affecting upper respiratory tract (nose, sinuses) in addition to kidneys, lower resp tract (lungs), and other organs
- Epi: incidence 12/million/y; any age but ↑ in young/middle-aged adults; ♂ = ♀
- Clinical manifestations
  - Constitutional: fever, fatigue, malaise, anorexia, **weight loss**
  - **Respiratory** (90%): Upper: **recurrent sinusitis**, rhinitis, oral/nasal ulcers, **nasal crusting**, **saddle-nose deformity**, otitis, hearing loss, subglottic stenosis Lower: infiltrates, nodules, & hemorrhage → cough, dyspnea, hemoptysis, pleurisy
  - **Renal** (80%): **RPGN**, microscopic hematuria (dysmorphic RBCs and casts)
  - Skin (50%): palpable purpura, livedo reticularis
  - Ocular (50%): episcleritis, scleritis, uveitis, orbital granulomas → proptosis, corneal ulcer

Neuro: cranial + peripheral neuropathies, **mononeuritis multiplex.**
Heme: ↑ incidence DVT/PE (20×) when disease active (*Ann Intern Med* 2005;142:620)

- Dx studies: **90%** ⊕ **ANCA** (80% PR3, 20% MPO), less Se in limited upper-airway disease
  CXR or CT → nodules, infiltrates, cavities; sinus CT → sinusitis ± bone erosions
  ↑ BUN & Cr, proteinuria, hematuria; sediment w/ RBC casts, dysmorphic RBCs
  Biopsy → necrotizing granulomatous inflammation of arterioles, capillaries, veins. Renal bx w/ pauci-immune (minimal immune deposition) necrotizing and crescentic GN.
- Treatment: assess severity w/ BVAS/GPA score (*Arth Rheum Dis* 2009;68:1827)
  Mild disease (no end-organ dysfxn; BVAS 0–3): **MTX** + **steroids** (*Arth Rheum* 2012;64:3472)
  Severe disease (end-organ damage incl. pulm hemorrhage, RPGN etc.; BVAS >3):
  Induction: [**RTX** 375 mg/m^2/wk × 4 wk or 1000 mg on d1 + d15 *or* **CYC** 2 mg/kg/d × 3–6 mo or pulse 15 mg/kg q2–3 wk] + **steroids** 1 g IV × 3 d → ~1 mg/kg/d (*Ann Rheum Dis* 2015;74:1178). RTX preferred as ↓ toxicity (*Arth Rheum* 2021;73:1366).
  Plasma exchange (PLEX) may ↓ risk of ESRD in those most at risk (*NEJM* 2020;382:622; *Arth Rheum* 2021;73:1366).
  Adding avacopan (oral C5a receptor inhibitor) increases remission rate and allows ↓ steroids (*NEJM* 2021;384:599)
  Maintenance: RTX q6mo superior to AZA or observ. (*Ann Intern Med* 2020;173:179)
  Relapse: mild → steroids ± MTX or AZA; severe → reinduce w/ steroids + RTX or CYC
  ↑ ANCA w/o clinical evidence of flare should *not* prompt Δ Rx (*Annals* 2007;147:611)

Microscopic polyangiitis (MPA) (*Rheum Dis Clin North Am* 2010;36:545)

- Similar to GPA, but **w/o ENT/upper airway involvement & nongranulomatous**
- Epidemiology: incidence 4/million/y. ♂ = ♀; avg onset 50–60 y
- Clinical manifestations

Constitutional, neuro sx similar to GPA
Renal (80–100%): glomerulonephritis
Skin lesions (eg, palpable purpura) in 30–60%
Pulmonary (25–50%): pulmonary capillary alveolitis, pulmonary fibrosis

- Dx studies: **70%** ⊕ **ANCA** (almost all anti-MPO)
  Biopsy → necrotizing, **nongranulomatous** inflammation of small vessels, pauci-immune
  Urine sediment and CXR findings similar to those seen in GPA
- Treatment: as for GPA (*Arth Rheum* 2021;73:1366); ↓ relapse rate compared to GPA

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)

- Similar to GPA w/ more frequent **cardiac involvement**, a/w **asthma** and **eosinophilia**
- Epi: rare (incidence 2/million/y); any age (typically 30–40 y); ♂ = ♀; a/w HLA-DRB4
- Clinical manifestations (*Rheumatol* 2020;59:iii84)
  Initial sx: **asthma**, sinusitis, allergic rhinitis (new asthma in adult raises suspicion)
  Eosinophilic infiltrative disease: transient **pulm infiltrates**, gastroenteritis, or esophagitis
  Systemic small-vessel vasculitis: **neuropathy** (mononeuritis multiplex), renal (glomerulonephritis), skin (palpable purpura, petechial, nodules)
  Cardiac: coronary arteritis, myocarditis, CHF, valvular insufficiency (*Medicine* 2009;88:236)
- Dx studies: 50% ⊕ ANCA (MPO >PR3), **eosinophilia** (>1500/uL or 10%, often >60%),
  biopsy → microgranulomas, fibrinoid necrosis, small artery/vein thromboses w/ eosinophilic infiltrate
- Treatment: high-dose **steroids** + mepolizumab (anti-IL-5) (if nonsevere) or RTX or CYC (if severe) (*Arth Rheum* 2021;73:1366); mepolizumab for relapse/refractory (*NEJM* 2017;376:1921)

Renal-limited vasculitis

- Small vessel pauci-immune vasculitis causing RPGN w/o other organ involvement
- Dx studies: 80% ⊕ ANCA (MPO >PR3); biopsy with pauci-immune GN ± granulomas
- Treatment identical to that for GPA/MPA

IMMUNE COMPLEX (IC)–ASSOCIATED SMALL-VESSEL VASCULITIS

IgA vasculitis (formerly Henoch-Schönlein purpura [HSP]) (*Rheumatol* 2019;58:1607)

- **IgA-mediated** small-vessel vasculitis w/ predilection for **skin**, **GI tract**, and **kidneys**
- Epidemiology: incidence 140/million/y; ♂ >♀, children >adults, winter >summer
- May develop ~10 d after onset of upper resp infx or after drug exposure
- Clinical manifestations
  - **Palpable purpura** on extensor surfaces (lower extremity first) & buttocks
  - **Polyarthralgias** (nondeforming) esp. involving hips, knees, & ankles
  - Colicky **abdominal pain** ± GIB or intussusception
  - Nephritis ranging from **microscopic hematuria** & proteinuria to ESRD
- Dx studies: **skin bx w/ immunofluorescence → leukocytoclastic vasculitis w/ IgA**
  and **C3** deposition in vessel wall; renal bx → mesangial IgA deposition
- Treatment: often self-limiting over 4 wk; steroids ± DMARDs for renal or severe disease

Cryoglobulinemic vasculitis (*Lancet* 2012;379:348; *Nat Rev Dis Primers* 2018;4:11)

- Cryoglobulins: proteins that **precipitate** from *serum or plasma* **on exposure to cold and redissolve on rewarming**, characterized by their composition; a/w chronic immune stimulation and/or lymphoproliferation

- Distinguish from *cryofibrinogenemia* = proteins (eg, fibrin, fibrinogen) that precipitate only from *plasma;* found in autoimmune dis, malignancies, infxns; unclear clinical significance

Types of Cryoglobulinemia (*J Autoimmun* 2019;105:102313)			
Feature	**Type I (monoclonal)**	**Type II (mixed)**	**Type III (mixed)**
Frequency	10–15%	50–60%	25–30%
Cryoglobulin composition	*Monoclonal* Ig (usually IgM or IgG)	*Monoclonal* IgM w/ RF activity + *polyclonal* IgG	*Polyclonal* IgG and IgM
Common etiologies	**Plasma cell dyscrasias**	**Infection, malignancy**, autoimmune syndromes	**Autoimmune synd.,** infxn
Primary manifestations	**Hyperviscosity** ± thrombosis → ischemia	**IC-mediated vasculitis**, w/ multiorgan involvement. Can be asx.	

- Epidemiology: ~1/100,000, but prevalence varies with HCV rates; ♀ > ♂
- Etiologies (idiopathic in ~10%)
  - **Hematologic diseases:** multiple myeloma, MGUS, Waldenström's, chronic lymphocytic leukemia in type I; B-cell lymphomas or solid-organ malignancies in type II
  - Infxns (types II & III): viral (**HCV** [>80% RNA ⊕], HBV, HIV, HAV, EBV, CMV), bacterial (endocarditis, strep, etc.), fungal (coccidiomycosis, etc.), parasitic (malaria, amoebiasis)
  - Autoimmune syndromes (type III >II): **Sjögren's syndrome**, SLE, RA, PAN
  - Renal transplant recipients (*Clin Nephrol* 2008;69:239)
- Pathophysiology
  - Type I: cryo precipitation in microcirculation → **hyperviscosity** & **vascular occlusion**
  - Types II/III: defective/insufficient immune complex (IC) clearance → IC-mediated inflammation of blood vessels w/ complement activation → **vasculitis**
- Clinical manifestations (most Pts w/o sx)

Type I: **hyperviscosity** (cold worsens sx) → HA, visual Δ, livedo, digital ischemia

Type II/III: **vasculitis** (not affected by cold) → fever, derm (54–80%; **purpura**, livedo reticularis, ulcers), **arthralgia** (44–70%; symmetric migratory, small/med joints), **glomerulonephritis** (50%; MPGN), neurologic (17–60%; **peripheral neuropathy** (polyneuropathy >mononeuritis multiplex), ↓ Hgb, ↓ plt, ↑ B-cell lymphoma risk, GI (5%; pain, HSM, ↑ LFTs). **"Meltzer's triad":** purpura, arthralgias, weakness in 25–30%.

- Dx studies
  - ✓ Cryoglobulins (keep blood *warmed to 37°C* en route to lab to avoid false ⊖, loss of RF and ↓↓ C3, C4). *Cryocrit* quantifies cryoprotein but not always indicative of disease activity. May see false ↑ in WBC or plt on automated CBC due to precipitation.
  - Type I: ✓ serum viscosity, symptomatic if ≥4.0 centipoise; complement normal.
  - Type II: ↓ **C4**, variable C3, ↑ ESR, ⊕ RF. ✓ **HCV, HBV, HIV** in mixed cryoglobulinemia. Bx: hyaline thrombi; small vessel leukocytoclastic vasculitis w/ mononuclear infiltrate.
- Treatment (*Blood* 2017;129:289; *J Inflamm Res* 2017;10:49): Rx underlying disorder. Heme malig → chemoradiation; HCV → antivirals; CTD → DMARD/steroids ± RTX. Type I: plasma exchange if hyperviscosity; steroids, alkylating agents, RTX, chemo. For mixed cryo, steroids and RTX; CYC or plasma exchange for major organ involvement.

Connective tissue disease–associated vasculitis

- Small-vessel vasculitis a/w **RA, SLE,** or **Sjögren's syndrome**
- Clinical sx: distal arteritis (digital ischemia, livedo reticularis, palpable purpura, cutaneous ulceration); visceral arteritis (pericarditis, mesenteric ischemia); peripheral neuropathy
- Dx studies: skin/sural nerve bx, EMG, angiography; ↓ C3, C4 in SLE; ⊕ RF, anti-CCP in RA
- Treatment: steroids, cyclophosphamide, MTX (other DMARDs)

Cutaneous leukocytoclastic angiitis (*Arthritis Rheumatol* 2018;70:171)

- Most common type of vasculitis; heterogeneous group of clinical syndromes due to **IC deposition** in capillaries, venules, and arterioles; includes ***hypersensitivity vasculitis***
- Etiol: **drugs** (PCN, ASA, amphetamines, levamisole, thiazides, chemicals, immunizations, etc.); **infection** (*Strep*, *Staph*, endocarditis, TB, hepatitis); **malignancy** (paraneoplastic)
- Clinical manifestations: abrupt onset of **palpable purpura** and **transient arthralgias** after exposure to the offending agent; visceral involvement rare but can be severe
- Dx studies: ↑ ESR, ↓ complement levels, eosinophilia; ✓ U/A; **skin biopsy** → leukocytoclastic vasculitis ***w/o IgA deposition*** in skin (to distinguish from IgA *vasculitis*); if etiology not clear, consider ANCA, cryoglobulins, hepatitis serologies, ANA, RF
- Treatment: withdrawal of offending agent ± rapid prednisone taper

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VARIABLE-VESSEL VASCULITIS

Behçet's syndrome (*Nat Rev Dis Primers* 2021;7:67)

- **Systemic vasculitis** affecting all vessel sizes, venous and arterial, a/w painful **oral and/or genital ulcers**
- Epi: usually young adults (25–35 y); ♂ = ♀, ↑ severity in ♂; a/w HLA-B51; ↑ prev on old Silk Road (Turkey, Middle East, Asia) w/ 5 vs. 370/100,000 in U.S. vs. Turkey
- Classification criteria (#1 + ≥2 others is 91% Se & 96% Sp; *Lancet* 1990;335:1078)
  1. Recurrent **oral aphthous ulceration** (≥3× in 1 y, usually 1st manifestation)
  2. Recurrent **genital ulceration** (labia in females, scrotum in males)
  3. **Eye lesions:** uveitis, scleritis, retinal vasculitis, optic neuritis; *may threaten vision*
  4. **Skin lesions:** pustules, papules, folliculitis, erythema nodosum (scarring)
  5. ⊕ pathergy test (prick forearm w/ sterile needle → pustule) (not sensitive in Caucasians)
- Other clinical manifestations: most recur but are not chronic
  Arthritis: mild, ± symmetric, nondestructive, involving knees and ankles

Neurologic: usually involvement of midbrain parenchyma; peripheral neuropathy rare

Vascular: superficial or deep vein thrombosis (25%); arterial stenosis, occlusion, and aneurysm can also occur; low incidence of thromboembolism

- Dx studies: ↑ ESR/CRP; ulcer swab to r/o HSV; ulcer bx nonspecific; ophtho eval if sx
- Treatment (*Ann Rheum Dis* 2018;77:808)

Mucocutaneous: Mild: **topical steroids**, **colchicine** (esp. for erythema nodosum), dapsone, apremilast (PDE-4 inhib) for oral ulcers and ? genital ulcers (*NEJM* 2019;381:1918). Severe: oral steroids, steroid-sparing agents.

Arthritis: NSAIDs, colchicine, steroids, steroid-sparing agents

Ocular: **topical and/or systemic steroids** ± steroid-sparing agents

Steroid-sparing: AZA, anti-TNF, CYC (large vessel and CNS ds), CsA, MTX, IFNα-2A

Venous thrombosis: steroids and anticoagulation (careful if aneurysm present)

AUTOINFLAMMATORY SYNDROMES

Immune-mediated diseases thought to result from overactivation of innate immunity

Familial Mediterranean fever (FMF) (*Ann Rhem Dis* 2016;75:644)

- Recessive *MEFV* mutations (activating pyrin, upstream of inflammasome)
- Febrile episodes for 1–3 d w/ abd pain (serositis, can mimic acute abdomen), pleurisy, lg joint monoarthritis/arthralgia, erysipelas-like skin lesions. Variable time between attacks.
- Epidemiology: ↑ prev in Armenians (1/500), Sephardic Jews, North Africans, Turks, Arabs; onset usually as child
- Risk of ESRD due to amyloidosis (AA), peritoneal adhesions, or infertility if untreated
- Colchicine effective prophylactic and ↓ amyloid; anti-IL1 is alternative (*NEJM* 2018;378:1908)

TNF receptor-associated periodic syndrome (TRAPS)

- TNF receptor mutations → febrile episodes q 5–6 wks each lasting >7 d w/ myalgia, abd pain/nausea, migratory rash, periorbital edema; risk of amyloidosis (AA)
- Epidemiology: autosomal dom. w/ variable penetr.; prev 1/million; onset usually as child
- Rx: steroid taper; NSAID alone if mild flare. If freq or severe flares, anti-IL1 (canakinumab) induction and maintenance (*NEJM* 2018;378:1908) appears more effective than anti-TNF

VEXAS (vacuoles, E**1** enzyme, X-linked, autoinflammatory, somatic) **syndrome**

- Acquired/mosaic *UBA1* (ubiquitylation enzyme on X chr) mutation in HSCs → myeloid + erythroid cytoplasmic vacuoles → heterogeneous but fever, cytopenias, chondritis, vasculitis, thrombosis, aveolitis, neutrophilic dermatoses common (*NEJM* 2020;383:2628)

- Epidemiology: ♂, mean onset age >60
- Steroids reduce symptoms but Rx otherwise unclear

Hemophagocytic lymphohistiocytosis (HLH)

- ↑↑ immune activity; failure to ↓ activated macrophages by NK cells/CTLs → ↑ cytokines (IFNλ, IL18) → macrophages phagocytize other blood cells, cytokine storm, organ failure
- Triggered by disruption of immune homeostasis: immune activation (infxn, autoimmune flare) or immunodeficiency; ~25% familial (mutations in perforin-mediated cytotoxicity)
- HLH 2/2 rheumatologic disease termed macrophage activation syndrome (MAS)
- Fever, ↑ spleen, cytopenias, ↑ TG, ↓ fibrinogen, ↑ LFTs, hemophagocytosis, ↓ NK cell activity, ↑ ferritin, ↑ soluble IL2R; H-score for HLH likelihood (*Arthritis Rheum* 2014;66:2613)
- Rx trigger (eg, rheum flare w steroids/biologics); if insufficient, HLH-04 protocol (etoposide + steroids ± CsA ± intrathecal MTX; BMT if genetic or relapsed/refractory; *Blood* 2017;130:2728), anti-IL1/IVIg/steroids (*Lancet Rheumatol* 2020:2:e358), or emapalumab (anti-IFNγ) (*NEJM* 2020;382:1811); high mortality if no Rx (*Blood* 2019;133:2465)

AMYLOIDOSIS

Deposition of misfolded proteins as insoluble fibrils (β-pleated sheets) in normal tissues

Classification of Amyloidosis				
Type	**%, Epi**	**Fibril**	**Etiologies**	**Main Organs**
AL (Primary)	55%; 10/million/y	Monoclonal light chain (λ>κ)	Plasma cell dyscrasia (MM, MGUS, WM)	**Renal, cardiac, GI, neuro, cutaneous,** hepatic, pulmonary
AA (Secondary)	3%; ↓ incid.	Serum amyloid A (SAA)	Inflam/chr infxn: RA, IBD, FMF / osteo, TB	**Renal, GI, hepatic,** neuro, cutaneous
Hereditary ATTR	↑V122I in Afr Am	Mutant TTR (mTTR)	TTR mutations, most low penetrance	**Neurologic, cardiac**
Wild type ATTR	14%; ♂ >> ♀	Normal (wt) TTR	a/w aging ("senile amyloid")	**Cardiac**, aorta, GI
Aβ$_2$M		β$_2$-microglobulin	Dialysis-assoc. (β$_2$m renally cleared)	Musculoskeletal
Localized		β-amyloid, Peptide horm.	Localized production and processing	Neurologic Endocrine

(*NEJM* 2007;356:2361; 2020;282:1567; *Circulation* 2020;142:e7; *Nat Rev Dis Primers* 2018;4:38)

Clinical Manifestations of Amyloidosis (*Lancet* 2016;387:2641; *JAMA* 2020;324:79)		
System	**Manifestations**	**Amyloid**
Renal	Proteinuria or nephrotic syndrome	AL, AA
Cardiac	Restrictive CMP (↓ EF late), thick walls but ↓ QRS amplitude, conduction abnl, AF, syncope	AL, mATTR, wt ATTR
GI	Diarrhea, malabsorption, protein loss; ulcers, hemorrhage, obstruction; macroglossia (dysphonia/dysphagia)	All systemic
Neuro	Periph neuropathy w/ painful paresthesia; carpal tunnel; Autonomic neuro → impotence, dysmotility, ↓ BP	mATTR, Aβ$_2$M, AL, localized
Skin	Waxy, nonpruritic papules; periorbital ecchymoses; "pinch purpura" = skin bleeds with minimal trauma	AL

Clinical Manifestations of Amyloidosis (*Lancet* 2016;387:2641; *JAMA* 2020;324:79)		
HSM	Hepatosplenomegaly w/o hepatic dysfnx or cytopenias	All systemic
Endo	Deposition with rare hormonal insufficiency	localized
MSK	Arthralgias and arthritis (especially shoulder)	AL, $A\beta_2M$
Pulm	Airway obstruction; pleural effusions	AL, AA
Heme	Factor X deficiency	AL

Diagnostic studies

- Biopsy (abd fat pad, rectal, etc.): apple-green birefring w/ **Congo red** (Se <85% Sp >90%)
- If suspect AL: SPEP & UPEP + immunofixation, free light chains, ± BM biopsy
- If suspect renal involvement: U/A for proteinuria
- If suspect CMP: ECG (↓ volt, conduction abnl), TTE (↓ longitudinal strain, LVH, valve & septal thickening, myocard. speckling), MRI (late gad. enhancement). R/o plasma cell dyscrasia; if ⊖ → (99m)Tc-pyrophosphate (PYP) SPECT for TTR. ± Cardiac bx.
- Mass spec of biopsy to ID fibril type. Genetic testing to distinguish wt vs. hereditary ATTR.

Treatment of Amyloidosis	
AL	Limited involvement: high-dose **melphalan → auto HSCT** (*NEJM* 2007;357:1083) Not HSCT candidate: dara-CyBorD [daratumumab + CYC + bortezomib + dexameth.] (*NEJM* 2021;385:46). [Low-dose melphalan + D] if Bor not tolerated. Relapse: dara, ixazomib, Bor, or lenalidomide (*Blood* 2020;136:2620)
AA	**Rx underlying disease.** Colchicine for FMF, esp. to ↓ renal dis. ? Anti-cytokine Rx (anakinra or tocilizumab) (*Clin Exp Rheumatol* 2015;33:46; *Amyloid* 2017;24:189).
ATTR	Stabilize TTR tetramers: diflunisal slows neuropathy; tafamidis ↑ QoL, ↓ CV hosp/mortality (*JAMA* 2013;310:2658; *NEJM* 2018;379:1007) ↓ hepatic mut TTR production: siRNA (patisiran) or anti-sense oligo (inotersen) -improve neuropathy (*NEJM* 2018;379:11 & 22); CRISPR in trials (*NEJM* 2021;385;493) Liver transplant can benefit some mATTR forms (*Muscle Nerve* 2013;47:157)

- Clearance of amyloid by Ab under study (*NEJM* 2015;373:1106; *Br J Haematol* 2020;189:228)
- Cardiac: diuretics; avoid CCB; ↑ dig toxicity risk (? amyloid binding); anticoag all AF

- Heart, kidney, and liver transplant may be considered in those w/ advanced disease
- Median survival: 5y AL (~6 m if CM); 11y AA; 4y wt ATTR & 2.5y *ATTR* V122I CM w/o Rx

CHANGE IN MENTAL STATUS

Consciousness/Arousal (description of patient & timing is most helpful)

- **Arousal:** spectrum from awake/alert → drowsy → stupor → coma. Terms vague & subjective, so most useful to describe response to increasing stimulation (eg, voice → noxious).
- **Coma:** lack of response to external stimuli. Degree formalized in Glasgow Coma Scale. Caused by focal lesions in brainstem (reticular activating system), thalamus, or diffuse dysfxn of both cerebral hemispheres. Mimics: locked-in synd., akinetic mutism, catatonia.
- **Delirium/acute confusional state:** altered attention & awareness, develops over hrs to days, often fluctuating, accompanied by cognitive Δs (eg, disorientation, memory loss, perceptual Δs); sometimes w/ sleep–wake dysregulation, autonomic Δs, emotionality
- **Dementia:** progressive cognitive impairment developing over mos to yrs; often affects memory, language, visuospatial, and executive function; attention often spared

Etiologies of Decreased Responsiveness	
1° **Neurologic** (*usually with focal signs*)	**Systemic** (*esp. in elderly or prior CNS injury*)

Etiologies of Decreased Responsiveness	
Vasc: ischemic stroke/TIA, ICH, VST, PRES, vasculitis, pituitary apoplexy Seizure: postictal, status, nonconvulsive Infxn: meningitis, encephalitis, abscess Trauma: TBI, concussion, diffuse axonal injury ↑ intracranial pressure: mass, edema, hydrocephalus, herniation Autoimmune/paraneoplastic enceph. Neurodeg: late-stage (eg, Alzheimer's) or rapidly progressive (eg, CJD)	Cardiac: global ischemia, HoTN, HTN enceph Pulmonary: ↓ P_aO_2, ↑ P_aCO_2 GI: liver failure, ↑ NH_3 Renal: uremia, dialysis, ↓ or ↑ Na, ↓ or ↑ Ca Heme: TTP/HUS, DIC, hyperviscosity Endo: ↓ glc, DKA/HHNS, hypothyr., Addisonian ID: pneumonia, UTI, endocarditis, sepsis Hypothermia & hyperthermia Meds: anticholin., anti-hist., psychotrop., digoxin Toxins/withdrawal: EtOH, sedative, opiate, CO Psychiatric: catatonia, serotonin synd., NMS

Initial evaluation

- **History** (witness & background *crucial*): tempo, premorbid sx (eg, focal neuro deficits, HA, infxn, pain, falls), medical conditions (eg, dementia, epilepsy, onc, cardiac, psych, infection/immune status), accompanied by head trauma, current meds (eg, sedatives, opioids, anticoag, anticonvulsants, immunosuppressants), drug/alcohol use
- **General exam:** *VS*, breathing pattern (eg, Cheyne-Stokes), tongue bite (seizure), *nuchal rigidity* (meningitis, SAH; *do not test* if c/f trauma/cervical spine fx), ecchymoses, rash, signs of head trauma (eg, Battle sign, raccoon eyes, hemotympanum, CSF rhinorrhea), asterixis, liver disease stigmata, embolic phenomena/endocarditis, s/s drug use
- **Neuro exam** (see below): perform off sedatives/paralytics if possible, look for focal deficits suggesting structural cause (eg, stroke, herniation), s/s of ↑ ICP (eg, HA, vomiting, papilledema, abducens nerve palsy, unilateral dilated pupil, ↑ BP/↓ HR, fixed downgaze)

Neuro Exam in Patients with Decreased Responsiveness	
Mental status	Arousal (behavioral response to ↑ intensity of stimulation, GCS)

Neuro Exam in Patients with Decreased Responsiveness	
Cranial nerves	Pupils: *pinpoint* → opiates, pontine lesion; *midposition & fixed* → midbrain lesion; *fixed & dilated* → severe anoxic injury, herniation, anti-cholin. Extraocular movements / vestibulo-ocular reflex tests: Oculocephalic maneuver ("doll's eyes"): nl = eyes move opposite head movement (do not test if possible cervical spine trauma) Vestibular (cold) caloric stimulation: in coma, nl = eyes move slowly to lavaged ear, then quickly away (*do not test w tymp memb perf)* Corneal reflex, facial grimace to nasal tickle Gag & cough reflexes (with ET tube manipulation if necessary)
Motor	Tone, spont movements, flexor/extensor posturing of arms/legs, strength
Sensory	Response to painful stimuli: purposeful vs. reflexive/posturing
Reflexes	Deep tendon reflexes, Babinski, "triple" flexion (ankle, knee, & hip flexion to noxious stimulation → not suggestive of intact cortical function)

Glasgow Coma Scale (sum points from each of 3 categories to calculate score)			
Eye Opening	**Best Verbal Response**	**Best Motor Response**	**Points**
		Follows commands	6
	Oriented	Localizes pain	5
Spontaneous	Confused	Withdraws from pain	4
To voice	Inappropriate words	Flexor posturing	3
To painful stimuli	Unintelligible sounds	Extensor posturing	2
None	None (intubated = 1T)	None	1

Initial treatment

- Empiric antibiotics if c/f CNS infection: vancomycin/CTX, consider acyclovir and ampicillin
- Immobilization of C-spine if concern for cervical trauma
- Thiamine 100 mg IV → dextrose 50 g IVP (this order to prevent exacerbation of Wernicke's)
- If opiates suspected: naloxone 0.01 mg/kg; if BDZ suspected, consider flumazenil 0.2 mg IV
- If concern for ↑ ICP ↑ herniation: ↑ head of bed; osmotherapy w/ mannitol or hypertonic saline; ↑ ventilation; dexamethasone for tumor edema; c/s neurosurgery (? decompress)

Diagnostic studies (*Lancet* 2014;384:2064)

- All patients: check fingerstick glucose, electrolytes, BUN/Cr, LFTs, CBC, tox screen, U/A
- *Based on clinical suspicion:*
  - Labs: NH_3, TSH, cort stim, B_{12}, ABG, HIV, ESR, ANA, TPO/anti-TG, BCx, drug levels
  - Imaging: head CT, then MRI; CTA if c/f stroke/SAH; radiographs to r/o C-spine fracture
  - Lumbar puncture to r/o meningitis, SAH, or noninfectious inflammation (eg, autoimmune)
  - EEG to evaluate for nonconvulsive seizures, toxic/metabolic encephalopathy

Further treatment of delirium (*NEJM* 2017;377:1456)

- Treat underlying acute illness, eliminate precipitating factors, & provide supportive care
- Address sensory & cognitive impairments (frequent reorientation, glasses/hearing aids, etc.)
- Decrease/prevent infection/restraints if possible, remove lines/catheters if unnecessary
- Promote good sleep: reduce noise & nighttime interventions; sedative med if necessary
- Meds: consider antipsychotics (but neither haloperidol nor ziprasidone ↓ delirium duration in ICU Pts; *NEJM* 2018;379:2506); avoid benzos except in EtOH withdrawal or seizures

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ANOXIC BRAIN INJURY (at risk if ≥5 min cerebral hypoxia)

Initial evaluation (*Circulation* 2010:S768)

- Neuro exam: arousal/verbal, eyes & other cranial nerves, motor response to pain
- Imaging: CT usually not informative w/in first day after arrest, but should be done prior to initiating targeted temp management if patient found down or has had head trauma

Targeted temperature management (*Circulation* 2015;132:2448)

- Indications: comatose (GCS <8) w/in 6 h after cardiac arrest (not isolated resp. arrest). Beneficial in both VT/VF and PEA/asystole.

Also consider 6–12 h post-arrest.

- Relative contraindic.: major head trauma, coagulopathy/bleeding, major surgery <14 d; CV instability no longer viewed as contraindication, but rather something to be managed.
- Target temp: 32–37.8°C × ≥24 h, rewarm, then maintain normothermia (37°C) for ~24 hrs.
- Initial studies showing benefit w/ 32–34°C, but subsequent studies showed ≈ outcomes for 36°C or 37.8°C vs. 33°C (*NEJM* 2013;369:2197 & 2021;384:2283)
- ∴ *prevent hyperthermia*, but need for hypothermia vs. normothermia unclear
- Method: ice packs to head/neck/torso; cooling blankets; cooling vest or endovascular catheter. Goal to achieve target temp <6 h. Pts should be sedated/paralyzed while cooled. Start rewarming 24 h after cooling initiated (rewarm ≤0.5°C per h).
- Can consider higher MAP goal of >70 mmHg
- Complications
  - Dysrhythmias (brady most common): if significant or hemodynamic instability → rewarm
  - Coagulopathy (can receive lytics, GP IIb/IIIa inhibitors, etc.); monitor PT & PTT
  - Infection: monitor surveillance blood cultures during cooling
  - Hyperglycemia during cooling, hypoglycemia w/ rewarming; stop insulin if glc <200 mg/dL
  - Hypokalemia during cooling, hyperkalemia w/ rewarming; keep K 4–5 mEq/L

Ongoing evaluation

- Neuro exam: daily focus on coma exam. No exam finding is reliable <24 h or on sedation. Should be off sedation for adequate time (depends on dose, duration, Pt's metabolism).
- Labs: daily CBC, PT/PTT, electrolytes. Serum neuron-specific enolase (NSE) on days 1–3.
- Imaging: noncontrast CT 24 h after arrest; if unrevealing, consider MRI around days 3–5
- EEG: consider in all to exclude seizures; greatest risk during rewarming. Unreactive background or abundant rhythmic or episodic discharges may convey poor prognosis.

- Somatosensory evoked potentials (SSEP): helpful for prediction of poor outcome if cortical responses are absent bilaterally; perform 48 h after arrest (72 h if cooled)

Prognosis (*Nat Rev Neuro* 2014;10:190)

- Prior to cooling era, poor prognosis at 72 h if absent pupillary & corneal reflexes and no motor response to pain; or absent SSEPs at 48 h. With cooling, unclear if prior measures as reliable. Overall ~12% survive to hosp. d/c; VT/VF 25-40%, PEA ~10%, asystole ~2%.
- Prognosis requires multifactorial assessment based on age, exam, comorbidities, ancillary data. Poor signs: absent brainstem reflexes, Rx-resistant myoclonus, EEG w/ absent background/reactivity, NSE >101, MRI w/ diffuse hypoxic injury. If doubt, err on more time.

SEIZURES

Definitions & clinical manifestations (*Epilepsia* 2017;58:522)

- **Seizure:** transient neurologic symptoms due to excessive synchronous neuronal activity; may be *provoked* by a reversible factor lowering the seizure threshold, or *unprovoked*
- **Epilepsy:** ≥2 unprovoked seizures occurring >24 h apart *or* 1 unprovoked seizure w/ ≥60% probability of further seizures over the next 10 y (see below for prognostication)
- **Generalized seizures** (involves brain diffusely)
  - *Tonic-clonic* (grand mal):
    - **Aura** (sec to mins): premonition with paresthesias, focal motor contractions, abnormal smells/tastes, fear, depersonalization, déjà vu, autonomic changes, automatisms
    - **Ictal period** (sec to mins): lateral gaze and head deviation, tonic contraction of muscles → intermittent relaxing and tensing of muscles, tongue biting, urinary incontinence, pooling of secretions
    - **Postictal period** (mins to h): slowly resolving period of confusion, disorientation, and lethargy. May be accompanied by focal neurologic deficits (Todd's paralysis).
  - *Absence* (petit mal): transient lapse of consciousness w/o loss of postural tone, usu pedi
  - *Myoclonic* (infantile spasms & juvenile myoclonic epilepsy): sudden, brief contraction
- **Focal seizures** (involves discrete brain area, often associated with a structural lesion)
  - *w/o impaired awareness:* focal motor/autonomic sx (formerly "simple partial seizure") or focal sensory/psychic symptoms (eg, aura)
  - *w/ impaired awareness:* dyscognitive features (formerly "complex partial seizure")

evolving to bilateral, convulsive seizure (formerly "secondarily generalized seizure")

- **Status epilepticus:** continuous convulsive seizure ≥5 min or >2 seizures w/o resolution of postictal encephalopathy; *life threatening*
- **Nonconvulsive status epilepticus:** alteration of awareness (ranging from confusion to coma) w/o motor manifestations of seizure; dx with EEG

Differential diagnosis

- **Syncope** (*Lancet Neurol* 2006;5:171)

Feature	Seizure	Syncope
Aura	Unusual behavior/automatisms	Diaphoresis, nausea, tunnel vision
Convulsions	Variable duration	Usually <10 sec
Postictal state	Yes; can be ≥30 min	None or short
Other clues	Tongue biting, incontinence	Skin pallor, clamminess

- **Nonepileptic seizure** (aka "psychogenic"): may see side-to-side head turning, asymmetric large-amplitude limb movements, hip thrusting, diffuse shaking w/o LOC, crying/talking during event; diagnosis requires spell capture on EEG with no EEG correlate
- Other: metabolic disorders (eg, alcoholic blackouts, hypoglycemia), migraine, TIA, transient global amnesia, narcolepsy (cataplexy), nonepileptic myoclonus, tics, asterixis

Etiologies of seizures (vary strongly by age)

- **Without focal lesion:** genetic predisposition to seizures or epilepsy syndrome; alcohol withdrawal, illicit drugs; meds (eg, β-lactams, bupropion, fluoroquinolones, tramadol, MNZ, meperidine, CsA); electrolyte (hyponatremia) & other metabolic (eg, uremia, liver failure, hypoglycemia); autoimmune encephalitis, idiopathic (~60%)
- **With focal lesion:** tumor, trauma, stroke, subdural hematomas, posterior reversible encephalopathy syndrome, mesial temporal sclerosis, abscess, focal cortical dysplasia

Clinical evaluation (*JAMA* 2016;316:2657)

- *History key in differentiating seizure from other causes of transient loss of consciousness*. Must talk to witnesses. Ask about prodrome, unusual behavior before spell, type & pattern of abnl movements incl. head turning & eye deviation (gaze preference usually *away* from seizure focus), loss of responsiveness.
- Recent events: illnesses/fevers, head trauma, sleep deprivation, stressors
- PMH: prior seizures or ⊕ FHx; prior CNS infection, stroke or head trauma; dementia
- Medications (new or noncompliance), alcohol and illicit drug use
- General physical exam should include the skin, looking for neuroectodermal disorders (eg, neurofibromatosis, tuberous sclerosis) that are a/w seizures
- Neurologic exam should look for focal abnormalities → underlying structural abnormality

Diagnostic studies (*Neurology* 2007;69:1996)

- Lab: full lytes, BUN, Cr, glc, LFTs, CK, lactate, tox screen, AED levels (except levetiracetam level rarely useful unless ? noncompliance), illicit drug screen, prolactin if drawn immediately after event (w/in 10–20 min)
- Routine EEG (~30 min): may help determine risk of seizure recurrence after 1st-time unprovoked seizure. Caveat: interictal EEG nl in 50% of Pts w/ epilepsy, and interictal epileptiform activity (spikes or sharp waves) seen in up to 2% of nl population; EEG w/in 24 h, sleep deprivation and repeated studies ↑ dx yield of EEG.
- Long-term EEG monitoring (hrs to days): if suspicion for nonconvulsive status or non-epileptic seizures; video monitoring may help w/ nonepileptic seizures
- MRI to r/o structural abnormalities; ↑ Se w/ fine coronal imaging of frontal & temporal lobes
- LP (if no space-occupying lesion on imaging): if suspect meningoencephalitis (eg, fever, ↑ WBC, nuchal rigidity), autoimmune encephalitis, and in *all* HIV ⊕ Pts

Treatment (*Neurology* 2015;84:1705; *Lancet* 2015;385:884)

- Treat any underlying precipitants, including CNS infections, intoxication, withdrawal, discontinuing provoking med, etc.
- Antiepileptic drug (AED) Rx usually reserved for Pts w/ ≥2 *unprovoked* seizures, single seizure w/ high risk of recurrence (see below), or underlying structural abnormality. *Provoked* seizures generally treated by addressing underlying cause; consider AED if status epilepticus on presentation, focal neuro exam, postictal Todd's paralysis.
- After 1st unprovoked sz, weigh risks of recurrence vs. AED. ↑ risk of recurrence if abnl EEG, MRI, or nocturnal sz. If EEG & MRI nl → 65% sz-free at 5 y (*Lancet Neurol* 2006;5:317).
- Immediate treatment w/ AED after 1st unprovoked seizure ↓ risk of recurrence over 2 y, but does not Δ long-term prognosis
- If AED Rx indicated, choice dependent on type of seizure, side effects, cost, mechanism of elimination (if hepatic or renal insufficiency), teratogenesis, and drug interactions
- Introduce gradually, monitor carefully
- Individual state laws mandate seizure-free duration before being allowed to drive

Antiepileptic Drugs and Side Effects

Medication	Avg Daily Dose	Common Side Effects	
		Systemic	*Neurologic (all: sedation)*
Carbamazepine	400–1600 mg	Aplastic anemia, ↓ WBC, rash, hepatotoxicity, ↓ Na	Diplopia, confusion, ataxia
Ethosuximide	500–1500 mg	Rash, BM suppression	Behavioral Δs
Gabapentin	900–3600 mg	GI upset, wt gain	Nystagmus, ataxia
Lacosamide	200–400 mg	Prolonged PR interval	Dizziness, diplopia
Lamotrigine	100–300 mg	Rash (Stevens-Johnson)	Tremor, HA, blurred vision, insomnia
Levetiracetam	1000–3000 mg	GI upset (rare)	Emotional lability
Oxcarbazepine	600–2400 mg	Hyponatremia, rash	Diplopia, dizziness
Phenobarbital	50–200 mg	Rash	Cognitive slowing
Phenytoin	200–400 mg	Gum hyperplasia	Dizziness, ataxia
Topiramate	100–400 mg	↓ wt, hypohidrosis, kidney stones, glaucoma, met acid	Cognitive slowing

Antiepileptic Drugs and Side Effects			
Valproic acid	500–2500 mg	Hepatotox, ↑ NH_3, ↑ wt, ↓ hair	Tremor
Zonisamide	200–600 mg	↓ wt, hypohidrosis, nephrolith	Cog slowing, fatigue

(*NEJM* 2008;359:166; *Lancet Neurol* 2011;10:446)

Status epilepticus (*Epilepsy Curr* 2016;16:48)

- ABCs: vital signs, oral airway or endotracheal intubation. Place Pt in semiprone position to ↓ risk of aspiration. Obtain IV access. Give thiamine, dextrose, IV normal saline.
- STAT POC glc, metabolic panel, CBC, tox screen, CK, lactate, AED levels, consider head CT, LP
- Start standing AED after loading dose.

Treatment of Status Epilepticus			
Time (min)	**Antiepileptic**	**Dosing Regimen**	**Typical Adult Dose**
5–20	**Lorazepam** or **Midazolam** or **Diazepam***	0.1 mg/kg IV>IM 0.2 mg/kg IM 0.2 mg/kg IV or 0.2–0.5 mg/kg PR	2–4 mg IV pushes, up to 8 mg Up to 10 mg x1 Up to 10 mg IV; up to 20 mg PR
20–40	**Phenytoin** or **Fosphenytoin** or **Valproate** or **Levetiracetam**	20 mg/kg 20 mg PE/kg 40 mg/kg 20–40 mg/kg	1.0–1.5 g IV (max 1.5 g) over 20 min 1.0–1.5 g PE IV over 5–10 min 1.0–1.5 g IV (max 3 g) over 5–10 min 2g IV (max 4.5 g) over 10–15 min
	Subsequent steps mandate intubation, EEG monitoring, and ICU admission		
40–60	General anesthesia with continuous midazolam, pentobarbital, or propofol		

PE, phenytoin equivalents. *Consider PR diazepam if no IV access and IM midazolam is contraindicated.

ALCOHOL WITHDRAWAL

Clinical manifestations

- Minor withdrawal: 6–48 h after last drink; mild anxiety, tremulousness, HA
- **Withdrawal seizures:** typically w/in 48 h after last drink; if unRx'd, 1/3 → delirium tremens
- **Alcoholic hallucinosis:** isolated hallucinations (typically visual) 12–48 h after last drink
- **Delirium tremens** (**DT**): disorientation, agitation, hallucinations, ↑ HR & BP, fever, diaphoresis; begins 48–96 h after last drink, lasts 5–7 d
- Consider other dx: CNS infxn or bleed, sz, drug O/D, co-ingestions, acute liver failure, GIB
- Ten-item scale (CIWA-Ar) used to assess and manage alcohol withdrawal (see Appendix)

Treatment (*J Addict Med* 2020;14:1)

- **Benzodiazepines**:
  - Drug: diazepam preferred (long-acting; ↓ risk of recurrent withdrawal), lorazepam (short-acting), chlordiazepoxide, oxazepam (no active metab; good if cirrhosis)
  - Dosing: typically start w/ diazepam 10–15 mg IV q10–15min (or lorazepam 2–4 mg IV q15–20min) until appropriate sedation achieved, then titrate to CIWA-Ar scale, evaluating q1–4 h until score <10 × 24 h, then q4–8 h × 24 h, and if stable, then q4 h
- **Phenobarbital:** adjunctive use in severe withdrawal may ↓ hospital stay, mech ventilation
- *Avoid* βB (mask sx)
- Mechanical restraints as needed until chemical sedation achieved
- Volume resuscitation as needed; thiamine *then* glc to prevent *Wernicke's encephalopathy* (ataxia, ophthalmoplegia, short-term memory loss); replete K, Mg, PO_4

- Ppx: if min sx or asx (ie, CIWA score <8) but prolonged heavy EtOH consumption or h/o withdrawal seizures or DTs → chlordiazepoxide 25–100 mg q6 h × 24 h, then taper

DIZZINESS

Differential diagnosis

- Includes a variety of sx. **Disequilibrium:** sense of imbalance, gait disturbance; **vertigo:** perception of spinning; **near syncope:** lightheadedness due to cerebral hypoperfusion.
- Dizziness can occur with PNS & CNS injury (vide infra) or in hematologic (eg, anemia), CV (eg, arrhythmia, orthostasis) & endocrine (eg, ↓ glc, thyroid) disorders, or due to meds
- Vertigo Ddx:
  - *Peripheral (inner ear/CNVIII)*
    - **BPPV:** dislodged canaliths in semicircular canal; episodic rotatory vertigo (<1 min episodes), triggered by changes in position; Rx: Epley/BBQ roll maneuver
    - **Meniere's disease:** ↑ endolymphatic pressure in inner ear; episodic rotatory vertigo (min-hrs), N/V, aural fullness, hearing loss, tinnitus; Rx: diuretics, ↓ salt
    - **Vestibular neuritis:** sudden-onset w/ gait ataxia; severe for 24–48 hrs followed by gradual improvement, often post-viral; w/ hearing loss = labyrinthitis
  - *Central (brainstem/cerebellum)*
    - **Posterior circulation stroke/TIA:** "5 Ds" of dizziness, diplopia, dysarthria, dysphagia, dystaxia; sudden onset (resolves after mins in TIA, persists in stroke)
    - **Other:** migraine, Chiari, epilepsy, MS, tumors, drugs/meds, concussion

Initial evaluation

- **Hx:** ask open-ended questions (description by Pt may be unreliable), pace of illness, episodic vs. chronic, meds, other sx of posterior circ including diplopia, dysarthria, ataxia

Exam	Peripheral Causes	Central Causes
Orthostatics	⊕ in orthostatic syncope	Typically absent

Eye movements	Nystagmus unidirectional if present, never vertical, suppressed w/ fixation	Nystagmus bidirectional, often vertical, not suppressed w/ fixation
Hearing	May be impaired in some peripheral causes of vertigo	Normal (rarely unilat. hearing loss in AICA-territory stroke)
Coord./gait	Normal	May reveal limb, trunk, gait ataxia

- **HINTS testing** (*Stroke* 2009;40:3504)
  - **H**ead **I**mpulse test: Pt fixates on examiner's nose during rapid passive head turn of ~10–20°; presence of "catch-up saccade" supports peripheral dysfunction to side of turn
  - **N**ystagmus (see table above)
  - **T**est of **S**kew: vertical refixation saccade on alternating eye cover supports central cause
- **Dix-Hallpike test:** Pt sitting → lying back w/ 45º head tilt; elicits rotatory nystagmus after delay of secs; fatigues if repeated; ⊕ suggests BPPV w/ affected ear down
- **Supine Roll test:** nystagmus elicited by head turn while patient supine; when ⊕ suggests BPPV w/ affected ear down (lateral canal, 8% of cases)
- **Studies:** orthostatic VS, basic labs, ECG; if concerning s/s HINTS → MRI brain
- **Rx:** Epley for BPP; vestib. PT; anti-hist., sedative or anti-emetic, steroid for vestib. neuritis

STROKE

ISCHEMIC STROKE

Etiologies

- Embolic: artery → artery, cardioembolic (~30% due to AF; *NEJM* 2014;370:2478), paradoxical
- Thrombotic: large vessel (atherosclerosis) vs. small vessel ("lacunar," lipohyalinosis of small arteries, often related to smoking, HTN, hyperlipidemia, & DM)
- Other: hypoperfusion, dissection, vasculopathy (vasculitis, radiation), vasospasm, hypercoag, hematologic (sickle cell, hyperviscosity), endocarditis, venous

Clinical manifestations

- Timing: embolic → sudden onset; thrombotic → may have stuttering course

Stroke Syndromes by Vascular Territory	
Artery	**Deficits**
ICA → Ophth	Amaurosis fugax (transient monocular blindness)
ACA	Hemiplegia (leg >arm), abulia, urinary incontinence, primitive reflexes
MCA	Hemiplegia (face & arm >leg); hemianesthesia; homonymous hemianopia Aphasia if dom. hemisphere: sup. div. → expressive; inf. div → receptive Apraxia & neglect if nondom. hemisphere.
PCA	Macular-sparing homonymous hemianopia; alexia w/o agraphia Thalamic syndromes with contralateral hemisensory disturbance
Vertebral, PICA	Wallenberg syndrome = numbness of ipsilateral face and contralateral limbs, diplopia, dysarthria, dysphagia, ipsilateral Horner's, hiccups

Stroke Syndromes by Vascular Territory	
Basilar	Pupillary Δs (midbrain=dilated, pons=pinpoint), long tract signs (quadriplegia, sensory loss), CN abnl, cerebellar dysfxn. Top of basilar → "locked in" synd.
Cerebellar	Vertigo, N/V, diplopia, dysarthria, nystagmus, ipsilateral limb ataxia
Lacunar (arterioles)	5 major syndromes: pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, dysarthria + clumsy hand, mixed sensorimotor

Transient ischemic attack (TIA)

- Sudden deficit due to cerebral ischemia; **no stroke on imaging;** most resolve in <1 h
- Ddx: seizure, migraine, hypoglycemia, amyloid spells, TGA, anxiety
- Risk of subsequent stroke ~2% by 1 wk (*NEJM* 2016;374:1533). Can stratify based on **ABCD$_2$: A**ge ≥60 y (+1); **B**P ≥140/90 (+1); **C**lin features: unilat. weak. (+2), speech impair. w/o weakness (+1); **D**uration ≥60 (+2) or 10–59 min (+1); **D**M (+1)

Physical exam

- General: murmurs, carotid & subclavian bruits, peripheral emboli, endocarditis stigmata
- Neurologic exam, NIH stroke scale (http://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf)

Acute workup

- Electrolytes, Cr (relevant for contrast); glc, CBC, coags (see exclusion criteria for lysis)
- Cardiac biomarkers, 12-lead ECG, tox screen
- **STAT CT** to r/o ICH prior to lysis (Se ICH ≈ MRI, CT faster). Early signs of stroke: hyperdense artery, loss of gray-white differentiation, edema, insular ribbon. CT can be nl initially, & not Se for small or brainstem stroke. CTA if possible endovascular Rx.

Acute treatment of ischemic stroke (*Stroke* 2019;50:e344; *JAMA* 2021;325:1088)

- **Thrombolysis (IV):** tPA 0.9 mg/kg (max 90 mg), w/ 10% as bolus over 1 min, rest over 1 h
  consider if onset w/in 4.5 h, Ø contraindic. (incl. current/prior ICH; head trauma or stroke w/in 3 mo; intracranial neoplasm, AVM

or aneurysm; recent intracranial/intraspinal surgery; active internal bleeding; noncompressible arterial puncture; ↑ BP; multilobar infarct; plt <100k, INR >1.7, on Xa inhib, PTT >40, glc <50)

0–3 h: 12% absolute ↑ in good neuro outcome (min/no disability), 5.8% absolute ↑ in ICH, trend toward 4% absolute ↓ mortality

3–4.5 h: 7.4% absolute ↑ in good neuro outcome, 1.8% absolute ↑ in ICH, Ø mortality benefit (nb, trial excluded patients with previous strokes + DM)

Data for tenecteplase (TNK), Rx up to 9 h or unknown timing, and for MRI imaging to guide Rx (*NEJM* 2018;378:1573 & 379:611; 2019;380:1795; *Lancet* 2020;396:1574)

- BP: lower to <185/110 to consider lysis; if lyse keep <180/105 × 24 h (consider IV labetalol or nicardipine), o/w permissive HTN unless >220/120 or sx; if sx HoTN consider vasopressors
- Initiate ASA w/in 24–48 h; avoid anticoagulation w/in 24 h of lysis; see below for long-term Rx
- Cerebral edema → herniation: 1–5 d post large MCA or cerebellar strokes, ↑ risk in young. Elevate HOB >30°; mannitol ± 23% NaCl. Hemicraniectomy ↓ mortality (*NEJM* 2014;370:1091). Neurosurgery consult in select MCA and all large cerebellar strokes.
- **Endovascular thrombectomy** if w/in 6 h of sx onset, pre mRS 0-1, occlusion in ICA or MCA, NIHSS ≥6, ASPECTS ≥6 (CT-based likelihood of recovery). May extend to 6–24 h if mismatch between infarct size and clinical deficits or stroke penumbra (*NEJM* 2018;378:11 & 708).

Workup to assess for etiology/modifiable risk factors

- Cardiac: monitor for AF (inPt and extended outPt); TTE to r/o thrombus/veg, w/ bubble study to r/o PFO/atrial septal aneurysm if suspect embolic
- Vessel imaging: CTA or MRA head/neck; carotid U/S w/ Doppler if contraindic to CTA/MRA
- Labs: lipids, HbA1c, TSH, homocysteine, Lp(a), hypercoag w/u (if <65 y or cryptogenic stroke; ideally drawn before starting anticoag), ESR/CRP, blood cx if s/s systemic infection
- **MRI** helpful if dx of stroke unclear (esp. post circ) or to define stroke subtype, age, exact size

DWI bright/*ADC* dark = earliest finding in acute ischemia (~w/in mins, up to days)

T2-FLAIR: hyperintense w/in about 6 hrs, persists for wks; *PWI* differentiates irreversibly infarcted core vs. viable penumbra; *T*1 *fat-sat* (neck vessels) if suspicious for dissection

Secondary stroke prevention (*Stroke* 2021;52:e364)

- **Antiplatelet therapy:** different agents likely have similar efficacy
  - **ASA** ↓ death & repeat stroke; equal to warfarin in nonembolic stroke (*NEJM* 2001;345:1444)
  - **clopidogrel:** marginally superior to ASA, slightly ↑ ICH (*Lancet* 1996;348:1329)
  - **$P2Y_{12}$** (clopi or ticag) + **ASA** (vs. ASA alone): Rx for 1–3 mos in *minor* strokes or TIA w/ high $ABCD^2$ → ↓ risk of ischemic stroke, ↑ ICH (*NEJM* 2018;379:215 & 2020;383:207). Rx for 90 d if stroke due to intracranial athero (*NEJM* 2011;365:993).
- **Anticoagulation (AC):** consider for AF (qv), cardiac/paradoxical emboli (except bacterial endocard); large extra-dural dissections; hypercoag; bridge to CEA in sx carotid stenosis
  - **Hold off on AC** in large strokes for ~2–4 wk given risk of hemorrhagic conversion
- Long-term SBP target <130/80 mmHg
- ↓ LDL-C (<< 70 mg/dL): ↓ recurrence w/ statin PCSK9i added to statin (*NEJM* 2017;376:1713)
- **Carotid revascularization** (*NEJM* 2013;369:1143)
  - **CEA** (*if* surgical morbidity & mortality ≤6%) indicated for:
    - *sx stenosis* 70–99% (benefit ↑ for males, >75 y, ≤2 wk from stroke) → 65% ↓ RR of repeat stroke, slight benefit for 50–69% stenosis (*NEJM* 1991;325:445; *Lancet* 2004;363:915)
    - *asx stenosis* 70–90%, <79 y: 50% ↓ RR of repeat stroke (*Lancet* 2010;376:1074)
  - **Stenting:** c/w CEA, ↑ periprocedural stroke (esp. in elderly) & ↓ MI (but many asx); subseq. ≈ rates of fatal or disabling stroke, but ↑ non-disabling stroke (*Lancet* 2021;398:1065)

Patent foramen ovale (PFO; in ~25% of population) (*NEJM* 2005;353:2361)

- ↑ stroke risk: ≥4 mm separation, R→L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- Risk scores assess likelihood stroke related to PFO. RoPE score: age (+1 for each decade <70); cortical stroke on imaging (+1); HTN, DM, h/o stroke/TIA, smoker (+1 for each *absent* risk factor). PASCAL classification also includes large shunt or atrial septal aneurysm.
- If PFO & stroke/TIA: no benefit of warfarin vs. ASA, but consider if high risk for or has DVT/PE
- Closure ↓ recurrence by ≥50%, with magnitude of benefit dependent on risk classification (RoPE ≥7 or PASCAL classification of possible or probable) (*JAMA* 2021;326:2277)

Intracranial Hemorrhage (ICH)

Classification by location

- Hemorrhagic strokes: intraparenchymal hemorrhage (IPH) & subarachnoid hemorrhage (SAH)
- Other ICH: epidural hematoma (EDH) & subdural hematoma (SDH)

Etiologies

- AVM, aneurysm, cerebral venous sinus thrombosis → IPH or SAH
- HTN (basal ganglia, cerebellum, brainstem), cerebral amyloid (lobar), tumor (esp. w/ melanoma, renal cell CA, chorio-CA, thyroid CA) → IPH
- Trauma → all locations (nb, IPH or SAH caused by trauma technically not a stroke)

Clinical manifestations (*Lancet* 2017;389:655 & *NEJM* 2017;377:257)

- ↓ consciousness, N/V, HA, progressive focal neurologic deficits
- *SAH:* thunderclap HA, onset w/ exertion; nuchal pain/rigidity; LOC. *EDH:* initial lucid interval.

Workup (*Acad Emerg Med* 2016;23:963)

- **STAT CT brain, angio (CT-A or conventional) if suspicious for vascular source**
- ? LP for xanthochromia if no evid of ICH on CT (although ⊖ LR 0.01) & suspicious for SAH
- Coags (PT, PTT, INR)

Management (*Crit Care Med* 2016;44:2251; *JAMA* 2019;321:1295)

- Reverse coagulopathy, INR <1.4. Plt >100k, no need for plt tfn if on antiplt Rx (? if ↑ ICH), DDAVP if uremic. 2–3 mo after recovers, can restart antiplt mono Rx (*Lancet* 2019;393:2013).
- BP control w/ art line, nicardipine or labetalol gtt. SBP goal <140 for 1st 24 h, then <160 (*NEJM* 2013;368:2355 & 2016;375:1033), though BP goals controversial (*NEJM* 2016;375:1033)
- SAH: endovasc coiling vs. surg clipping (depends on location, comorbid.; *Lancet* 2015;385:691) of aneurysm/AVM; nimodipine to ↓ risk of vasospasm (monitor w/ TCDs), seizure Ppx
- Surg evac: EDH; SDH if >1 cm or rapid ↑, Rx-resistant epilepsy; IPH: no obvious benefit
- Venous sinus thrombosis: start anticoagulation, manage ↑ ICP and seizures as needed

WEAKNESS & NEUROMUSCULAR DYSFUNCTION

Feature	Upper Motor Neuron	Lower Motor Neuron	Neuromuscular Junction	Myopathy
Distribution of weakness	UE Ext, LE Flex, hip abductors	Distal, segmental	Ocular, bulbar, proximal limb	Proximal, symmetric
Atrophy	None	Severe	None	Mild
Fasciculations	None	Common	None	None
Tone	↑	↓	Normal	Normal or ↓
Reflexes (DTRs)	↑	↓	Normal	Normal or ↓
Toes (Babinski)	Upgoing	Downgoing	Downgoing	Downgoing

PERIPHERAL NEUROPATHIES

Etiologies based on presentation

- **Mononeuropathy** (1 nerve): *acute* → trauma; *chronic* → entrapment, compression, DM, Lyme. Common: median nerve (carpal tunnel); ulnar (elbow or wrist); radial (spiral groove); com. peroneal (fibular head w/ leg crossing); lat. femoral cutan. (inguinal lig)
- **Mononeuropathy multiplex** (axonal loss of multiple, noncontig. nerves): vasculitic synd. (eg, PAN, EGPA, GPA, SLE, RA, Sjögren's, cryo, HCV), DM, Lyme, HIV, leprosy, hereditary neurop. w/ pressure palsies, infiltrative (sarcoid, lymphoma, leukemia)
- **Polyneuropathy** (multiple symmetric nerves, generally length dependent): 30% idiopathic;
  W/ autonomic features: DM, EtOH, paraneoplastic, B_{12} def, amyloid, chemo, 1° dysauto
  Painful (small fiber nerves): DM, EtOH, amyloid, chemo, sarcoid, heavy metals, porphyria
  Demyelinating. Acute: AIDP (Guillain-Barré), diphtheria. Subacute: meds (taxanes), paraneoplastic. Chronic: idiopathic,

DM, CIDP, anti-MAG, HIV, hypothyroidism, toxins, paraproteinemia, hereditary (eg, CMT).

Axonal. Acute: acute motor axonal neuropathy, porphyria, vasculitis, uremia, critical illness. Subacute: EtOH, sepsis, paraneoplastic, meds (cisplatin, paclitaxel, vincristine, INH, ddI, amio). Chronic: DM, uremia, lead, arsenic, HIV, paraproteinemia, B_{12} defic.

Clinical manifestations

- Weakness, fasciculations, cramps, numbness, dysesthesias (burning/tingling), allodynia
- ↑ Autonomic dysfxn (orthostasis, constipation, urinary retention, impotence, abnl sweating)
- Depressed or absent DTRs (may be normal in small fiber neuropathy)

Diagnostic studies

- Distal symmetric polyneuropathy: CBC, lytes, BUN/Cr, Hb_{A1C}, B_{12}, ESR, SPEP + IF
- EMG/NCS (often no change in 1st 10–14 d or in small-fiber neuropathy)
- Based on H&P: LFTs, celiac Abs, ANA, anti-Ro/La, HIV, Cu, Lyme, RPR, UA, UPEP+IF, ACE, ANCA, heavy metals, LP (AIDP/CIDP), cryo, paraneoplastic Abs, genetic testing. Autonomic testing/skin bx (small fiber), nerve bx (mononeuropathy multiplex), fat pad bx (amyloid).
- MRI if possible radiculopathy or plexopathy (after EMG)

Pharmacologic treatment of neuropathic pain (*Lancet Neurol* 2015;14:162)

- Gabapentin, pregabalin, TCAs (nortriptyline, amitriptyline), SNRIs (duloxetine, venlafaxine)
- 2nd line: tramadol, topicals (lido, capsaicin); 3rd line: nerve block, botulinum toxin A

Guillain-Barre Syndrome (GBS)

Definition & epidemiology (*Lancet* 2021;397:1214)

- AIDP (60–80%); acute motor axonal neuropathy (AMAN; 7–30%; a/w anti-GM1, anti-GD1a Abs; worse prognosis); Miller Fisher synd. (ophthalmoplegia & ataxia; a/w anti-GQ1b Ab)
- Incidence 1–2 per 100,000; most common acute/subacute paralysis
- Precipitants in 60%: viral illness (influenza, CMV, EBV, HIV, Zika, COVID-19), URI (*Mycoplasma*), gastroenteritis (*Campylobacter*), Lyme, immunizations, immune checkpoint inhibitors, surgery

Clinical manifestations (*Nat Rev Neurol* 2019;15:671)

- Pain (55–90%), distal sensory dysesthesias & numbness often 1st sx, back pain common
- Progressive symmetric paralysis in legs and arms over hrs to days; plateau in 1–4 wk
- Hypoactive then absent reflexes. <10% w/ reflexes on presentation, but all develop hypo/areflexia during course. Minority of AMAN w/ preserved reflexes throughout.
- Resp failure requiring mech vent occurs in 25%; autonomic instability & arrhythmias in 60%

Diagnostic studies (results may be normal in first several days)

- LP: albuminocytologic dissociation = ↑ protein w/o pleocytosis (<10 WBCs) seen in up to 64% of Pts. ↑ protein in ½ in 1st wk, ¾ by 3rd wk of sx. Unlikely to be GBS if WBC >50
- EMG/NCS: ↓ conduction velocity, conduction block, abnl F-waves; can be nl in 1st 2 wk
- FVC & NIF: to assess for risk of resp. failure (cannot rely on P_aO_2 or S_aO_2 alone)

Treatment

- **Plasma exchange or IVIg of equal efficacy** (*Neuro* 2012;78:1009); steroids not beneficial
- Supportive care with monitoring in ICU setting if rapid progression or resp. failure
- Watch for autonomic dysfunction: labile BP, dysrhythmias, urinary retention, ileus
- Erasmus GBS outcome score can help w/ prognostication (*Lancet Neurol* 2007;6:589). Most recover near baseline in 1 y; 3–5% mortality. Residual deficits: pain, fatigue.

MYASTHENIA GRAVIS (MG)

Definition & epidemiology (*Lancet Neurol* 2015;14:1023; *NEJM* 2016;375:2570)

- Autoimmune disorder with Ab against acetylcholine receptor (AChR, 80%), muscle-specific kinase (MusK, 4%), lipoprotein-related protein 4 (LRP4, 2%), or other NMJ proteins
- Prevalence: 150–250 per million; all ages, peak incidence 20s–30s (F), 60s–70s (M)
- 15% of AchR MG a/w thymoma; 30% of pts w/ thymoma develop AchR MG

Clinical manifestations

- Fluctuating weakness w/ *fatigability* (worse w/ repetitive use, relieved by rest)
- Cranial muscles involved early → 60% present initially w/ ocular sx (ptosis, diplopia); 15% confined to ocular sx; 15% w/ bulbar (difficulty chewing, dysarthria, dysphagia)
- Limb weakness proximal >distal; DTRs preserved; minimal/no atrophy
- MusK MG (F >>M): more severe limb/facial/bulbar weakness, muscle atrophy
- Exacerb. triggers: URI, surgery, preg/postpartum, meds (eg, Mg, AG, macrolides, FQ, procainamide, phenytoin, D-penicillamine, β-blocker). Prednisone can *worsen* sx acutely.
- Myasthenic crisis = sx exacerbation, risk of respiratory compromise
- Cholinergic crisis = excessive Rx with anticholinesterases: salivation, cramping, diarrhea

Diagnostic studies

- Bedside: ptosis, worse after >45 sec of sustained upgaze; improved with ice pack over eyes for 2–5 min (Se 77%, Sp 98%), ophthalmoplegia, weakness
- Neostigmine test: temporary ↑ strength; false ⊕ & ⊖ occur; premedicate w/ atropine
- EMG: ↓ response with repetitive nerve stimulation (vs. ↑ response in Lambert-Eaton)
- Anti-AChR Ab (Se 80%, 50% if ocular disease only, Sp >90%); muscle specific receptor tyrosine kinase (MuSK) Ab; AchR

modulating Ab
- CT or MRI of thorax to evaluate thymus (65% hyperplasia, 10% thymoma)

Treatment (*Neurology* 2021;96:114)
- Thymectomy if thymoma and in Ab ⊕ Pts w/o thymoma (*NEJM* 2016;375:511)
- Cholinesterase inhibitor (eg, pyridostigmine) is most rapid acting (30–60 min). Less effective for MusK MG. Side effects: cholinergic stim (brady, diarrhea, drooling).
- Immunosuppression: prednisone (benefit in wks; don't start during crisis) + steroid-sparing agent: AZA (benefit in 6–15 mo), MMF. Refractory: rituximab, MTZ, eculizumab.
- Myasthenic crisis: treat precipitant; d/c cholinesterase inhibitor if suspect cholinergic crisis. IVIg or plasmapheresis; if no response, high-dose glucocorticoids (monitor for initial worsening). ICU if rapid or severe (follow FVC, NIF).

MYOPATHIES

Etiologies (*Front Neurol* 2011;2:49)
- Hereditary: Duchenne, Becker, limb-girdle, myotonic, metabolic, mitochondrial
- Endocrine: hypothyroidism, hyperparathyroidism, Cushing syndrome
- Toxic: statins, fibrates, steroids, zidovudine, EtOH, cocaine, colchicine, penicillamine
- Infectious: HIV, HTLV-1, trichinosis, toxoplasmosis, COVID-19
- Inflammatory: polymyositis, dermatomyositis, inclusion body myositis, anti-HMGCR

Clinical manifestations
- Progressive or episodic weakness (not fatigue)
- Weakness most often symmetric, proximal >distal (stairs, rising from sitting, etc.)
- ↑ Myalgias (though not prominent or frequent), cramps, myotonia (impaired relaxation)
- May develop either pseudohypertrophy (dystrophies) or mild muscle atrophy

- Assoc. organ dysfxn: cardiac (arrhythmia, CHF), pulmonary (ILD), dysmorphic features

Diagnostic studies

- CK, aldolase, LDH, electrolytes, ALT/AST, PTH, TSH, ESR, HIV
- Autoantibodies: ANA, RF, anti-Jo1, antisynthetase, anti-Mi-2, anti-SRP, anti-HMGCR, 5TN1CA (in inclusion body myositis)
- EMG/NCS: low-amplitude, polyphasic units w/ early recruitment, ↑ fibrillation potentials
- Muscle biopsy, molecular genetic testing (where indicated)
- Age-appropriate cancer screening if polymyositis or dermatomyositis suspected

HEADACHE

Primary headache syndromes (*Cephalgia* 2018;38:1)

- **Tension-type:** bilateral, pressure-like pain of mild–mod intensity, not throbbing or aggravated by physical activity. A/w photophobia or phonophobia, not N/V. Freq a/w myofascial sensitivity in neck/head. Triggers: stress, sleep deprivation, dehydration, hunger. Episodic HA Rx: NSAIDs, acetaminophen (risk of med overuse HA); chronic HA Rx: TCAs.
- **Cluster HA** and other trigeminal autonomic cephalalgias (TACs) (*Continuum* 2018;24:1137)

  Characterized by unilateral headache a/w ipsilateral autonomic sx (rhinorrhea, red/tearing eye, miosis, ptosis, lid edema, sweating), subtypes differentiated by timing.

  Cluster: ♂ >♀, unilateral pain w/ autonomic sx & restlessness; attacks 15 min–3 h, up to 8/d (circadian). Rx: high-flow O_2 (12–15 L/min), sumatriptan. Ppx: CCB (verapamil).

  Paroxysmal hemicrania: similar to cluster, but ♀ >♂, attacks 2–30 min. Rx: indomethacin.

  Hemicrania continua: ♀ >♂, ice pick–like pain lasting >3 mo. Rx: indomethacin.

  Short-lasting unilateral neuralgiform HA (SUNA/SUNCT)*:* ♂ >♀, excruciating, stabbing, electrical pain, 5 sec–4 min, up to 200×/d. Rx: lamotrigine, gabapentin, topiramate.
- **Migraine:** *see below*

Secondary causes of headaches (*Neurology* 2019;92:134)

- Traumatic: post-concussion, SAH, SDH, postcraniotomy
- ↑ ICP: mass (tumor, abscess, vascular malformations, ICH), hydrocephalus, idiopathic intracranial hypertension (pseudotumor cerebri), altitude-associated cerebral edema
- ↓ ICP: post-LP headache, CSF leak/dural tear, overshunting

- Vascular: stroke (esp. posterior circ), dissection, vasculitis (incl. temporal arteritis), reversible cerebral vasoconstriction syndrome (RCVS), ICH, venous sinus thrombosis
- Meningeal irritation: meningitis, SAH
- Extracranial: sinusitis, TMJ syndrome, glaucoma
- Systemic: hypoxia (OSA), hypercapnia, dialysis, HTN, cardiac cephalalgia, hypoglycemia, ↓ TSH, pheo, medication overuse (analgesics), withdrawal (caffeine, opioids, estrogen)

Clinical evaluation (*Neurology* 2019;92:134 & *JAMA* 2021;325:1874)

- Hx: onset (sudden vs. gradual), quality, evolution (progressive), severity, location, duration, triggers, alleviating factors, positional, hormonal (menstruation), preceding trauma, assoc. sx (visual Δs, "floaters," N/V, photophobia, focal neuro sx), meds (new, analgesics), substance abuse (opioids, caffeine), personal/family hx of HA; neoplasm, preg
- General and neurologic exam (including funduscopic exam, visual fields). Headache diary.
- **Warning signs (should prompt neuroimaging)**
  - *Explosive onset* (vasc); "worst HA of life" (SAH, RCVS); *meningismus* (SAH, infxn)
  - *Positional:* lying >standing (↑ ICP); *N/V* (↑ ICP; migraines); coughing/bearing down (↑ ICP)
  - *Visual sx:* diplopia, blurring, ↓ acuity (GCA, glaucoma, ↑ ICP); *eye pain* (glaucoma, trigeminal autonomic cephalalgia, optic neuritis)
  - *Abnl exam* (struct. lesion, poss. in migraine); ↓ *consciousness*; systemic sx (fever)
  - *Age >65 y; immunosuppression* (CNS infections, PRES)
- Imaging: CT or MRI; consider CTA (beading in vasculitis/RCVS/vasospasm), CTV/MRV
- LP if ? SAH (✓ for xanthochromia), idiopathic intracranial HTN (✓opening press); image first!

MIGRAINE (*NEJM* 2017;377:553)

Definition & clinical manifestations (*Lancet* 2018;391:1315 & *Continuum* 2021;27:586)

- **Epidemiology:** affects 15% of women and 6% of men; onset usually by 30 y
- **Migraine w/o aura** (most common): ≥5 attacks lasting 4–72 h with both (a) N/V *or* photophobia & phonophobia, and (b) ≥2 of following: unilateral, pulsating, mod–severe intensity, or aggravated by routine activity
- **Migraine w/ aura:** ≥2 attacks w/: (a) aura defined as ≥1 fully reversible sx: visual Δs (flickering spots, visual loss), sensory sx (paresthesias, numbness), speech disturbance; *and* (b) unilateral progression of sx over ≥5 but ≤60 min; *and* (c) HA w/in 60 min of aura
- Aura may occur w/o HA ("acephalgic migraine"), must r/o TIA/stroke (typically rapid onset)
- If motor weakness, consider **sporadic or familial hemiplegic migraine**: aura of reversible motor weakness (up to 24 h), a/w CACNA1A, ATP1A2, or SCN1A mutations
- Precipitants: stress, foods (cheese, chocolate, MSG), fatigue, EtOH, menses, exercise

Treatment (*Lancet* 2021;397:1505 & *Continuum* 2021;27:613)

- Abortive Rx: 5-HT_1 agonists (triptans) effective if given early in migraine attack; contraindicated if motor aura, CAD, prior stroke. Also consider acetaminophen, caffeine, NSAIDs (ketorolac), steroids, Mg, metoclopramide, prochlorperazine, valproate, dihydroergotamine (caution if CAD, recent triptan use). *Avoid butalbital, opioids.*
- Prophylaxis: AEDs (topiramate, VPA), β-blockers (propranolol first-line), TCAs (amitriptyline), Mg, B2, botox, anti-CGRP, & receptor mAbs (*Lancet* 2021;397:51)

BACK AND SPINAL CORD DISEASE

Differential diagnosis of back pain

- **Musculoskeletal:** involving spine (vertebra, facet joints), paraspinal muscles & ligaments, sacroiliac joint, or hip joint. Spondylolisthesis, vertebral fx, OA, inflam. spondyloarthritis (qv), musculoligamentous "strain," myofascial pain syndrome, trochanteric bursitis.
- **Spinal cord** (myelopathy)**/nerve root** (radiculopathy):
  - Degenerative/traumatic: disc herniation, foraminal or lumbar stenosis, spondylolisthesis
  - Neoplastic: lung, breast, prostate, RCC, thyroid, colon, multiple myeloma, lymphoma
  - Infectious: osteomyelitis/discitis, epidural abscess, zoster, Lyme, CMV, HIV, spinal TB
  - Vascular: spinal cord ischemia, dural AV fistula
- **Referred pain from visceral disease:**
  - GI: PUD, cholelithiasis, pancreatitis, pancreatic cancer
  - GU: pyelonephritis, nephrolithiasis, uterine or ovarian cancer, salpingitis
  - Vascular: aortic dissection, leaking aortic aneurysm

Initial evaluation (*Lancet* 2017;389:736 & *Continuum* 2021;27:12)

- **History:** location, timing (acute/subacute/chronic), worse w/ Valsalva, radiation, trauma, wt loss, cancer, fever, immunocompromised, IVDU, neurologic sx, saddle anesthesia, Lhermitte phenomenon, bowel/bladder/sexual sx (retention, incontinence)
- **General physical exam:** local tenderness, ROM, signs of infection or malignancy; paraspinal tenderness or spasm in musculoskeletal strain
- **Signs of radiculopathy** (sharp/lancinating pain radiating into limb):
  - *Spurling sign* (cervical radiculopathy): radicular pain w/ downward force to extended & ipsilaterally rotated head; 30% Se, 93%

Sp

Straight leg raise (sciatica or lumbosacral radiculopathy): radicular pain at 30–70°; ipsilateral: 92% Se, 28% Sp; crossed (contralateral leg raised): 28% Se, 90% Sp

Patrick/FABER test (SI joint synd): severe pain on hip ext rotation; 70% Se, 100% Sp

Neurogenic claudication in lumbar stenosis (see table on next page)

- **Neuro exam:** full motor (incl. sphincter tone); gait; sensory (temp/pain, position, vibration; ↑ perineal; ? dermatomal); reflexes incl. bulbocavernous, anal wink (S4), cremasteric (L2)
- **Red flags:** acute change (pain, weakness), upper motor neuron signs (hyperreflexia, upgoing toes), cauda equina or conus medullaris syndromes (saddle anesthesia, bowel/bladder or sexual dysfunction, reduced rectal tone, loss of sacral reflexes), dyspnea when flat (C3–C5), pain at rest or at night
- **Laboratory** (depending on suspicion): CBC w/ diff, ESR/CRP, Ca, PO_4, CSF, BCx
- **Neuroimaging:** low yield if nonradiating pain, high false ⊕ rate (incidental spondylosis); depending on suspicion: X-rays, CT or CT myelography, MRI, bone scan
- **EMG/NCS:** may be useful to distinguish root/plexopathies from peripheral neuropathies

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Spinal Cord Compression

Clinical features (*Continuum* 2021;27:163)

- Etiologies: **tumor** (vertebral mets, intradural meningioma/neurofibroma), **epidural abscess/ hematoma**, vascular malformation (dural AV fistula), degen. dis. (spondylosis), trauma
- Acute: flaccid paraparesis and absent reflexes (“spinal shock”)
- Subacute–chronic: spastic paraparesis and hyperreflexia (upgoing toes ± ankle clonus)
- Posterior column dysfunction in legs (loss of vibratory and/or proprioceptive sense)

• Sensory loss below level of lesion (truncal level ↑ bilateral leg sx is clue for cord process)

Evaluation & treatment

• Empiric spine immobilization (collar, board) for all trauma patients
• STAT MRI (at and above clinical spinal level, with gadolinium) or CT myelogram
• Emergent neurosurgical and/or neurology consultation. Urgent radiation therapy ↑ surgery for compression if due to metastatic disease (*Lancet Oncol* 2017;18:e720).
• Empiric broad-spectrum antibiotics ± surgery if c/f epidural abscess
• High-dose steroids depending on cause:
  Tumor: dexamethasone 16 mg/d IV (usually 4 mg q6 h) with slow taper over wks
  Trauma: methylprednisolone 30 mg/kg IV over 15 min then 5.4 mg/kg/h × 24 h (if started w/in 3 h of injury) or × 48 h (if started 3–8 h after injury) (*Cochrane* 2012:CD001046)

NERVE ROOT COMPRESSION

Clinical features (*NEJM* 2015;372:1240 & *Continuum* 2021;27:163)

• Radicular pain aggravated by activity (esp. bending, straining, coughing), relieved by lying
• Sciatica = radicular pain radiating from buttocks down lateral aspect of leg, often to knee or lateral calf ± numbness and paresthesias radiating to lateral foot. Caused by compression of nerve roots, plexus, or sciatic nerve.

Pathophysiology

• <65 y: 90% from disc herniation. ≥65 y also w/ more degenerative contributors: ligamentous hypertrophy, osteophyte formation, facet arthropathy, neural foraminal narrowing
• Spinal stenosis: central canal narrowing → root compression via direct impingement, CSF flow obstruction, vascular compromise

Disc Herniation: Cervical and Lumbar Radiculopathy					
Disc	**Root**	**Pain/Paresthesias**	**Sensory Loss**	**Motor Loss**	**Reflex Loss**
C4–C5	C5	Neck, shoulder, upper arm	Shoulder, lateral arm	Deltoid, biceps, infraspinatus	Biceps
C5–C6	C6	Neck, shoulder, lat. arm, radial forearm, thumb & index finger	Radial forearm, thumb, & index finger	Biceps brachioradialis	Biceps, brachio-radialis, supinator
C6–C7	C7	Neck, lat. arm, ring & index fingers	Index & middle fingers	Triceps, extensor carpi ulnaris	Triceps, supinator
C7–T1	C8	Ulnar forearm and hand	Ulnar half of ring finger, little finger	Intrinsic hand muscles, flexor dig profundus	Finger flexion
L3–L4	L4	Anterior thigh, inner shin	Anteromedial lower leg, inner foot	Quadriceps	Patella
L4–L5	L5	Lat. thigh & calf, dorsum of foot, great toe	Lat. calf & great toe	Foot dorsiflex., invers. & evers., toe extension	Medial hamstring
L5–S1	S1	Back of thigh, lateral posterior calf, lat. foot	Lateral foot & toes, sole of foot	Gastrocnemius	Achilles

Nb, lumbar disc protrusion tends to compress the nerve root that exits 1 vertebral level below the protrusion.

Neurogenic vs. Vascular Claudication		
Features	**Neurogenic Claudication**	**Vascular Claudication**
Cause	Lumbar spinal stenosis (with nerve root compression)	Peripheral artery disease (with limb ischemia)
Pain	Radicular back/buttock pain Radiating down legs	Cramping leg pain Mostly in calves; radiating up legs
Worse with	Walking & standing Hyperextension/lying prone	Walking Biking
Better with	Bending forward, sitting	Rest (standing or sitting)
Other sx	Numbness/paresthesias	Pale, cool extremity

Neurogenic vs. Vascular Claudication		
Exam	± Focal weakness, ↓ reflexes ↓ Lumbar extension Preserved pulses	Diminished/absent pulses (dorsalis pedis/posterior tibialis) Pallor
Diagnostic studies	MRI lumbar spine CT myelogram (if no MRI) EMG/NCS	Arterial Doppler studies Ankle-brachial index (ABI) Arteriography
Treatment	PT (flexion exercise), NSAIDs, epidural steroid injections (ESI) Surgery (if other Rx fails)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient.

Evaluation & treatment of nerve root compression (*NEJM* 2016;374:1763)

- MRI if sx not improved after 6 wk of conservative tx; if nondiagnostic, consider EMG/NCS
- Conservative: avoid bending/lifting; soft collar (cervical radiculopathy); NSAIDs; muscle relaxants; lidocaine patch/ointment; Rx neuropathic pain (see “Peripheral Neuropathies”); physical/occup therapy. Insufficient evidence for oral steroids.
- Avoid opiates when possible; risks outweigh benefits in noncancerous back pain
- Spinal epidural steroid injections (ESI): limited short-term relief of refractory radicular pain
- Surgery: cord compression or cauda equina syndrome; progressive motor dysfunction/EMG/NCS pathologic findings; bowel/bladder dysfunction; intractable pain w/ failure to respond to conservative Rx after 3 mo

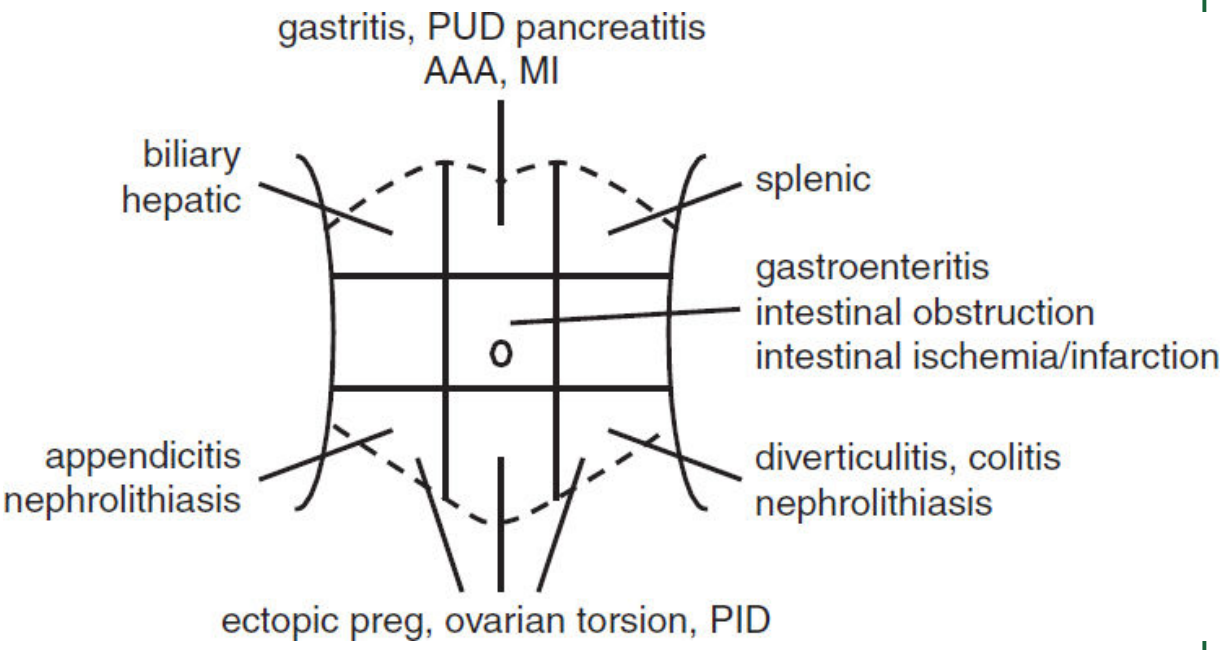
SURGICAL ISSUES

ABDOMINAL PAIN

Visceral Pain		
Anatomic Division	**Viscera**	**Area to Which Pain Referred**
Foregut	Esophagus & duodenum	Epigastrium
Midgut	Jejunum to mid-transverse colon	Umbilicus
Hindgut	Mid-transverse colon to rectum	Hypogastrium

Pain due to pancreatitis and nephrolithiasis commonly radiates to the back

Figure 10-1 Etiologies of abdominal pain based on location



Initial evaluation

- History: onset of pain, location, exacerbating/relieving factors
- Assoc. sx: fevers/chills, N/V, Δ in bowel habits (diarrhea/constipation, stool diam. or color, hematochezia, melena), flatus, jaundice, Δ in urine color, Δ in wt, menstrual hx in women

- PMHx: previous incisions or abdominal surgeries; Ob/Gyn hx
- Exam: VS; general posture of Pt; comprehensive abdominal exam looking for signs of peritonitis, which include rebound tenderness and involuntary guarding, abdominal wall rigidity, pain w/ percussion/minimal palpation; presence of hernias; rectal/pelvic
- Labs: CBC, electrolytes, LFTs, amylase/lipase, pregnancy test
- Imaging: depends on suspected etiology, may include RUQ U/S for biliary/hepatic disease, KUB for intestinal obstruction, CT for pancreatitis or intestinal disease. Do not delay resuscitation or surgical consultation for ill Pt while waiting for imaging.

Acute Abdomen

Definition
- Acute onset abdominal pain that portends need for urgent surgery

Etiologies
- Perforated viscus → peritonitis (perforated ulcer, complicated diverticulitis, trauma)
- Intraperitoneal or retroperitoneal bleed (also see "Acute Aortic Syndromes")
- Bowel obstruction (adhesions from previous surgeries, malignancies, hernias, volvulus)
- Acute mesenteric ischemia (esp. if AF, low flow states, "pain out of proportion to exam")
- Mimics: severe pancreatitis can resemble peritonitis; renal colic causes severe abdominal pain but not abdominal rigidity

Initial evaluation
- H&P as above
- Labs as above plus: PT/INR, PTT, lactate, type & screen (crossmatch if active bleeding)
- Imaging: upright CXR/KUB; if stable, CT A/P w/ IV contrast (IV/PO if suspect obstruction)

Initial management
- Immediate surgical consultation for suspected acute abdomen
- NPO, start IV fluids (NS or LR), Foley, NGT placement if obstruction suspected

• Broad spectrum abx if perforation suspected

EXTREMITY EMERGENCIES

Acute limb ischemia (see "Peripheral Artery Disease" for details)
• Definition: sudden ↓ in perfusion causing threat to limb viability
• Eval: detailed vascular exam (incl. pulses & Doppler signals, motor/sensory function); CTA
• Initial management: anticoag for embolism/thrombosis (heparin dose 80 U/kg bolus, then 18 U/kg drip); immediate surgical consultation

Compartment syndrome (*Clin Orthop Relat Res* 2010;468:940)
• Definition: ↑ intracompartmental pressure w/ compressive closure of venules → ↑ hydrostatic force resulting in further increases in compartment pressure
• Etiologies: orthopedic (fracture), vascular (ischemia-reperfusion), iatrogenic (eg, vascular injury in anticoagulated Pt), soft-tissue injury (eg, prolonged limb compression)
• Clinical manifestations: pain espec. on passive movement, swollen/tense compartment, paraesthesia, pallor, pulselessness, paralysis (late)
• Evaluation: surgical evaluation of compartment pressures; intracompartment pressure >30 or difference between diastolic & intracompartment pressure of >10–30 is diagnostic
• Treatment: fasciotomy

SURGICAL TUBES, DRAINS, WOUNDS

Tracheostomy (*Otolaryngol Head Neck Surg* 2013;148:6)
• Typically a cuffed tube, which creates a tight seal to facilitate ventilation throughout tube
• Speaking valve (eg, Passy-Muir): 1-way valve that allows inhalation through tube, but exhalation around tube through vocal cords (nb, cuff should not be inflated)
• 1st routine tube Δ for *percutaneously* placed tubes should be ~10 d postop; *surgically* placed tubes can be Δ'd >5 d postop; first Δ should be overseen by experienced person
• Accidental dislodgement: intubate from above (if airway/vent nec & anatomically possible)

w/in 7 d of placement: emergent surgical consultation
>7 d after placement: replace with a similar size tube or smaller

Chest tubes (*Eur J Cardiothorac Surg* 2011;40:291)

- Inserted for PTX, chest trauma or after thoracic surg for drainage of air/fluid from thoracic cavity. Range from small (8–10 Fr for spont. PTX) to large (28–32 Fr after pulm. resections)
- Connected to 3-chamber chest drainage system:
  - 1st: collection chamber for pleural fluid
  - 2nd: water seal chamber used to allow air to exit pleural space on exhalation and prevent air from entering on inhalation
  - 3rd: suction control chamber which regulates suction transmitted to pleural space
- Monitor for output and presence of air leak (indicated by bubbling in *water seal chamber*)
- Removal determined by overall daily outputs and absence of air leak
- If accidentally removed or dislodged, tube should be completely removed and an occlusive dressing (eg, 4 × 4 covered w/ Tegaderm or silk tape) should be placed *rapidly* over site. CXR STAT; new tube should be placed if persistent PTX.

Gastrostomy/jejunostomy tubes (*Paediatr Child Health* 2011;16:281)

- Placed for tube feedings, hydration, and delivery of medications
- Should not be removed for ≥6–8 wk to allow establishment of mature gastrocutaneous tract
- Obstructed tubes can be cleared by flushing with agents such as carbonated water, meat tenderizer, & pancreatic enzymes. ↓ obstruction by flushing before & after meds and flushing q4–6h when receiving continuous feeds.
- Inadvertent removal: place Foley catheter of similar size or smaller into tract *immediately* to prevent stoma from closing. Tube then replaced and confirmed via fluoro study.

Suture/staple removal

- Should be done in consultation w/ surgical team; timing depends on location of wound
- *Should not be removed if there is evidence of wound separation during removal!*
- After removal, wound should be reapproximated w/ Steri-Strips

Decubitus ulcers (*J Wound Ostomy Continence Nurs* 2012;39:3)

- Sores in dependent areas exposed to repeated pressure (commonly sacrum, heels)
- Risk factors: immobility, poor nutritional status
- Stage I (non-blanchable erythema); Stage II (partial thickness); Stage III (full-thickness skin loss); Stage IV (full-thickness tissue loss)
- Treatment: offload area, air mattress, pillows and/or support boots, nutritional support
- Surgical consultation for debridement of ulcers with necrotic or infected tissue, may require plastic surgical reconstruction for advanced ulcers once clean

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MAXIMIZING A SURGICAL CONSULT

- For ill Pt, call surgical consult early, do not wait for labs & imaging results
- If potential surgical emergency, make Pt NPO, start IVF, ✓ coags, type, & screen
- Have appropriate-level MD who knows & has examined Pt call consult

OB/GYN ISSUES

VAGINAL BLEEDING

Bleeding from lower (vulva, vagina, cervix) or upper genital tract (uterus)

Etiologies

- Premenopausal
  - Not pregnant: menses, lower tract (trauma, STI, cervical dysplasia/cancer), & abnormal uterine bleeding (polyp, adenomyosis, leiomyoma, hyperplasia/cancer, coagulopathy, ovulatory dysfunction, endometrial, & iatrogenic)
  - Pregnant
    - 1st trimester: threatened abortion, spont. abortion (missed, incomplete, or complete), ectopic preg, molar preg (partial/complete hydatidiform mole)
    - 2nd or 3rd trimester: preterm labor/labor, placenta previa, placental abruption
- Postmenopausal: atrophy, polyp, leiomyoma, endometrial hyperplasia/cancer

History & exam

- Age, menopausal status, gestational age if preg, volume & duration of current bleeding
- If premenopausal: menstrual hx including age of onset, interval between & duration of menses, any assoc. sx & LMP to assess timing of menstrual cycle
- Past Ob/Gyn hx: incl. any structural abnl, STI, & contraception
- Health maint.: Pap smear, HPV screening, domestic violence, anticoag/antiplt meds
- General physical & abdominal exam (incl. tenderness, masses)
- Pelvic exam: external (quantity of bleeding seen on vulva, any lesions, any trauma), speculum exam (quantity of bleeding, cervical

os open/close; & if open, dilation, any polyps), & bimanual exam (cervical dilation, uterine size/tenderness, adnexal mass/tenderness)

Laboratory evaluation & imaging

- Urine (rapid test) & serum preg test (βhCG), Hct/hemoglobin
- Pelvic U/S: visualize leiomyoma & if preg, intrauterine preg & placental position to r/o placenta previa/abruption
- If preg & intrauterine preg not seen, *must r/o ectopic as life-threatening dx* (βHCG > discrim. zone → ? ectopic; if βHCG <discrim. zone → follow βHCG) (*JAMA* 2013;309:1722)

VAGINAL DISCHARGE

Fluid or mucus from vagina, cervix, or uterus

Etiologies

- Infectious: bacterial vaginosis, candida vulvovaginitis, trichomoniasis
- Noninfectious: physiologic (in preg/non-preg), rupture of membranes, foreign-body rxn

Initial evaluation

- Age, LMP, gestational age if preg or menopausal status
- Discharge quantity, color, consistency, odor, assoc. sx (itchiness, redness, abd/pelvic pain)
- Past Gyn hx: incl. STI and contraception usage (condoms ↓ STI risk)
- Tampon or condom use as risk factors for retained foreign body
- Pelvic exam: external (quantity & quality of discharge on vulva, any lesions), speculum (discharge, appearance of cervix), bimanual (cervical motion tenderness)
- Laboratory: pH of discharge, microscopy (saline & KOH wet mounts), urine preg test

Treatment

- Bacterial vaginosis: oral/vaginal metronidazole or clindamycin
- Candida vulvovaginitis: oral/topical antimycotic medications
- Trichomoniasis: oral metronidazole

ADNEXAL MASS IN NON-PREGNANT WOMAN

Mass arising from ovary, fallopian tube, or surrounding connective tissue

Etiologies

- Ovarian: functional cyst (follicular/corpus luteum), hemorrhagic cyst, endometriomas, ovarian torsion, tubo-ovarian abscess, benign & malignant ovarian tumors
- Fallopian tube: paratubal cyst, hydrosalpinx, ovarian torsion, tubo-ovarian abscess

Initial evaluation

- LMP/menopausal status, assoc. sx of abd/pelvic pain, FHx of gyn cancers
- Abd exam (distension, tenderness, masses), bimanual (uterine or adnexal masses)
- Preg test if premenopausal (if ⊕, then mass likely preg), CA-125 if postmenopausal
- Pelvic U/S (even if mass 1st identified on CT, because U/S is best modality), U/S appearance of mass important factor to determine risk of malignancy

OPHTHALMIC ISSUES

INITIAL EVALUATION

- Ocular symptom: onset (sudden or progressive) & duration of sx; unilateral vs. bilateral; pain; photophobia; discharge; Δ in near (eg, book) or far (eg, TV across room) vision
- Preexisting ocular conditions, eye meds (incl any Δs), recent h/o ocular surgery, trauma
- Ocular exam: vision (✓ with Pt's correction [glasses/contacts]) w/ each eye; pupillary exam; EOM; confrontation visual fields (important if suspect CNS problem)
- Overall: VS, immunocomp., s/s of infxn, h/o malig, CNS issues, Δ in meds, CBC, coags

COMMON VISUAL SYMPTOMS

- **Fluctuation in vision (ie, blurry):** med-induced refractive error (eg, systemic steroids, chemoRx), hyperglycemia, dry eye (common). **Visual defect** may p/w "blurred vision." Bilateral: glaucoma (common), homonymous contral. CNS lesion; bitemporal: pituitary, toxic/nutritional. Unilateral: ipsilateral orbital, retinal, or optic nerve lesion.
- **Red eye:**
  - Bilateral: viral conjunct. (starts in 1 eye; also w/ lid swelling, discharge); chronic inflammation (dry eyes, rosacea, autoimmune disease)
  - Unilateral: subconj. hemorrhage, infxn, or inflam (eg, episcleritis, iritis, uveitis, scleritis); acute angle closure (qv). Scleritis & acute angle closure p/w severe pain, H/A, nausea.
- **Double vision (diplopia):** fixed double vision w/ ophthalmoplegia from orbital process or cranial nerve palsy (III, IV, VI). Transient "diplopia" due to fatigue or sedation.

- **Flashing lights/floaters:** vitreous detach. (common, benign); retinal detach. (unilateral visual field defect; urgent ophthalmology consult); hemorrhage; intraocular lymphoma

ACUTE VISUAL CHANGES

Etiologies of Acute Vision Loss (italics indicates a/w pain)		
	Unilateral	**Bilateral**
Transient (<24 h, often <1 h)	Ret. art. embolism, impending retinal artery or vein occlusion (amaurosis fugax), vasospasm, carotid disease	Ocular surface dis. (dry eye), bilat. carotid dis., TIA, migraine, high ICP (papilledema)
Prolonged (>24 h)	Retinal art/vein occl, retinal detach., retina/vitreous heme, retinitis, ant. optic neurop./*corneal ulcer, GCA, acute angle closure glaucoma*	Visual cortex stroke, post. ischemic neuropathy (profound hypotension during surgery), post. reversible enceph. synd., *GCA*

COMMON OCULAR CONDITIONS (FRONT TO BACK)

- **Orbit: orbital cellulitis** (fever, proptosis, ↓ EOM; *emergent abx, scan, & referral*)
- **Lids:** hordeolum or chalazion (stye); preseptal cellulitis; **ptosis** (age; Horner's; **CN III palsy:** EOM restricted in all directions except laterally (eye is "down & out"), a/w ptosis & mydriasis, seen w/ uncal herniation, aneurysm of post com art., GCA, HTN, DM); incomplete lid closure (**CN 7th palsy**)
- **Conjunctiva:** conjunctivitis (**red eye**); subconj. hemorrhage (HTN, blood thinner); ocular surface disease (dry eyes); episcleritis/scleritis (deep vessels of sclera)
- **Cornea: contact lens-related ulcer;** herpetic keratitis/scarring/neurotropic ulcers **(CN V paresis);** pterygium; keratoconus; corneal dystrophy
- **Ant. chamber:** iritis (inflam. cells); hyphema (blood, post trauma); hypopyon (inflam./infxn)
- **Pupil:** Anisocoria (physiologic asymmetry); Horner's, CN III
- **Lens:** cataract (age, trauma, medication, radiation, congenital); post cataract surgery infxn
- **Vitreous/Retina/Macula:** diabetic retinopathy; macular degen; retinal detachment; retinal ± vitreous hemorrhage; retinitis

(infectious)

- **Optic nerve (CN II):** ischemic neuropathy p/w acute unilat. visual loss, altitudinal field defect; a/w GCA; nonarteritic a/w HTN, hyperchol., DM, thrombophilia. Optic neuritis: often p/w unilat. central scotoma, pain w/ EOM, ↑ visual loss over days; a/w demyelinating disease (eg, MS), also seen w/ sarcoidosis & CTD. Optic neuropathy (glaucoma common).

OCULAR EMERGENCIES

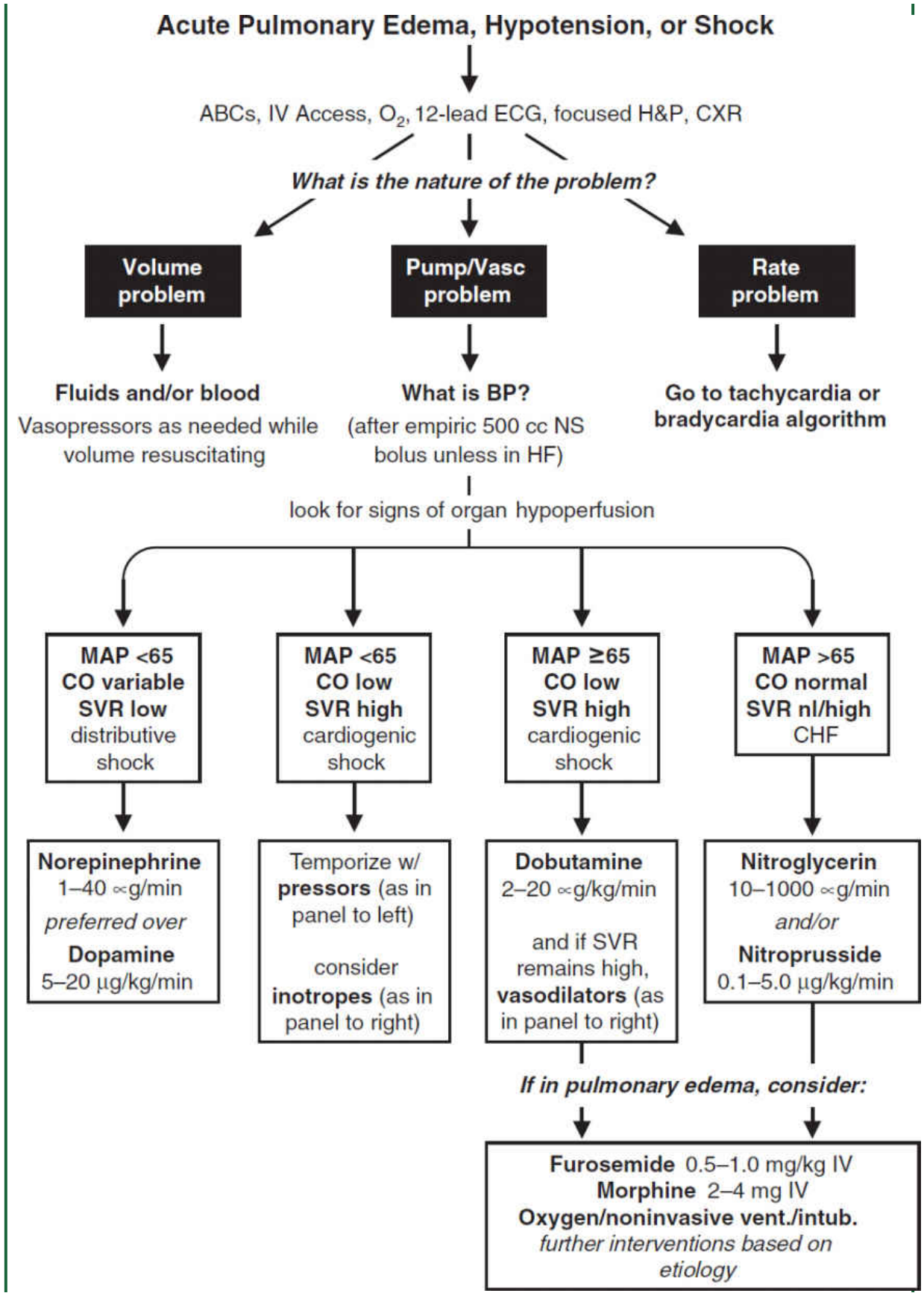
- **Chemical splash:** alkali worse than acid; immediate eye flush; pH 7.3–7.4 normal
- **Acute angle closure glaucoma:** fixed mid-dilated pupil, corneal edema, high intraocular pressure (typically >50; normal 8–21). Rx w/ topical drops; may require AC tap/laser.
- **Penetrating eye injury:** protect eye (no patching), IV abx, tetanus, NPO, surgical prep

ICU MEDICATIONS

Drug	Class	Dose	
		per kg	average
Pressors, Inotropes, and Chronotropes			
Phenylephrine	α_1	10–300 µg/min	
Norepinephrine	$\alpha_1 > \beta_1$	1–40 µg/min	
Vasopressin	V_1	0.01–0.1 U/min (usually <0.04)	
Epinephrine	α_1, α_2, β_1, β_2	2–20 µg/min	
Isoproterenol	β_1, β_2	0.1–10 µg/min	
Dopamine	D β, D α, β, D	0.5–2 µg/kg/min 2–10 µg/kg/min >10 µg/kg/min	50–200 µg/min 200–500 µg/min 500–1000 µg/min
Dobutamine	$\beta_1 > \beta_2$	2–20 µg/kg/min	50–1000 µg/min
Milrinone	PDE	± 50 µg/kg over 10 min then 0.25–0.75 µg/kg/min	3–4 mg over 10 min then 20–50 µg/min
Vasodilators			
Nitroglycerin	NO	5–500 µg/min	
Nitroprusside	NO	0.25–10 µg/kg/min	10–800 µg/min
Labetalol	α_1, β_1, and β_2 blocker	20–80 mg q10min or 10–120 mg/h	
Fenoldopam	D	0.1–1.6 µg/kg/min	10–120 µg/min
Clevidipine	CCB	1–32 mg/h	
Epoprostenol	vasodilator	2–20 ng/kg/min	
Antiarrhythmics			
Amiodarone	K et al. (Class III)	150 mg over 10 min, then 1 mg/min × 6 h, then 0.5 mg/min × 18 h	
Lidocaine	Na channel (Class IB)	1–1.5 mg/kg then 1–4 mg/min	100 mg then 1–4 mg/min
Procainamide	Na channel (Class IA)	17 mg/kg over 60 min then 1–4 mg/min	1 g over 60 min then 1–4 mg/min
Ibutilide	K channel	1 mg over 10 min,	

	(Class III)	may repeat × 1	
Propranolol	β blocker	0.5–1 mg q5min then 1–10 mg/h	
Esmolol	$\beta_1 > \beta_2$ blocker	500–1000 µg/kg then 50–200 µg/kg/min	20–40 mg over 1 min then 2–20 mg/min
Verapamil	CCB	2.5–5 mg over 1–2′, repeat 5–10 mg in 15–30′ prn 5–20 mg/h	
Diltiazem	CCB	0.25 mg/kg over 2 min reload 0.35 mg/kg × 1 prn then 5–15 mg/h	20 mg over 2 min reload 25 mg × 1 prn then 5–15 mg/h
Adenosine	purinergic	6 mg rapid push; if no response: 12 mg → 12–18 mg	
Sedation			
Morphine	opioid	1–30 (in theory, unlimited) mg/h	
Fentanyl	opioid	50–100 µg then 50–800 (? unlimited) µg/h	
Propofol	anesthetic	1–3 mg/kg then 0.3–5 mg/kg/h	50–200 mg then 20–400 mg/h
Dexmedetomidine	α_2 agonist	1 µg/kg over 10 min → 0.2–0.7 µg/kg/h	
Diazepam	BDZ	1–5 mg q1–2h then q6h prn	
Midazolam	BDZ	0.5–2 mg q5min prn; 0.02–0.1 mg/kg/h or 1–10 mg/h	
Lorazepam	BDZ	0.01–0.1 mg/kg/h	
Naloxone	opioid antag.	0.4–2 mg q2–3min to total of 10 mg	
Flumazenil	BDZ antag.	0.2 mg over 30 sec then 0.3 mg over 30 sec prn may repeat 0.5 mg over 30 sec to total of 3 mg	
Miscellaneous			
Aminophylline	PDE	5.5 mg/kg over 20 min then 0.5–1 mg/kg/h	250–500 mg then 10–80 mg/h
Octreotide	somatostatin analog	50 µg then 50 µg/h	
Glucagon	hormone	3–10 mg IV slowly over 3–5 min then 3–5 mg/h	
Mannitol	osmole	1.5–2 g/kg over 30–60 min repeat q6–12h to keep osm 310–320	

Figure 11-1 ACLS pulmonary edema, hypotension or shock algorithm


Acute Pulmonary Edema, Hypotension, or Shock
ABCs, IV Access, O_2, 12-lead ECG, focused H&P, CXR
What is the nature of the problem?
Volume problem
Pump/Vasc problem
Rate problem
Fluids and/or blood
Vasopressors as needed while volume resuscitating
What is BP?
(after empiric 500 cc NS bolus unless in HF)
Go to tachycardia or bradycardia algorithm
look for signs of organ hypoperfusion
MAP <65
CO variable
SVR low
distributive shock
MAP <65
CO low
SVR high
cardiogenic shock
MAP ≥65
CO low
SVR high
cardiogenic shock
MAP >65
CO normal
SVR nl/high
CHF
Norepinephrine
1–40 ∝g/min
preferred over
Dopamine
5–20 µg/kg/min
Temporize w/ pressors (as in panel to left)
consider inotropes (as in panel to right)
Dobutamine
2–20 ∝g/kg/min
and if SVR remains high, vasodilators (as in panel to right)
Nitroglycerin
10–1000 ∝g/min
and/or
Nitroprusside
0.1–5.0 µg/kg/min
If in pulmonary edema, consider:
Furosemide 0.5–1.0 mg/kg IV
Morphine 2–4 mg IV
Oxygen/noninvasive vent./intub.
further interventions based on etiology

(Adapted from ACLS 2005 Guidelines)

ANTIBIOTICS

The following tables of spectra of activity for different antibiotics are generalizations. Sensitivity data at your own institution should be used to guide therapy.

Penicillins		
Generation	**Properties**	**Spectrum**
Natural (penicillin)	Active vs. many GPC, GPR, anaerobes (not *Bacteroides*), some Gram ⊖ coccobacilli & Gram ⊖ diplococci	Most streptococci, many enterococci, *Listeria, C. acnes, Pasteurella, Actinomyces*, syphilis
Anti-staph (eg, nafcillin)	Active vs. PCNase-producing Staph Little activity vs. Gram ⊖	Staphylococci (except MRSA) Streptococci
Amino (eg, ampicillin)	Penetrate porin channel of Gram ⊖ Not stable against PCNases	PCN plus *E. coli, Proteus, H. influenzae, Salmonella, Shigella*
Extended (eg, piperacillin)	Penetrate porin channel of Gram ⊖ More resistant to PCNases	Most GNR incl. *Enterobacter, Pseudomonas, Serratia*
β-lact. inhib. (eg, sulbactam, clavulanate) with PCN derivative	Inhibits some plasma-mediated β-lactamases	Adds staph (not MRSA), most PCN-R anaerobes, & some GNR (*H. flu, M. cat*, some enterics); intrinsic activity against *Acinetobacter*

Cephalosporins		
Resistant to most penicillin b*-lactamases. No activity vs. enterococci.*		
Generation	**Spectrum**	**Indications**
1st (eg, cefazolin)	Most GPC (incl. staph & strep, not MRSA); some GNR (incl. *E. coli, Proteus, Klebsiella*)	Used for surgical Ppx & skin infxns
2nd (eg, cefuroxime, cefotetan)	↓ activity vs. GPC, ↑ vs. GNR. 2 subgroups: Resp: *H. influenzae* & *M. catarrhalis* GI/GU: ↑ activity vs. *B. fragilis*	PNA/COPD flare Abdominal infxns

Cephalosporins		
3rd (eg, ceftriaxone, ceftazidime)	Broad activity vs. GNR (not ESBL), streptococci, & some anaerobes. Ceftazidime active vs. *Pseudomonas*, less vs. strep	PNA, sepsis, meningitis
4th (eg, cefepime)	↑ resistance to β-lactamases (incl. *Enterobacter*)	Similar to 3rd gen. MonoRx for nonlocalizing febrile neutropenia
5th (eg, ceftaroline)	Only class of cephalosporin with MRSA activity. GN activity similar to ceftriaxone. NOT active vs. *Pseudomonas*.	MRSA. Not 1st line for MRSA bacteremia.
Combination (eg, ceftolozane-tazobactam, ceftazidime-avibactam)	MDR GNRs, incl. *Pseudomonas*. Ceftaz-avi has activity vs. some carbapenemases.	Complicated UTIs, complicated intra-abdominal infections.

Other Beta-Lactams		
Class	**Properties**	**Spectrum**
Carbapenems (eg, imipenem)	Resistant to most β-lactamases	Most Gram ⊕ & ⊖, incl. anaerobes; *not* MRSA or VRE
Monobactams (aztreonam)	Active vs. Gram ⊖ but not Gram ⊕	Gram ⊖ bacterial infxn in Pt w/ PCN or Ceph allergy

Other Antibiotics	
Antibiotic	**Spectrum**
Vancomycin	Gram ⊕ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)
Linezolid	GPC incl. MRSA & VRE (check susceptibility for VRE)
Daptomycin	
Quinolones	GNR & atypicals. Levo and esp moxi ↑ activity vs. Gram ⊕.
Aminoglycosides	GNR. Synergy w/ cell-wall active abx (β-lactam, vanco) vs. GPC. ↓ activity in low pH (eg, abscess). No activity vs. anaerobes.
Macrolides	GPC, some respiratory Gram ⊖, atypicals
TMP/SMX	Most enteric GNR, Staph incl CA-MRSA, *Stenotrophomonas*, *Nocardia, Toxo*, *Pneumocystis*
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (increasing resistance, especially GI)

Other Antibiotics	
Metronidazole	Almost all anaerobic Gram ⊖, most anaerobic Gram ⊕, some protozoa (*Entamoeba*, *Trichomonas*, et al.)
Doxycycline	*Rickettsia, Ehrlichia, Anaplasma, Chlamydia, Mycoplasma, Nocardia*, Lyme; many Staph and GNR
Tigecycline	Many GPC incl. MRSA & VRE; most GNR incl. ESBL but not *Pseudomonas* or *Proteus*; most anaerobes

Treatment for Common Fungi
("x" indicates activity, shaded boxes indicate 1st-line treatment)

Antifungal	*C. albicans*	*C. glabrata & krusei*	Crypto	Endemic Histo, Blasto, Coccidio	Aspergillus	Mucor
Fluconazole	x		x			
Itraconazole	x		x	x		
Voriconazole	x	x	x	x	x	
Posaconazole	x	x	x	x	x	x
Isavuconazole	x		x	(x)	x	x
Micafungin	x	x			x	
Ampho B	x	x	x	x	x	x

FORMULAE AND QUICK REFERENCE

CARDIOLOGY

Hemodynamic Parameters	Normal Value
Mean arterial pressure $(MAP) = \frac{SBP + (DBP \times 2)}{3}$	70–100 mmHg
Heart rate (HR)	60–100 bpm
Right atrial pressure (RA)	≤6 mmHg
Right ventricular (RV)	systolic 15–30 mmHg diastolic 1–8 mmHg
Pulmonary artery (PA)	systolic 15–30 mmHg mean 9–18 mmHg diastolic 6–12 mmHg
Pulmonary capillary wedge pressure (PCWP)	≤12 mmHg
Cardiac output (CO)	4–8 L/min
Cardiac index $(CI) = \frac{CO}{BSA}$	2.6–4.2 L/min/m^2
Stroke volume $(SV) = \frac{CO}{HR}$	60–120 mL/contraction
Stroke volume index $(SVI) = \frac{CI}{HR}$	40–50 mL/contraction/m^2
Systemic vascular resistance (SVR)	800–1200 dynes × sec/cm^5

$= \frac{\text{MAP} - \text{mean RA}}{\text{CO}} \times 80$	
Pulmonary vascular resistance (PVR) $= \frac{\text{mean PA} - \text{mean PCWP}}{\text{CO}} \times 80$	120–250 dynes × sec/cm^5

"Rule of 6s" for PAC: RA ≤6, RV ≤30/6, PA ≤30/12, WP ≤12. Nb 1 mmHg = 1.36 cm water or blood.

Fick cardiac output

Oxygen consumption (L/min) = CO (L/min) × arteriovenous (AV) oxygen difference

CO = oxygen consumption/AV oxygen difference

Oxygen consumption must be measured (can estimate w/ 125 mL/min/m^2, but inaccurate)

AV oxygen difference = Hb (g/dL) × 10 (dL/L) × 1.36 (mL O_2/g of Hb) × (S_aO_2–$S_{MV}O_2$)

S_aO_2 is measured in any arterial sample (usually 93–98%)

$S_{MV}O_2$ (mixed venous O_2) is measured in RA, RV, or PA (assuming no shunt) (nl ~75%)

$$\therefore \textbf{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dL)} \times 13.6\ (S_aO_2 - S_vO_2)}$$

Assessment of RV function (*Circ* 2017;136:314)

PAPi = Pulmonary artery pulsatility index = [PA systolic – PA diastolic] / RA pressure ≤0.9 predicts RV failure in acute MI; <1.85 predicts RV failure after LVAD

Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein } O_2 \text{ sat} - \text{Pulm. artery } O_2 \text{ sat}} \quad (\text{if no R} \rightarrow \text{L shunt, PV } O_2 \text{ sat} \approx S_aO_2)$$

$$Q_s = \frac{\text{Oxygen consumption}}{S_aO_2 - \text{mixed venous } O_2 \text{ sat}} \quad (MVO_2 \text{ drawn proximal to potential L} \rightarrow \text{R shunt})$$

$$\frac{Q_p}{Q_s} = \frac{S_aO_2 - \text{MV } O_2 \text{ sat}}{\text{PV } O_2 \text{ sat} - \text{PA } O_2 \text{ sat}} \approx \frac{S_aO_2 - \text{MV } O_2 \text{ sat}}{S_aO_2 - \text{PA } O_2 \text{ sat}} \quad (\text{if only L} \rightarrow \text{R and no R} \rightarrow \text{L shunt})$$

Valve equations

Simplified Bernoulli: Pressure gradient (∇P) = $4 \times v^2$ (where v = peak flow velocity)

Continuity (conservation of flow): $\text{Area}_1 \times \text{Velocity}_1 = A_2 \times V_2$ (where 1 & 2 different points)

$$\text{or AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{LVOT}}{V_{AoV}}\right) \quad (\text{all of which can be measured on echo})$$

$$\text{Gorlin equation: Valve area} = \frac{CO/(\text{DEP or SEP}) \times HR}{44.3 \times \text{constant} \times \sqrt{\nabla P}} \quad (\text{constant} = 1 \text{ for AS, } 0.85 \text{ for MS})$$

$$\text{Hakki equation: Valve area} \approx \frac{CO}{\sqrt{\nabla P}}$$

PULMONARY

Chest Imaging (CXR & CT) Patterns		
Pattern	**Pathophysiology**	**Ddx**
Consolidation	Radiopaque material in air space & interstitium patent airway → "air bronchograms"	*Acute:* water **(pulm. edema)**, pus **(PNA), blood** *Chronic:* neoplasm (BAC, lymphoma), aspiration, inflammatory (COP, eosinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoid)
Ground glass (CT easier than CXR)	Interstitial thickening or partial filling of alveoli (but vessels visible)	*Acute:* pulm. edema, infxn (PCP, viral, resolving bact. PNA) Chronic: ILD w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF

Chest Imaging (CXR & CT) Patterns		
Septal lines Kerley A & B	Radiopaque material in septae	**Cardiogenic pulm. edema**, interstitial PNA viral, mycoplasma, lymphangitic tumor
Reticular	Lace-like net (ILD)	**ILD** (esp. IPF, CVD, bleomycin, asbestos)
Nodules	Tumor Granulomas Abscess	*Cavitary:* **Primary or metastatic cancer**, **TB** (react. or miliary), **fungus**, Wegener's, RA **septic emboli**, PNA *Noncavitary:* any of above + **sarcoid**, hypersens. pneum., HIV, Kaposi's sarcoma
Wedge opac.	Peripheral infarct	**PE**, cocaine, angioinv. aspergillus, Wegener's
Tree-in-bud (best on CT)	Inflammation of small airways	**Bronchopneumonia**, endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, COP
Hilar fullness	↑ LN or pulm. arteries	**Neoplasm** (lung, mets, lymphoma) **Infxn** (AIDS); **Granuloma** (sarcoid/TB/fungal) Pulmonary hypertension
Upper lobe	n/a	**TB**, fungal, sarcoid, hypersens. pneum., CF, XRT
Lower lobe	n/a	**Aspiration**, bronchiect., IPF, RA, SLE, asbestos
Peripheral	n/a	COP, IPF & DIP, eos PNA, asbestosis

CXR in heart failure

- ↑ cardiac silhouette (in systolic dysfxn, not in diastolic)
- Pulmonary venous hypertension: cephalization of vessels (vessels size >bronchi in upper lobes), peribronchial cuffing (fluid around bronchi seen on end → small circles), Kerley B lines (horizontal 1- to 2-cm lines at bases), ↑ vascular pedicle width, loss of sharp vascular margins, pleural effusions (~75% bilateral)
- Pulmonary edema: ranges from ground glass to consolidation; often dependent and central, sparing outer third ("bat wing" appearance)

Dead space = lung units that are ventilated but not perfused

Intrapulmonary shunt = lung units that are perfused but not ventilated

Alveolar gas equation: $P_AO_2 = [F_IO_2 \times (760 - 47)] - \frac{P_aCO_2}{R}$ (where R ≈ 0.8)

$$P_AO_2 = 150 - \frac{P_aCO_2}{0.8} \text{ (on room air)}$$

A-a gradient = $P_AO_2 - P_aO_2$ [normal A-a gradient ≈ 4 + (age/4)]
Minute ventilation (V_E) = tidal volume (V_T) × respiratory rate (RR) (nl 4–6 L/min)
Tidal volume (V_T) = alveolar space (V_A) + dead space (V_D)

Fraction of tidal volume that is dead space $\left(\frac{V_D}{V_T}\right) = \frac{P_aCO_2 - P_{expired}CO_2}{P_aCO_2}$

$$P_aCO_2 = k = \times \frac{CO_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

GASTROENTEROLOGY

Modified Child-Turcotte-Pugh (CPS) Scoring System			
	Points Scored		
	1	**2**	**3**
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec >control) or INR	<4 <1.7	4–6 1.8–2.3	>6 >2.3
Classification			
	A	**B**	**C**
Total points	5–6	7–9	10–15
1-y survival	100%	80%	45%

NEPHROLOGY

Anion gap (AG) = Na – (Cl + HCO_3) (normal = [alb] × 2.5; typically 12 ± 2 mEq)

Delta-delta (ΔΔ) = [Δ AG (ie, calc. AG – expected) / Δ HCO_3 (ie, 24 – measured HCO_3)]

Urine anion gap (UAG) = (U_{Na} + U_K) – U_{Cl}

Calculated osmoles $= (2 \times Na) + \left(\frac{glc}{18}\right) + \left(\frac{BUN}{2.8}\right) + \left(\frac{EtOH}{4.6}\right)$

Osmolal gap (OG) = measured osmoles – calculated osmoles (normal <10)

Estimated creatinine clearance $= \frac{[140 - \text{age (yr)}] \times \text{wt (kg)}}{\text{serum Cr (mg/dL)} \times 72}$ (× 0.85 in women)

Fractional excretion of Na (FE_{Na}, %) $= \left[\frac{\frac{U_{Na}\,(mEq/L)}{P_{Na}\,(mEq/L)} \times 100\%}{\frac{U_{Cr}\,(mg/mL)}{P_{Cr}\,(mg/dL)} \times 100\ (mL/dL)}\right] = \frac{\frac{U_{Na}}{P_{Na}}}{\frac{U_{Cr}}{P_{Cr}}}$

Corrected Na in hyperglycemia

estimate in all Pts: corrected Na = measured Na + $\left[2.4 \times \frac{(\text{measured glc} - 100)}{100}\right]$

however, Δ in Na depends on glc (*Am J Med* 1999;106:399)
Δ is 1.6 mEq per each 100 mg/dL ↑ in glc ranging from 100–440
Δ is 4 mEq per each 100 mg/dL ↑ in glc beyond 440

Total body water (TBW) = 0.60 × IBW (× 0.85 if female and × 0.85 if elderly)

Free H_2O deficit $= TBW \times \left(\frac{[Na]_{serum} - 140}{140}\right) \approx \left(\frac{[Na]_{serum} - 140}{3}\right)$ (in 70-kg Pt)

Trans-tubular potassium gradient (TTKG) = [U_K / P_K] / [U_{Osm} / P_{Osm}]

HEMATOLOGY

Peripheral Smear Findings (also see Photo Inserts)	
Feature	**Abnormalities and Diagnoses**
Size	normocytic vs. microcytic vs. macrocytic → see below

Peripheral Smear Findings (also see Photo Inserts)	
Shape	**Anisocytosis** → unequal RBC size; **poikilocytosis** → irregular RBC shape acanthocytes = **spur** cells (irregular sharp projections) → liver disease **Bite** cells (removal of Heinz bodies by phagocytes) → G6PD deficiency echinocytes = **burr** cells (even, regular projections) → uremia, artifact **Pencil cell** → long, thin, hypochromic–very common in adv. iron deficiency **Rouleaux** → hyperglobulinemia (eg, multiple myeloma) **Schistocytes**, helmet cells → MAHA (eg, DIC, TTP/HUS), mechanical valve **Spherocytes** → HS, AIHA; **sickle** cells → sickle cell anemia **Stomatocyte** → central pallor appears as curved slit → liver disease, EtOH **Target** cells → liver disease, hemoglobinopathies, splenectomy **Tear drop** cells = dacryocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia
Intra- RBC findings	**Basophilic stippling** (ribosomes) → abnl Hb, sideroblastic, megaloblastic **Heinz bodies** (denatured Hb) → G6PD deficiency, thalassemia **Howell-Jolly bodies** (nuclear fragments) → splenectomy or functional asplenia (eg, advanced sickle cell) **Nucleated** RBCs → hemolysis, extramedullary hematopoiesis
WBC findings	**Blasts** → leukemia, lymphoma; **Auer rods** → acute myelogenous leukemia **Hypersegmented** (>5 lobes) PMNs: megaloblastic anemia (B_{12}/folate def.) **Pseudo-Pelger-Huët anomaly** (bilobed nucleus, "pince-nez") → MDS **Toxic granules** (coarse, dark blue) and **Döhle bodies** (blue patches of dilated endoplasmic reticulum) → (sepsis, severe inflammation)
Platelet	**Clumping** → artifact, repeat plt count **#** → periph blood plt count ~10,000 plt for every 1 plt seen at hpf (100×) **Size** → MPV (mean platelet volume) enlarged in ITP

(*NEJM* 2005;353:498)

Heparin for Thromboembolism	
80 U/kg bolus 18 U/kg/h	
PTT	**Adjustment**
<40	bolus 5000 U, ↑ rate 300 U/h
40–49	bolus 3000 U, ↑ rate 200 U/h
50–59	↑ rate 150 U/h
60–85	no Δ

Heparin for Thromboembolism	
86–95	↓ rate 100 U/h
96–120	hold 30 min, ↓ rate 100 U/h
>120	hold 60 min, ↓ rate 150 U/h

(Modified from *Chest* 2008;133:141S)

Heparin for ACS	
60 U/kg bolus (max 4000 U) 12 U/kg/h (max 1000 U/h)	
PTT	**Adjustment**
<40	bolus 3000 U, ↑ rate 100 U/h
40–49	↑ rate 100 U/h
50–75	no Δ
76–85	↓ rate 100 U/h
86–100	hold 30 min, ↓ rate 100 U/h
>100	hold 60 min, ↓ rate 200 U/h

(Modified from *Circ* 2007;116:e148 & *Chest* 2008;133:670)

✓ PTT q6h after every Δ (t. of heparin ~90 min) and then qd or bid once PTT is therapeutic
✓ CBC qd (to ensure Hct and plt counts are stable)

Warfarin Loading Nomogram					
Day	**INR**				
	<1.5	**1.5–1.9**	**2–2.5**	**2.6–3**	**>3**
1–3	5 mg (7.5 mg if >80 kg)		2.5–5 mg	0–2.5 mg	0 mg
4–5	10 mg	5–10 mg	0–5 mg		0–2.5 mg
6	Dose based on requirements over preceding 5 d				

(*Annals* 1997;126:133; *Archives* 1999;159:46) or, go to www.warfarindosing.org

Warfarin-heparin overlap therapy

- Indications: when failure to anticoagulate carries ↑ risk of morbidity or mortality (eg, DVT/PE, intracardiac thrombus)
- Rationale:(1) Half-life of factor VII (3–6 h) is shorter than half-life of factor II (60–72 h);
  ∴ warfarin can elevate PT *before achieving a true antithrombotic state*
  (2) Protein C also has half-life less than that of factor II;

∴ theoretical concern of *hypercoagulable state* before antithrombotic state

- Method: (1) Therapeutic PTT is achieved using heparin
  (2) Warfarin therapy is initiated
  (3) Heparin continued until INR therapeutic for ≥2 d and ≥4–5 d of warfarin (roughly corresponds to ~2 half-lives of factor II or a reduction to ~25%)

Common Warfarin-Drug Interactions	
Drugs that ↑ PT	**Drugs that ↓ PT**
Amiodarone Antimicrobials: erythromycin, ? clarithro, ciprofloxacin, MNZ, sulfonamides Antifungals: azoles Acetaminophen, cimetidine, levothyroxine	Antimicrobials: rifampin CNS: barbiturates, carbamazepine, phenytoin (initial transient ↑ PT) Cholestyramine

ENDOCRINOLOGY

Examples of Various Cosyntropin Stimulation Test Results			
0′	**30′**	**60′**	**Interpretation**
5.3	15.5	23.2	Normal stimulation test
1.5	13.3	21.1	Acute central AI (eg, apoplexy or CNS bleed). Can look normal.
1.2	1.5	2.0	1° AI (eg, Addisons or adrenal bleed). Flat or minimal stim.
0.8	10.0	19.7	Acute effect of glucocorticoids: low initial value but stims >threshold
5.3	7.2	8.9	Chronic 2° AI: some cortisol production and stim, but evidence of adrenal atrophy
6.7	19.5	17.2	“Early peak” (fast metab): ~5% of Pts peak at 30’ rather than 60’
6.3	11.5	16.2	Equivocal test. Can occur due to mild AI, acute illness, liver disease, low cortisol binding protein, renal disease, etc.

NEUROLOGY

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)					
Assign points for each of the 10 criteria; each criteria is scored 0–7, except orientation, which is scored 0–4; add points to calculate score.					
Points	**Anxiety**	**Agitation**	**Tremor**	**HA**	**Orientation**
0	None	None	None	None	Oriented
1		Somewhat	Not visible, but felt at fingertips	Very mild	Cannot do serial additions
2				Mild	Disorient. by ?2 d
3				Moderate	Disorient. by >2 d
4	Guarded	Restless	Moderate w/ hands extended	Mod severe	Disoriented to person or place
5				Severe	n/a
6				Very severe	n/a
7	Panic	Pacing or thrashing	Severe	Extremely severe	n/a
Points	**N/V**	**Sweats**	**Auditory Hallucinations**	**Visual Halluc.**	**Tactile Disturb**
0	None	None	None	None	None
1		Moist palms	Very mild	Very mild photosens.	Very mild paresthesias
2			Mild	Mild photosens.	Mild paresth.
3			Moderate	Mod photosens.	Mod paresth.
4	Intermit. w/ dry heaves	Beads	Mod severe	Mod severe visual halluc.	Mod severe hallucinations
5			Severe	Severe	Severe
6			Very severe	Very severe	Very severe
7	Constant	Drenching	Cont.	Continuous	Continuous
SCORE: <8 none to minimal withdrawal; 8–15 mild; 16–20 moderate; >20 severe					

OTHER

Ideal body weight (IBW) = [50 kg (men) or 45.5 kg (women)] + 2.3 kg/inch over 5 feet

Body surface area (BSA, m^2) = $\sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$

		Disease	
		present	absent
Test	⊕	a (true ⊕)	b (false ⊕)
	⊖	c (false ⊖)	d (true ⊖)

Sensitivity = $\frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a + c}$ **Specificity** = $\frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{b + d}$

⊕ **Predictive value** = $\frac{\text{true positives}}{\text{all positives}} = \frac{a}{a + b}$

⊖ **Predictive value** = $\frac{\text{true negatives}}{\text{all negatives}} = \frac{d}{c + d}$

NOTES

ABBREVIATIONS

5′-NT	5′-nucleotidase
6-MP	6-mercaptopurine
AAA	abdominal aortic aneurysm
AAD	antiarrhythmic drug
Ab	antibody
ABE	acute bacterial endocarditis
ABG	arterial blood gas
abnl	abnormal
ABPA	allergic bronchopulmonary aspergillosis
abx	antibiotics
a/c	anticoagulation
AC	assist control
ACE	angiotensin-converting enzyme
ACEI	ACE inhibitor
ACI	anemia of chronic inflammation
ACL	anticardiolipin antibody
ACLS	advanced cardiac life support
ACS	acute coronary syndrome
ACTH	adrenocorticotrophic hormone
ACV	acyclovir
ADA	adenosine deaminase
ADH	antidiuretic hormone
ADL	activities of daily living
AF	atrial fibrillation
AFB	acid-fast bacilli
AFL	atrial flutter
AFP	α-fetoprotein
AFTP	ascites fluid total protein
AG	aminoglycoside anion gap
Ag	antigen
AGN	acute glomerulonephritis
AI	adrenal insufficiency aortic insufficiency aromatase inhibitor
AIDS	acquired immunodefic. synd.
AIH	autoimmune hepatitis
AIHA	autoimmune hemolytic anemia
AIN	acute interstitial nephritis
AIP	acute interstitial pneumonia

AKI	acute kidney injury
ALF	acute liver failure
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
AMI	anterior myocardial infarction
AML	acute myelogenous leukemia
amy	amylase
ANA	antinuclear antibody
ANCA	antineutrophilic cytoplasmic Ab
AoD	aortic dissection
AoV	aortic valve
APAP	acetyl-para-aminophenol
APC	activated protein C
APL	acute promyelocytic leukemia
APLA	antiphospholipid Ab
APS	antiphospholipid Ab synd.
ARB	angiotensin receptor blocker
ARDS	acute resp distress synd.
ARV	antiretroviral
ARVC	arrhythmogenic RV CMP
AS	aortic stenosis
ASA	aspirin
ASD	atrial septal defect
AST	aspartate aminotransferase
asx	asymptomatic
AT	atrial tachycardia
ATII	angiotensin II
ATIII	antithrombin III
ATN	acute tubular necrosis
ATRA	all-trans-retinoic acid
AV	atrioventricular
AVA	aortic valve area
AVB	atrioventricular block
AVNRT	AV nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	AV reciprocating tachycardia
a/w	associated with
AZA	azathioprine
Aϕ	alkaline phosphatase
BAL	bronchoalveolar lavage
βB	beta-blocker
BBB	bundle branch block
b/c	because
BCx	blood culture

BD	bile duct
BDZ	benzodiazepines
bili.	bilirubin
BiPAP	bilevel positive airway pressure
BiV	biventricular
BM	bone marrow
	bowel movement
BMD	bone mineral density
BMI	body mass index
BMS	bare metal stent
BNP	B-type natriuretic peptide
BP	blood pressure
BPH	benign prostatic hypertrophy
BRBPR	bright red blood per rectum
BS	breath sounds
BT	bleeding time
BUN	blood urea nitrogen
bx	biopsy
BYCE	buffered charcoal yeast extract
C′	complement
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
CALLA	common ALL antigen
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CBD	common bile duct
CCB	calcium channel blocker
CCl4	carbon tetrachloride
CCP	cyclic citrullinated peptide
CCS	Canadian Cardiovascular Society
CCY	cholecystectomy
CD	Crohn's disease
CEA	carcinoembryonic antigen
	carotid endarterectomy
ceph.	cephalosporin
c/f	concern for
CF	cystic fibrosis
CFU	colony forming units
CHB	complete heart block
CHD	congenital heart disease
CHF	congestive heart failure
CI	cardiac index
CIAKI	contrast-induced AKI
CIDP	chronic inflammatory demyelinating polyneuropathy
CJD	Creutzfeldt-Jakob disease

CK creatine kinase
CKD chronic kidney disease
CLL chronic lymphocytic leukemia
CMC carpometacarpal (joint)
CML chronic myelogenous leukemia
CMML chronic myelomonocytic leukemia
CMP cardiomyopathy
CMV cytomegalovirus
CN cranial nerve
CNI calcineurin inhibitor
CNS central nervous system
coagulase-negative *Staphylococci*
CO carbon monoxide
cardiac output
COP cryptogenic organizing PNA
COPD chronic obstructive pulm. dis.
COX cyclo-oxygenase
CP chest pain
CPAP continuous positive airway pressure
CPP cerebral perfusion pressure
CPPD calcium pyrophosphate dihydrate
Cr creatinine
CrAg cryptococcal antigen
CRC colorectal cancer
CrCl creatinine clearance
CRP C-reactive protein
CRT cardiac resynchronization therapy
c/s consult
CsA cyclosporine A
CSF cerebrospinal fluid
CSM carotid sinus massage
CT computed tomogram
CTA CT angiogram
CTD connective tissue disease
CTX ceftriaxone
CV cardiovascular
CVA cerebrovascular accident
CVD cerebrovascular disease
collagen vascular disease
CVID common variable immunodefic.
CVP central venous pressure
CVVH continuous veno-venous hemofiltration
c/w compared with
consistent with
CW chest wall
cx culture

CXR	chest radiograph
CYC	cyclophosphamide
d	day
D	death
ΔMS	change in mental status
DA	dopamine
DAD	diffuse alveolar damage
DAH	diffuse alveolar hemorrhage
DAT	direct antiglobulin test
DBP	diastolic blood pressure
d/c	discharge
	discontinue
DCCV	direct current cardioversion
DCIS	ductal carcinoma in situ
DCMP	dilated cardiomyopathy
DCT	distal collecting tubule
Ddx	differential diagnosis
DES	drug-eluting stent
DFA	direct fluorescent antigen detection
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
diff.	differential
DIP	desquamative interstitial pneumonitis
	distal interphalangeal (joint)
DKA	diabetic ketoacidosis
DLCO	diffusion capacity of the lung
DLE	drug-induced lupus
DM	dermatomyositis
	diabetes mellitus
DMARD	disease-modifying anti-rheumatic drug
DOE	dyspnea on exertion
DRE	digital rectal exam
DRESS	drug reaction w/ eosinophilia & systemic symptoms
DSE	dobutamine stress echo
DST	dexamethasone suppression test
DTRs	deep tendon reflexes
DU	duodenal ulcer
DVT	deep vein thrombosis
dx	diagnosis
EAD	extreme axis deviation
EAV	effective arterial volume
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EDP	end-diastolic pressure

EDV end-diastolic volume
EEG electroencephalogram
EF ejection fraction
EGD esophagogastroduodenoscopy
EGFR epidermal growth factor receptor
EGPA eosinophilic granulomatosis with polyangiitis
EI entry inhibitor
EIA enzyme-linked immunoassay
ELISA enzyme-linked immunosorbent assay
EM electron microscopy
EMB ethambutol
ENaC epithelial Na channel
ENT ears, nose, & throat
e/o evidence of
EOM extraocular movement/muscles
EP electrophysiology
Epo erythropoietin
EPS electrophysiology study
ERCP endoscopic retrograde cholangiopancreatography
ERV expiratory reserve volume
ESA erythropoiesis-stimulating agents
ESBL extended spectrum beta-lactamase
ESP end-systolic pressure
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
ESV end-systolic volume
ET endotracheal tube
essential thrombocythemia
EtOH alcohol
ETT endotracheal tube
exercise tolerance test
EUS endoscopic ultrasound
EVAR endovascular aneurysm repair

FDP fibrin degradation product
FEV_1 forced expir. vol in 1 sec
FFP fresh frozen plasma
FHx family history
FI fusion inhibitor
FMD fibromuscular dysplasia
FMF familial Mediterranean fever
FNA fine-needle aspiration
FOB fecal occult blood
FOBT fecal occult blood testing
FQ fluoroquinolone
FRC functional residual capacity
FSGS focal segmental glomerulosclerosis

FSH	follicle-stimulating hormone
FTI	free thyroxine index
FUO	fever of unknown origin
f/up	follow-up
FVC	forced vital capacity
G6PD	glc-6-phosphate dehydrogenase
GB	gallbladder
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
GCA	giant cell arteritis
GCS	Glasgow coma scale
G-CSF	granulocyte colony-stimulating factor
GE	gastroesophageal
gen.	generation
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GIB	gastrointestinal bleed
GIST	gastrointestinal stromal tumor
glc	glucose
GMCSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis
GNR	gram-negative rods
GnRH	gonadotropin-releasing hormone
GPA	granulomatosis w/ polyangiitis
GPC	gram-positive cocci
GPI	glycoprotein IIb/IIIa inhibitor
GRA	glucocorticoid-remediable aldosteronism
GU	gastric ulcer
GVHD	graft-versus-host disease
h	hour
H2RA	H2-receptor antagonist
HA	headache
HACA	human antichimeric antibody
HAV	hepatitis A virus
Hb	hemoglobin
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCMP	hypertrophic cardiomyopathy
Hct	hematocrit
HCV	hepatitis C virus
HCW	health care worker
HD	hemodialysis
HDL	high-density lipoprotein

HDV hepatitis D virus
HELLP hemolysis, abnl LFTs, low plts
HEV hepatitis E virus
HF heart failure
HGPRT hypoxanthine-guanine phosphoribosyl transferase
HHS hyperosmolar hyperglycemic state
HIT heparin-induced thrombocytopenia
HK hypokinesis
HL Hodgkin lymphoma
h/o history of
HOB head of bed
HoTN hypotension
hpf high-power field
HPT hyperparathyroidism
HR heart rate
HRT hormone replacement therapy
HS hereditary spherocytosis
HSCT hematopoietic stem cell transplantation
HSM hepatosplenomegaly
HSP Henoch-Schönlein purpura
HSV herpes simplex virus
HTN hypertension
HUS hemolytic uremic syndrome
hx history

I&D incision & drainage
IABP intra-aortic balloon pump
IBD inflammatory bowel disease
IBS irritable bowel syndrome
IC inspiratory capacity
ICa ionized calcium
ICD implantable cardiac defibrillator
ICH intracranial hemorrhage
ICP intracranial pressure
ICU intensive care unit
IE infective endocarditis
IGF insulin-like growth factor
IGRA interferon-γ release assay
II integrase inhibitor
IIP idiopathic interstitial PNA
ILD interstitial lung disease
IMI inferior myocardial infarction
infxn infection
inh inhaled
INH isoniazid
INR international normalized ratio
IPAA ileal pouch-anal anastomosis

IPF idiopathic pulmonary fibrosis
ITP idiopathic thrombocytopenic purpura
IVB intravenous bolus
IVC inferior vena cava
IVDU intravenous drug use(r)
IVF intravenous fluids
IVIg intravenous immunoglobulin

JVD jugular venous distention
JVP jugular venous pulse

KS Kaposi's sarcoma
KUB kidney-ureter-bladder (radiography)

LA left atrium
long-acting
lupus anticoagulant
LABA long-acting β_2-agonist
LAD left anterior descending coronary artery
left axis deviation
LAE left atrial enlargement
LAN lymphadenopathy
LAP left atrial pressure
leukocyte alkaline phosphatase
LBBB left bundle branch block
LCA left coronary artery
LCIS lobular carcinoma in situ
LCx left circumflex cor. art.
LDH lactate dehydrogenase
LDL low-density lipoprotein
LE lower extremity
LES lower esophageal sphincter
LFTs liver function tests
LGIB lower gastrointestinal bleed
LGV lymphogranuloma venereum
LH luteinizing hormone
LLQ left lower quadrant
LM left main coronary artery
LMWH low-molecular-weight heparin
LN lymph node
LOC loss of consciousness
LOS length of stay
LP lumbar puncture
lpf low-power field
LQTS long QT syndrome
LR lactated Ringer's
LUSB left upper sternal border
LV left ventricle

LVAD LV assist device
LVEDP LV end-diastolic pressure
LVEDV LV end-diastolic volume
LVESD LV end-systolic diameter
LVH left ventricular hypertrophy
LVOT left ventricular outflow tract
LVSD LV systolic dimension

mAb monoclonal antibody
MAC mitral annular calcification
Mycobacterium avium complex
MAHA microangiopathic hemolytic anemia
MALT mucosa-assoc. lymphoid tissue
MAO monoamine oxidase
MAP mean arterial pressure
MAT multifocal atrial tachycardia
MCD minimal change disease
MCP metacarpal phalangeal (joint)
MCS mechanical circulatory support
MCTD mixed connective tissue dis.
MCV mean corpuscular volume
MDI metered dose inhaler
MDMA 3,4-methylenedioxymetham- phetamine (Ecstasy)
MDR multidrug resistant
MDS myelodysplastic syndrome
MEN multiple endocrine neoplasia
MG myasthenia gravis
MGUS monoclonal gammopathy of uncertain significance
MI myocardial infarction
min minute
min. minimal
MM multiple myeloma
MMEFR max. mid-expir. flow rate
MMF mycophenolate mofetil
MN membranous nephropathy
MNZ metronidazole
mo month
mod. moderate
MODS multiple organ dysfxn synd.
MPA microscopic polyangiitis
MPGN membranoproliferative glomerulonephritis
MPN myeloproliferative neoplasm
MR magnetic resonance
mitral regurgitation
MRA magnetic resonance angiography
MRCP MR cholangiopancreatography
MRI magnetic resonance imaging

MRSA methicillin-resistant *S. aureus*
MS mitral stenosis
MSA multisystem atrophy
MSK musculoskeletal
MTb *Mycobacterium tuberculosis*
mTOR mechanistic target of rapamycin
MTP metatarsal phalangeal (joint)
MTX methotrexate
MV mitral valve
MVA mitral valve area
MVP mitral valve prolapse
MVR mitral valve replacement
Mϕ macrophage

NAC N-acetylcysteine
NAFLD non-alcoholic fatty liver disease
NASH non-alcoholic steatohepatitis
NG nasogastric
NGT nasogastric tube
NHL non-Hodgkin lymphoma
niCMP non-ischemic CMP
NIF negative inspiratory force
NJ nasojejunal
nl normal
NM neuromuscular
NMJ neuromuscular junction
NNRTI non-nucleoside reverse transcriptase inhibitor
NNT number needed to treat
NO nitric oxide
NPJT nonparoxysmal junctional tachycardia
NPO nothing by mouth
NPPV noninvasive positive pressure ventilation
NPV negative predictive value
NRTI nucleoside reverse transcriptase inhibitor
NS normal saline
NSAID nonsteroidal anti-inflam. drug
NSCLC non-small cell lung cancer
NSF nephrogenic systemic fibrosis
NTG nitroglycerin
N/V nausea and/or vomiting
NVE native valve endocarditis
NYHA New York Heart Association

O/D overdose
o/w otherwise
O&P ova & parasites
OA osteoarthritis
OCP oral contraceptive pill

OG osmolal gap
OGT orogastric tube
OGTT oral glucose tolerance test
OI opportunistic infection
OM obtuse marginal cor. art.
OS overall survival
OSA obstructive sleep apnea
OTC over-the-counter

p/w present(s) with
PA pulmonary artery
PAC pulmonary artery catheter
PAD peripheral artery disease
PAN polyarteritis nodosa
PASP PA systolic pressure
PAV percutaneous aortic valvuloplasty
pb problem
PBC primary biliary cholangitis
PCI percutaneous coronary intervention
PCN penicillin
PCP *Pneumocystis jiroveci* pneumonia
PCR polymerase chain reaction
PCT porphyria cutanea tarda
PCWP pulmonary capillary wedge pressure
PD Parkinson's disease
peritoneal dialysis
PDA patent ductus arteriosus
posterior descending cor. art.
PE pulmonary embolism
PEA pulseless electrical activity
PEEP positive end-expiratory pressure
PEF peak expiratory flow
PET positron emission tomography
PEx physical examination
PFO patent foramen ovale
PFS progression-free survival
PFT pulmonary function test
PGA polyglandular autoimmune syndrome
PHT pulmonary hypertension
PI protease inhibitor
PID pelvic inflammatory disease
PIF prolactin inhibitory factor
PIP peak inspiratory pressure
proximal interphalangeal (joint)
PKD polycystic kidney disease
PM polymyositis
PMF primary myelofibrosis

PMHx past medical history
PMI point of maximal impulse
PML progressive multifocal leukoencephalopathy
PMN polymorphonuclear leukocyte
PMR polymyalgia rheumatica
PMV percutaneous mitral valvuloplasty
PMVT polymorphic ventricular tachycardia
PNA pneumonia
PND paroxysmal nocturnal dyspnea
PNH paroxysmal nocturnal hemoglobinuria
PNS peripheral nervous system
PO oral intake
POTS postural orthostatic tachycardia syndrome
PPD purified protein derivative
PPH primary pulmonary HTN
PPI proton pump inhibitors
Pplat plateau pressure
PPM permanent pacemaker
PPV positive predictive value
Ppx prophylaxis
PR PR segment on ECG
pulmonary regurgitation
PRBCs packed red blood cells
PRL prolactin
PRPP phosphoribosyl-I-pyrophosphate
PRWP poor R wave progression
PS pressure support
pulmonic stenosis
PSA prostate specific antigen
PsA *Pseudomonas aeruginosa*
PSC primary sclerosing cholangitis
PSGN post streptococcal glomerulonephritis
PSHx past surgical history
PSV pressure support ventilation
Pt patient
PT prothrombin time
PTA percutaneous transluminal angioplasty
PTH parathyroid hormone
PTH-rP PTH-related peptide
PTT partial thromboplastin time
PTU propylthiouracil
PTX pneumothorax
PUD peptic ulcer disease
PUVA psoralen + ultraviolet A
PV polycythemia vera
portal vein

PVD peripheral vascular disease
PVE prosthetic valve endocarditis
PVR pulmonary vascular resistance
PZA pyrazinamide

qac before every meal
qhs every bedtime
QoL quality of life
Qw Q wave

RA refractory anemia
rheumatoid arthritis
right atrium
RAA renin-angiotensin-aldosterone
RAD right axis deviation
RAE right atrial enlargement
RAI radioactive iodine
RAIU radioactive iodine uptake
RAS renal artery stenosis
RAST radioallergosorbent test
RBBB right bundle branch block
RBC red blood cell
RBF renal blood flow
RBV ribavirin
RCA right coronary artery
RCMP restrictive cardiomyopathy
RCT randomized controlled trial
RDW red cell distribution width
RE reticuloendothelial
RF rheumatoid factor
risk factor
RFA radiofrequency ablation
RHD rheumatic heart disease
r/i rule in
RI reticulocyte index
RIBA recombinant immunoblot assay
RMSF Rocky Mountain spotted fever
r/o rule out
ROS review of systems
RPGN rapidly progressive glomerulonephritis
RR respiratory rate
RRT renal replacement therapy
RT radiation therapy
RTA renal tubular acidosis
RTX rituximab
RUQ right upper quadrant
RUSB right upper sternal border
RV residual volume

	right ventricle
RVAD	RV assist device
RVH	right ventricular hypertrophy
RVOT	RV outflow tract
RVSP	RV systolic pressure
Rx	therapy
RYGB	roux-en-Y gastric bypass
SA	sinoatrial
SAAG	serum-ascites albumin gradient
SAH	subarachnoid hemorrhage
SB	small bowel
SBE	subacute bacterial endocarditis
SBO	small bowel obstruction
SBP	spontaneous bacterial peritonitis
	systolic blood pressure
SBT	spontaneous breathing trial
SC	subcutaneous
SCD	sudden cardiac death
SCID	severe combined immunodefic.
SCLC	small-cell lung cancer
s/e	side effect
Se	sensitivity
sec	second
SERM	selective estrogen receptor modulator
sev.	severe
SHBG	steroid hormone binding globulin
SIADH	synd. of inappropriate ADH
SIBO	small intestine bacterial overgrowth
SIEP	serum immunoelectrophoresis
SIHD	stable ischemic heart disease
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SMX	sulfamethoxazole
SOS	sinusoidal obstructive synd.
s/p	status post
Sp	specificity
SPEP	serum protein electrophoresis
SR	sinus rhythm
s/s	signs and symptoms
SSCY	*Salmonella, Shigella, Campylobacter, Yersinia*
SSRI	selective serotonin reuptake inhibitor
SSS	sick sinus syndrome

SSZ	sulfasalazine
ST	sinus tachycardia
STD	ST-segment depression
STE	ST-segment elevation
STI	sexually transmitted infection
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
sx	symptom(s) or symptomatic
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
T_3RU	T_3 resin uptake
TAA	thoracic aortic aneurysm
TAVI	transcatheter aortic valve implantation
TB	tuberculosis
TBG	thyroid binding globulin
TCA	tricyclic antidepressant
TCD	transcranial Doppler
TCN	tetracycline
Tdap	tetanus, diphtheria, pertussis
TdP	torsades de pointes
TdT	terminal deoxynucleotidyl transferase
TEE	transesophageal echo
tfn	transfusion
TFTs	thyroid function tests
TG	triglycerides
TGA	transposition of the great arteries
TIA	transient ischemic attack
TIBC	total iron binding capacity
TINU	tubulointerstitial nephritis and uveitis
TIPS	transjugular intrahepatic portosystemic shunt
TKI	tyrosine kinase inhibitor
TLC	total lung capacity
TLS	tumor lysis syndrome
TMP	trimethoprim
Tn	troponin
TP	total protein
TPMT	thiopurine methyltransferase
TPN	total parenteral nutrition
Tpo	thrombopoietin
TPO	thyroid peroxidase
TR	tricuspid regurgitation
TRALI	transfusion-related acute lung injury
TRH	thyrotropin-releasing hormone
TRS	TIMI risk score

TRUS	transrectal ultrasound
TS	tricuspid stenosis
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TSS	toxic shock syndrome transsphenoidal surgery
TTE	transthoracic echo
TTKG	transtubular potassium gradient
TTP	thrombotic thrombocytopenic purpura
TV	tricuspid valve
Tw	T wave
TWF	T-wave flattening
TWI	T-wave inversion
Tx	transplant
TZD	thiazolidinediones
U/A	urinalysis
UA	unstable angina
UAG	urine anion gap
UC	ulcerative colitis
UCx	urine culture
UES	upper esophageal sphincter
UFH	unfractionated heparin
UGIB	upper gastrointestinal bleed
UIP	usual interstitial pneumonitis
ULN	upper limit of normal
UOP	urine output
UPEP	urine protein electrophoresis
UR	urgent revascularization
UrA	uric acid
URI	upper resp. tract infxn
U/S	ultrasound
UTI	urinary tract infection
V/Q	ventilation-perfusion
VAD	ventricular assist device
VAP	ventilator-associated PNA
VATS	video-assisted thoracoscopic surgery
VBI	vertebrobasilar insufficiency
VC	vital capacity
VD	vessel disease
VDRL	venereal disease research laboratory (test for syphilis)
VEGF	vascular endothelial growth factor
VEXAS	vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic
VF	ventricular fibrillation
VLDL	very-low-density lipoproteins
VOD	veno-occlusive disease
VS	vital signs

VSD	ventricular septal defect
Vt	tidal volume
VT	ventricular tachycardia
VTE	venous thromboembolus
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZV	varicella zoster virus
w/	with
WBC	white blood cell (count)
WCT	wide-complex tachycardia
WHO	World Health Organization
wk	week
WM	Waldenström's macroglobulinemia
WMA	wall motion abnormality
w/o	without
WPW	Wolff-Parkinson-White syndrome
w/u	workup
XRT	radiation therapy

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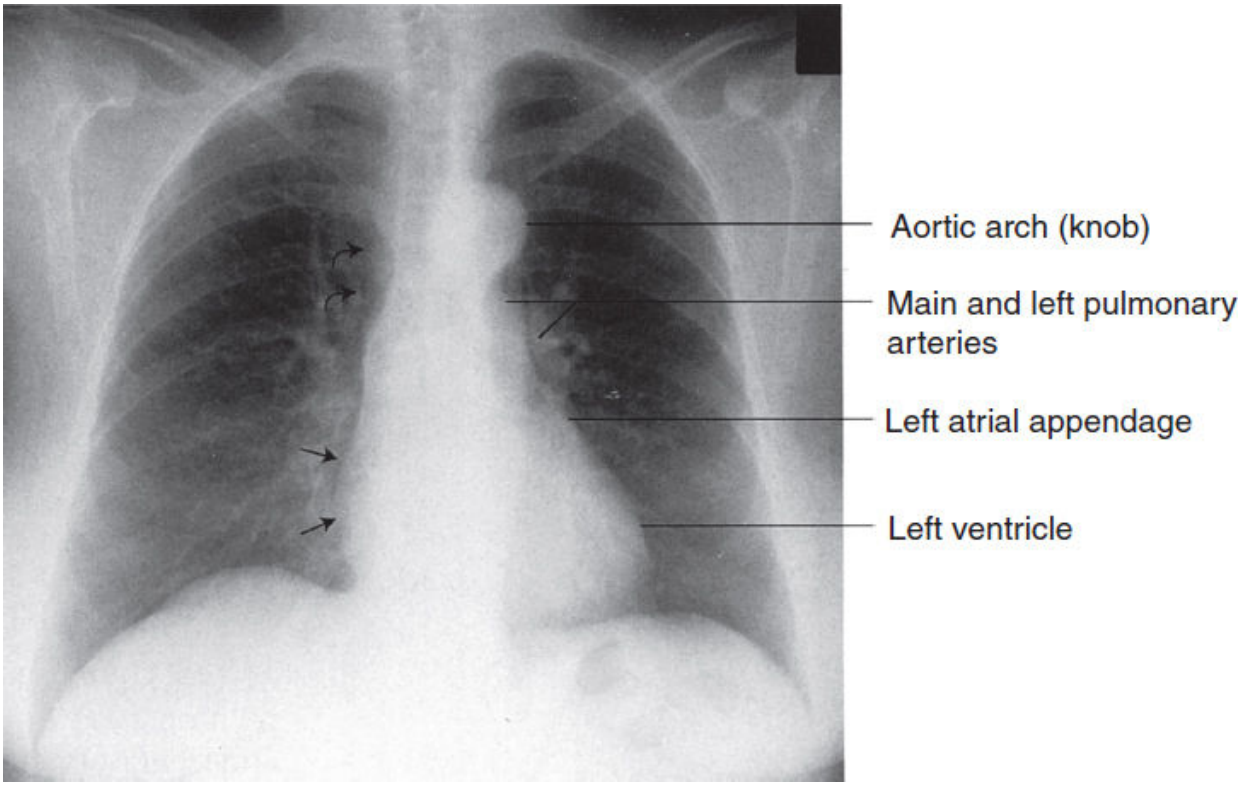
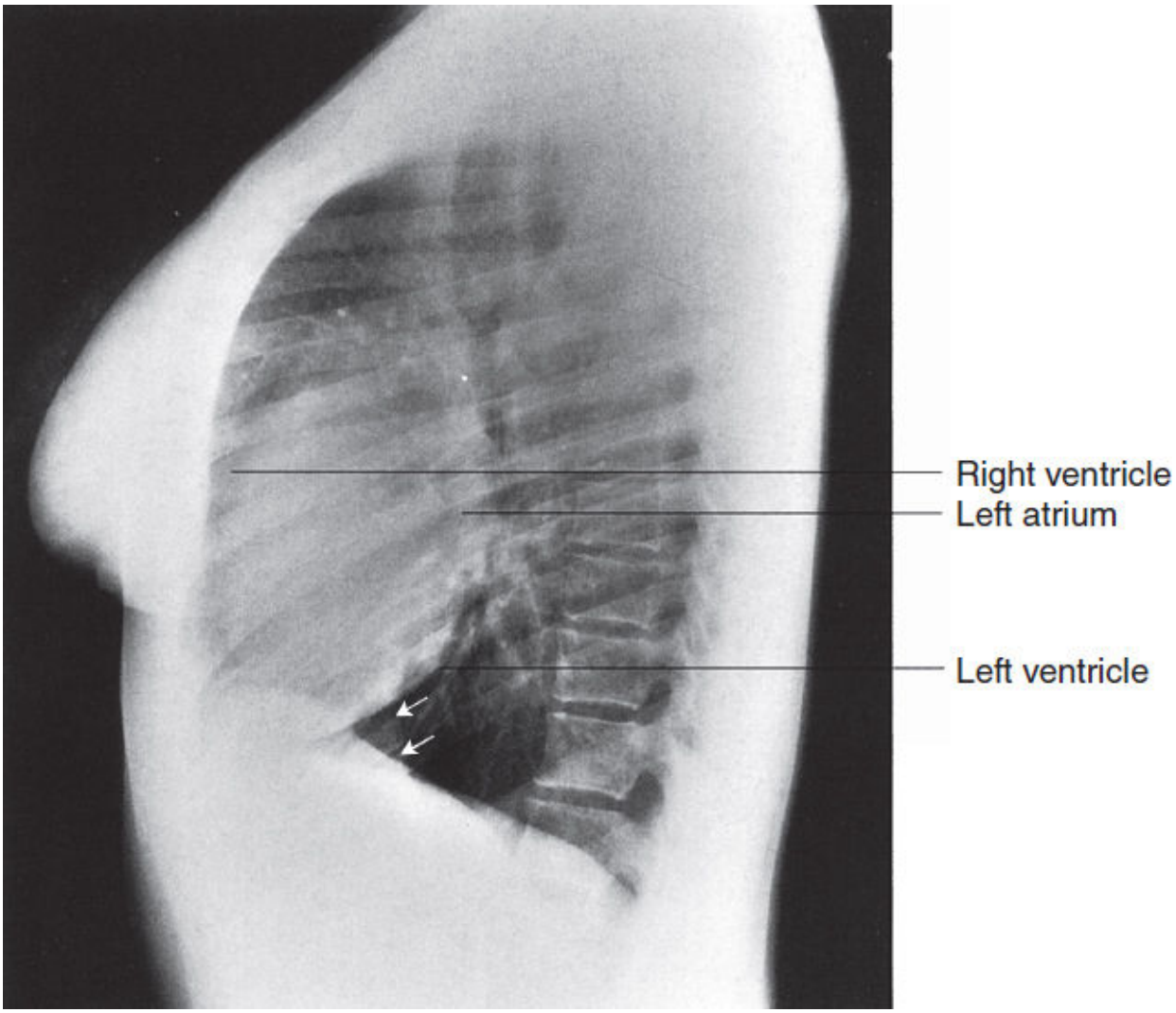
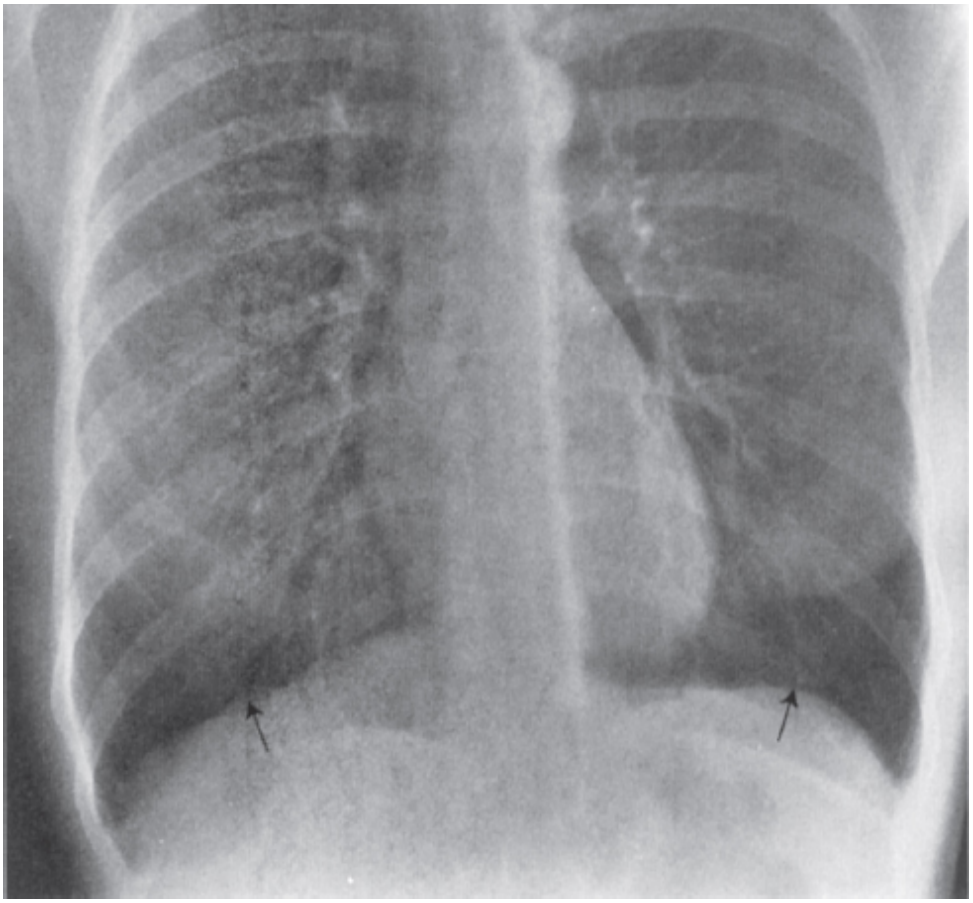


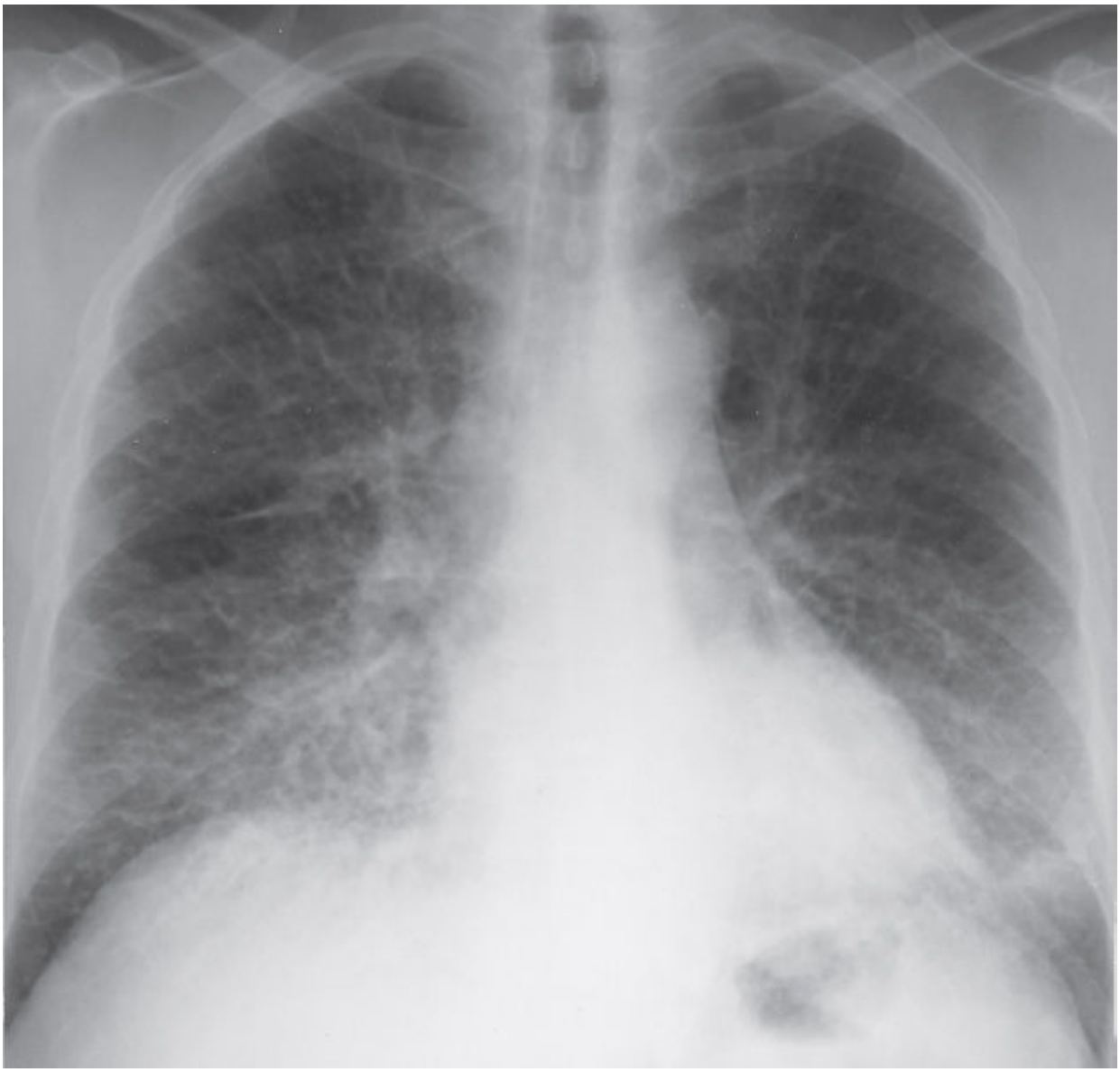
1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicate the location of the superior vena cava. The left cardiac and great vessels border what might be considered as 4 skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (*Radiology* 101, 3rd ed, 2009.)



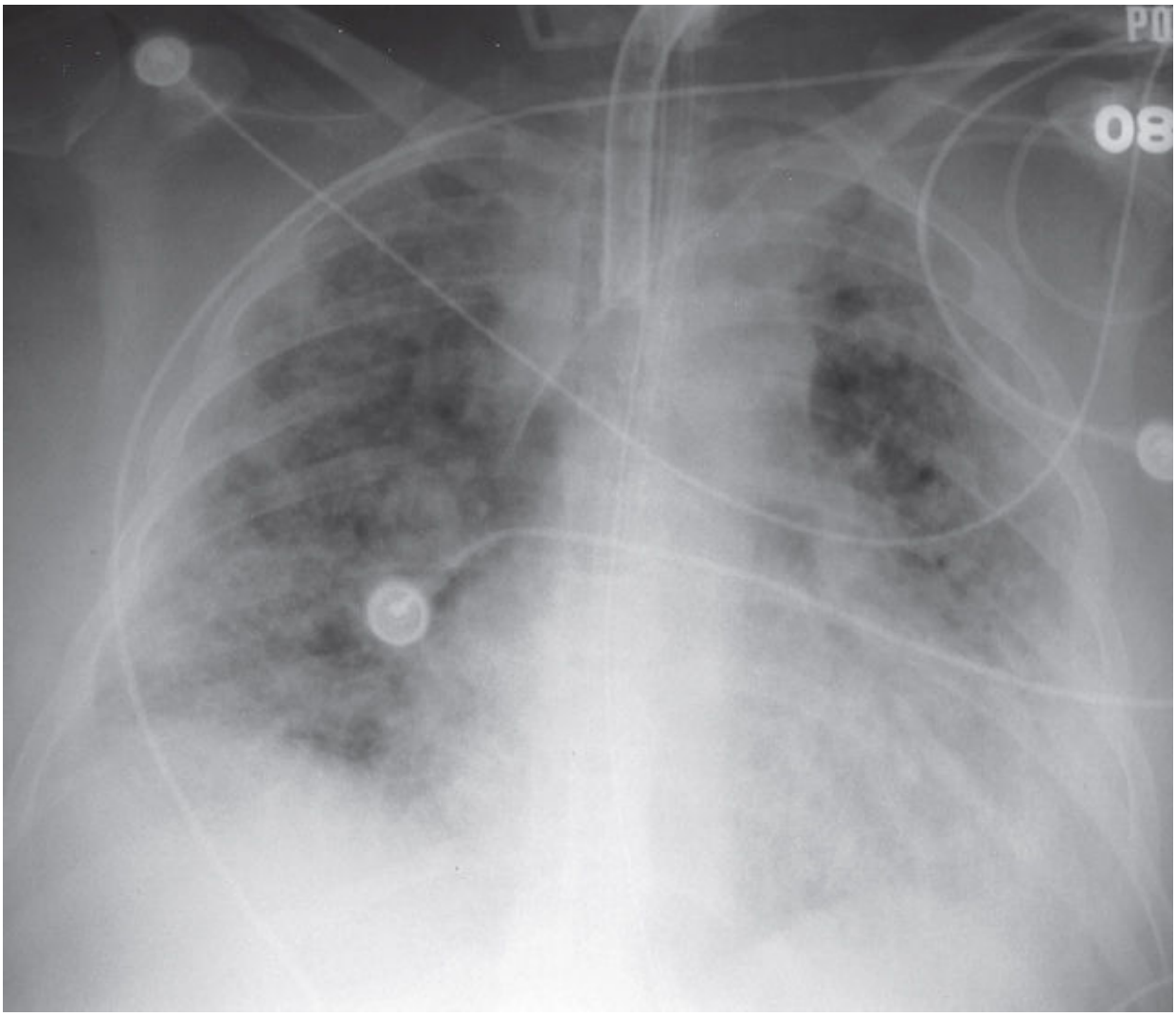
2 Normal lateral CXR. (*Radiology* 101, 3rd ed, 2009.)



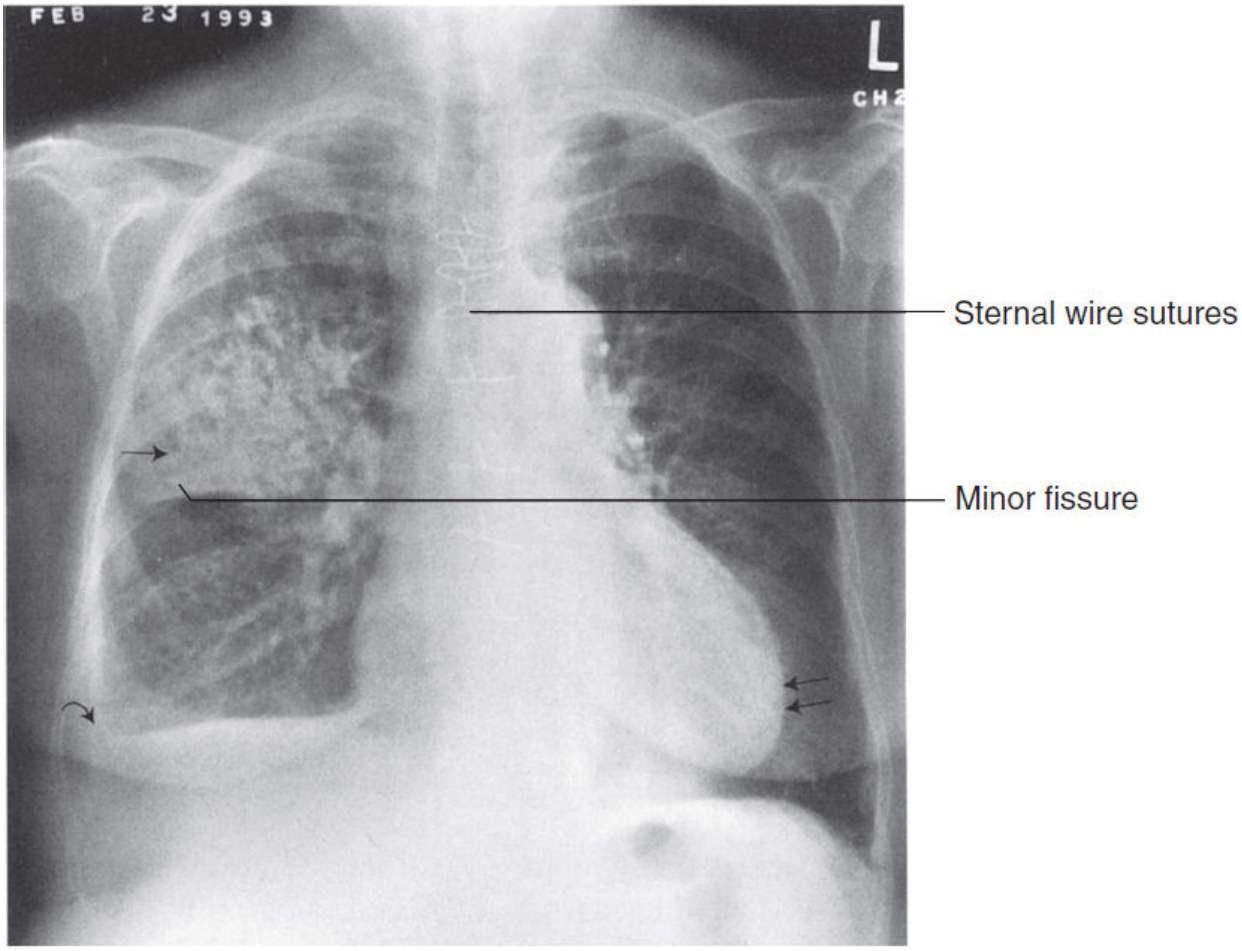
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology* 101, 3rd ed, 2009.)



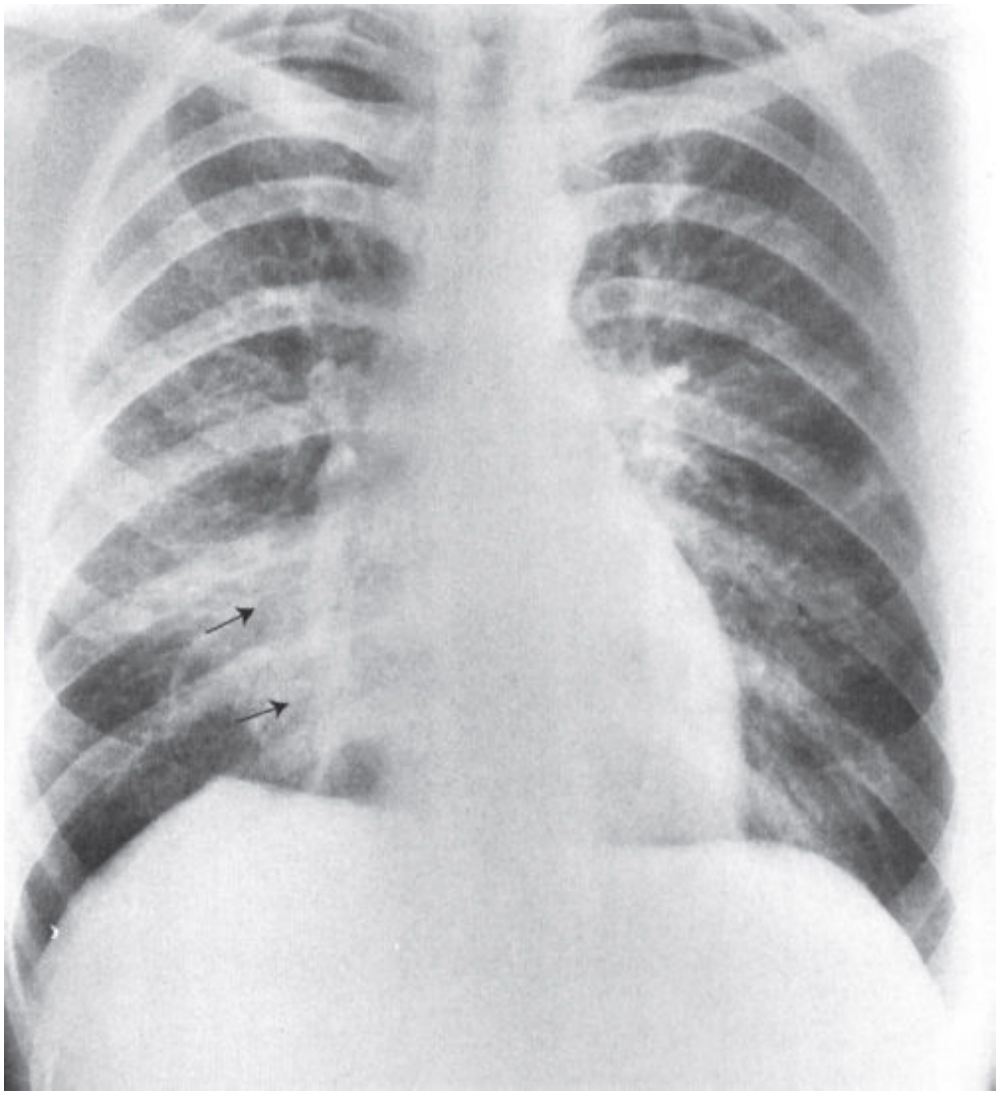
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology,* 3rd ed, 2006.)



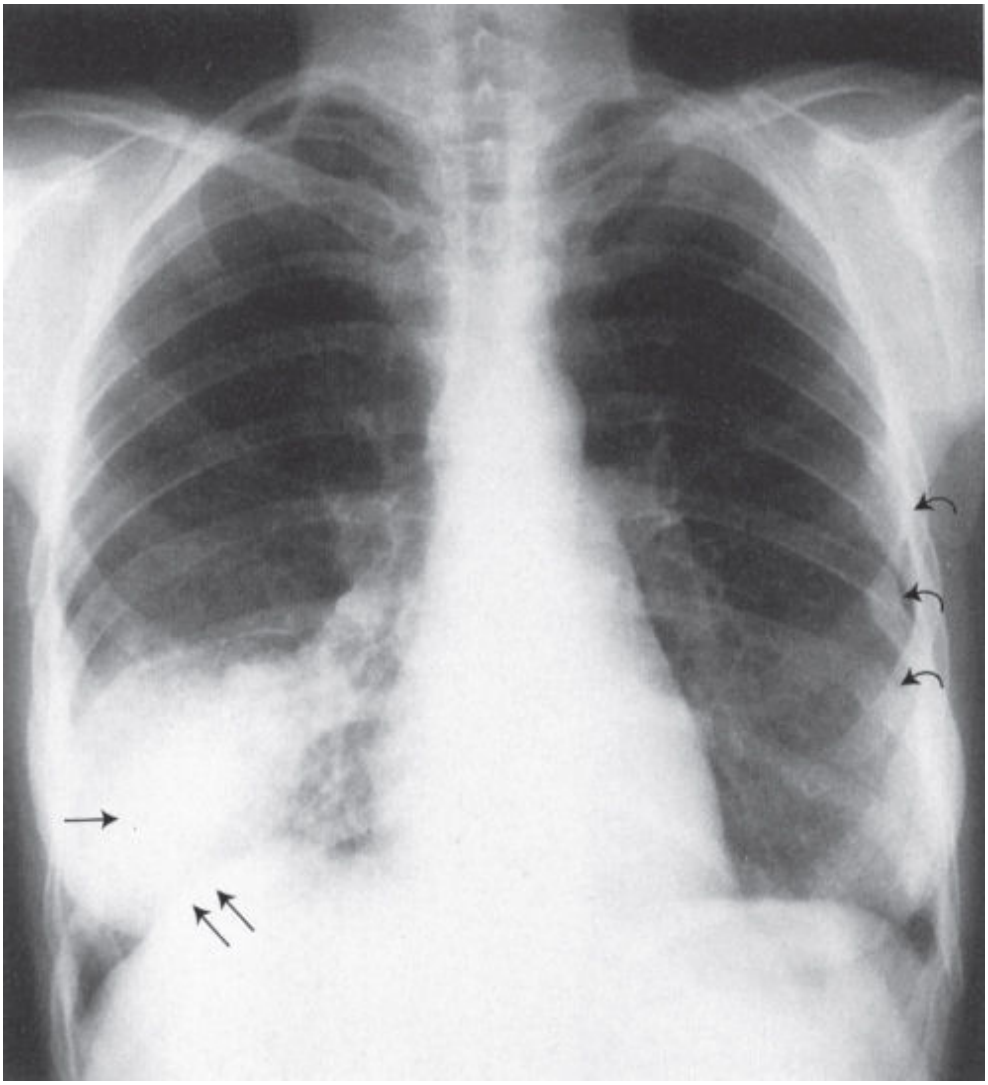
5 Alveolar pulmonary edema. (*Fund. Diag. Radiology,* 3rd ed, 2006.)



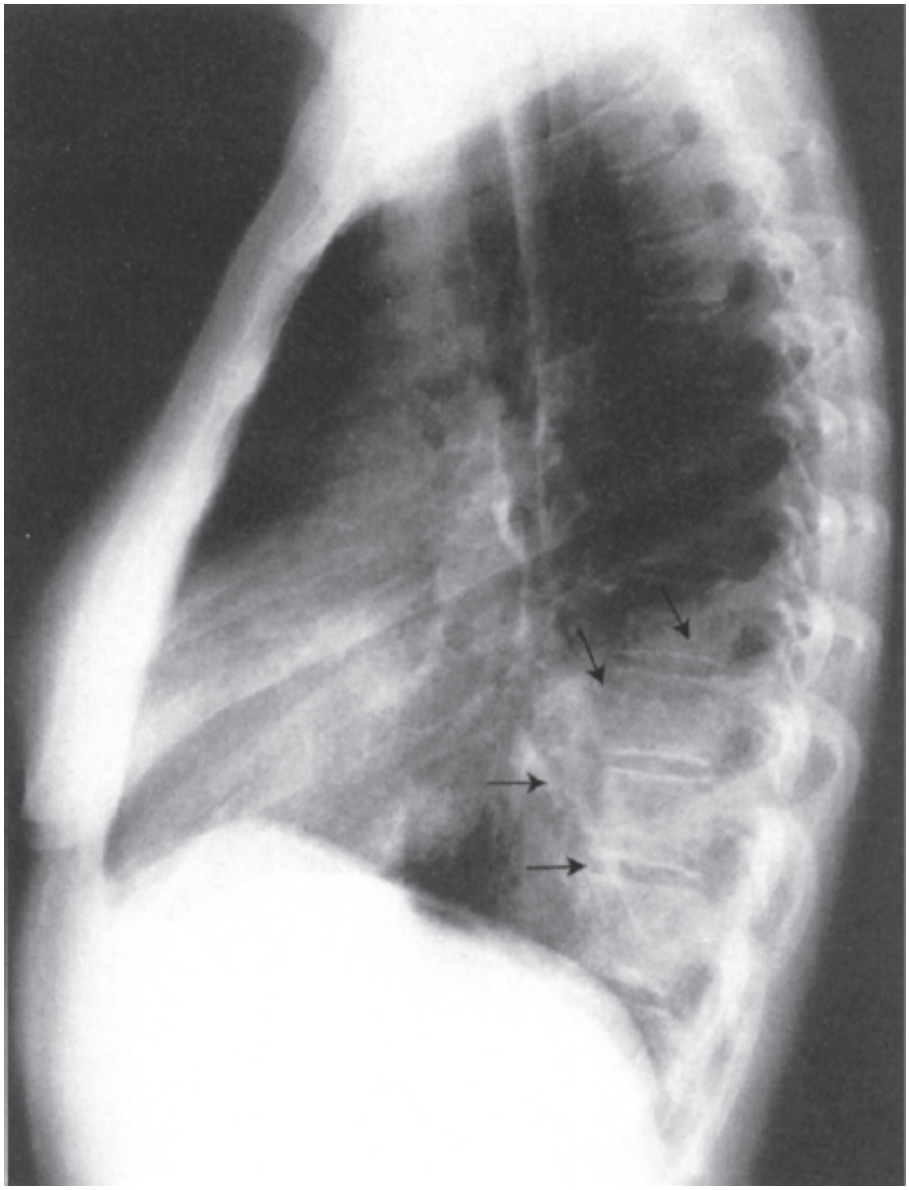
6 Right upper lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



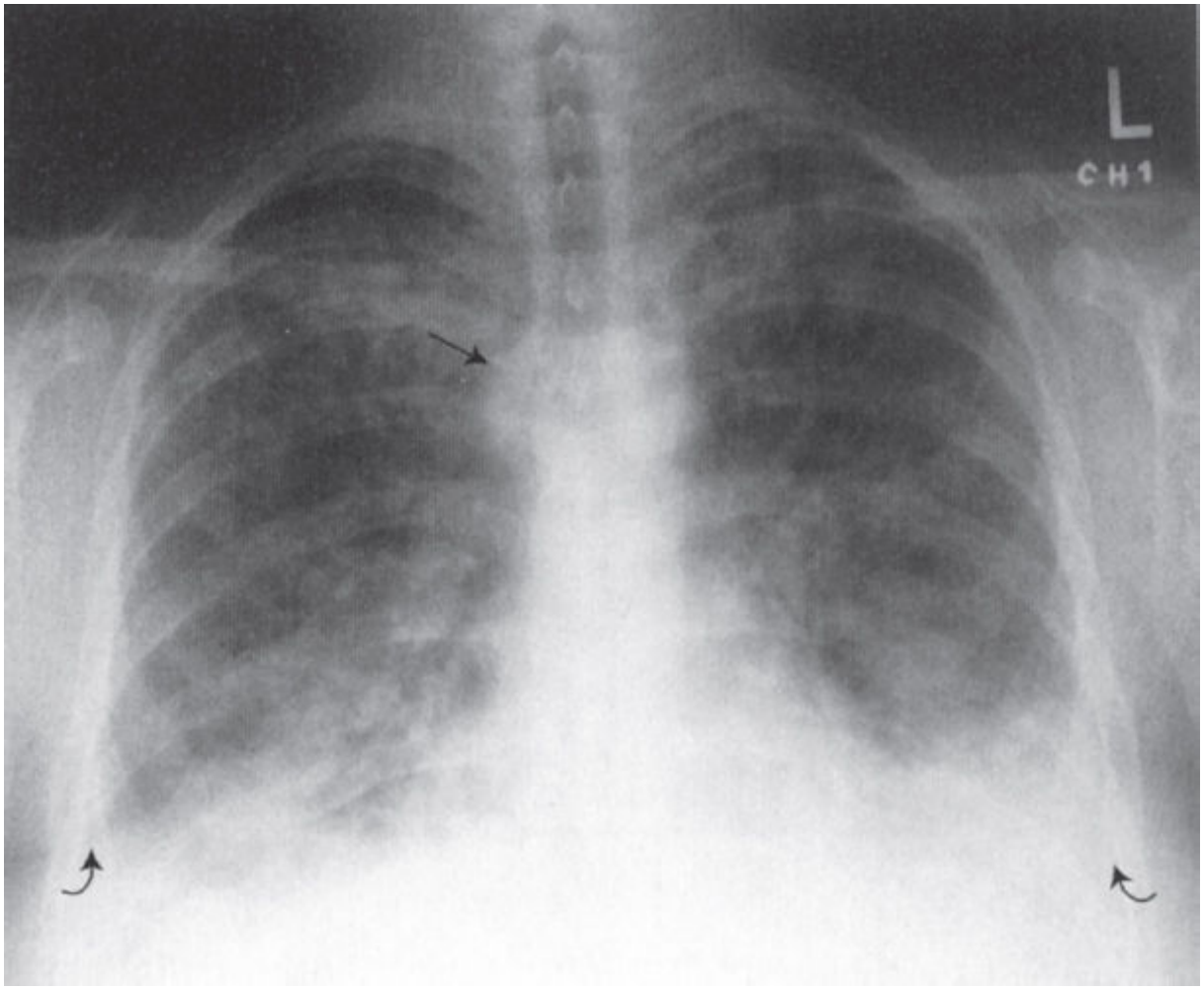
7 Right middle lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



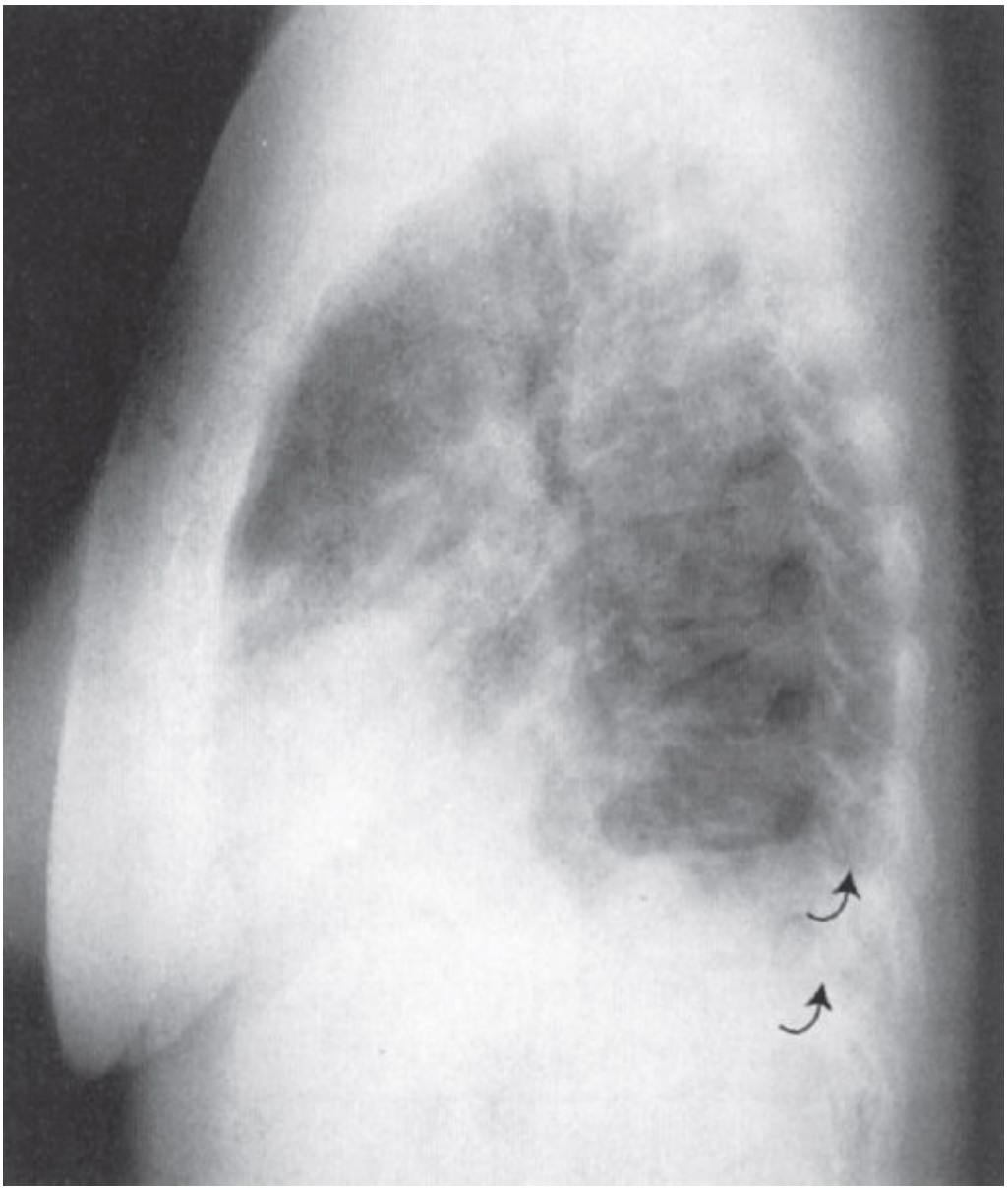
8 Right lower lobe pneumonia (PA). (*Radiology* 101, 3rd ed, 2009.)



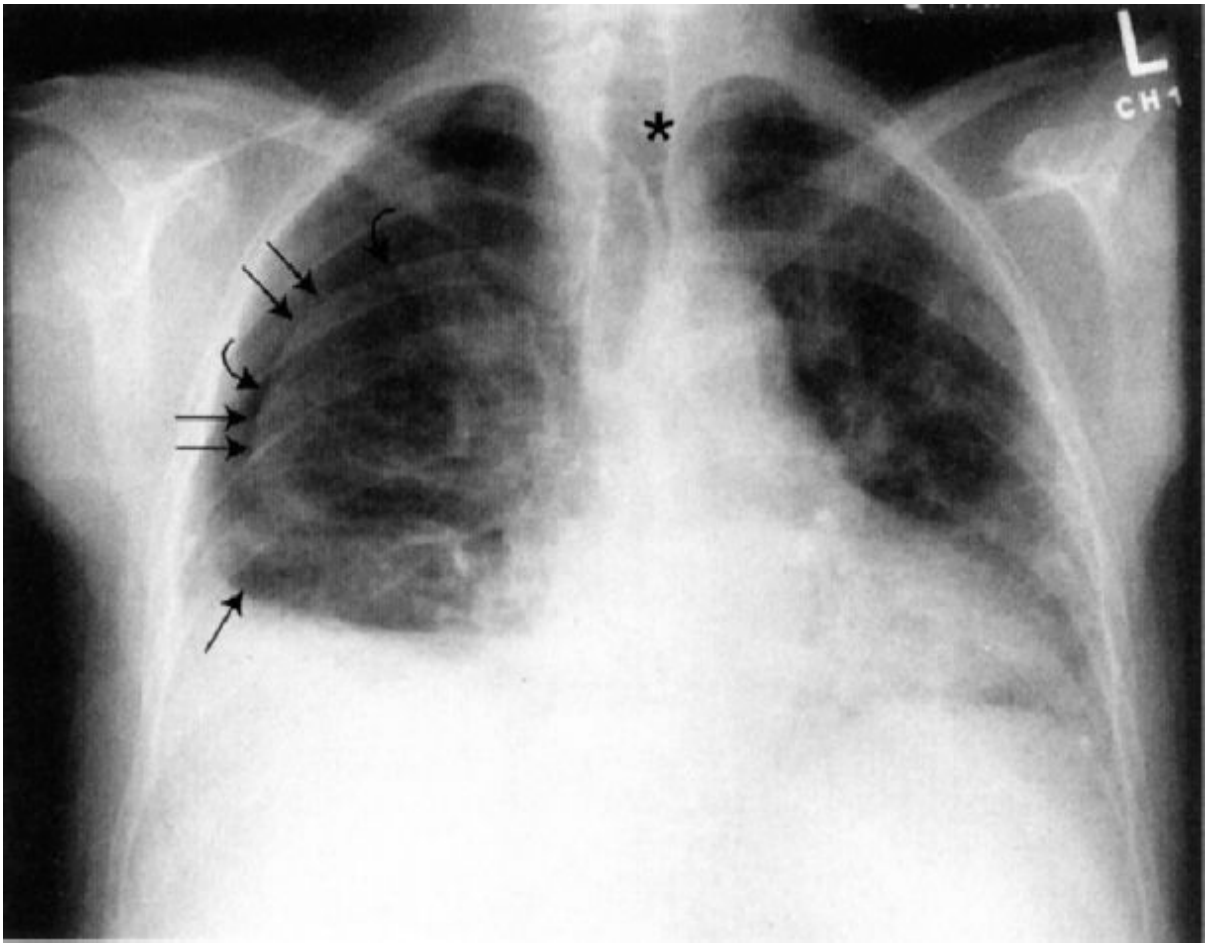
9 Right lower lobe pneumonia (lateral). (*Radiology* 101, 3rd ed, 2009.)



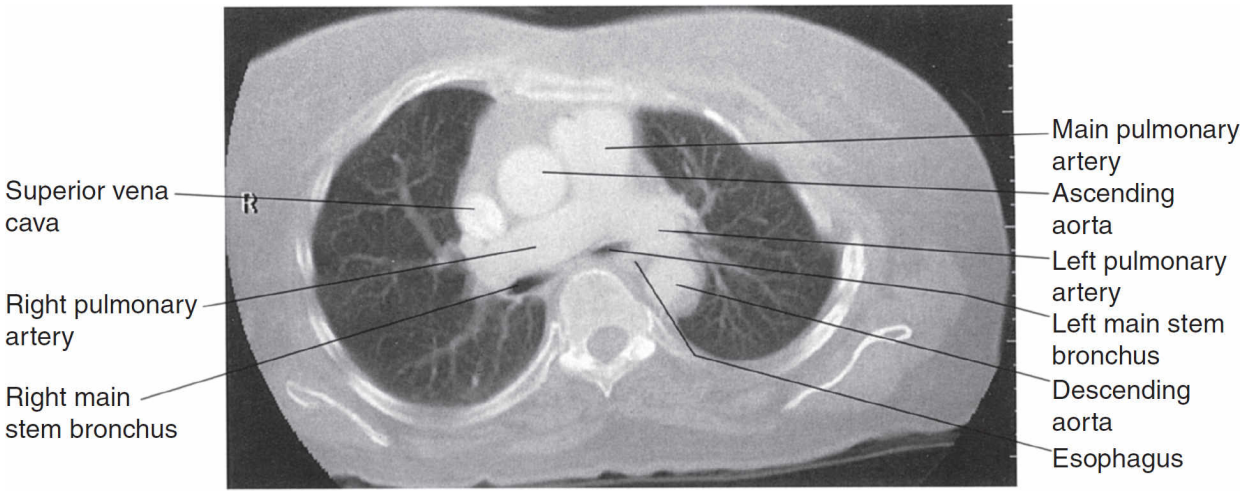
10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow). (PA). (*Radiology* 101, 3rd ed, 2009.)



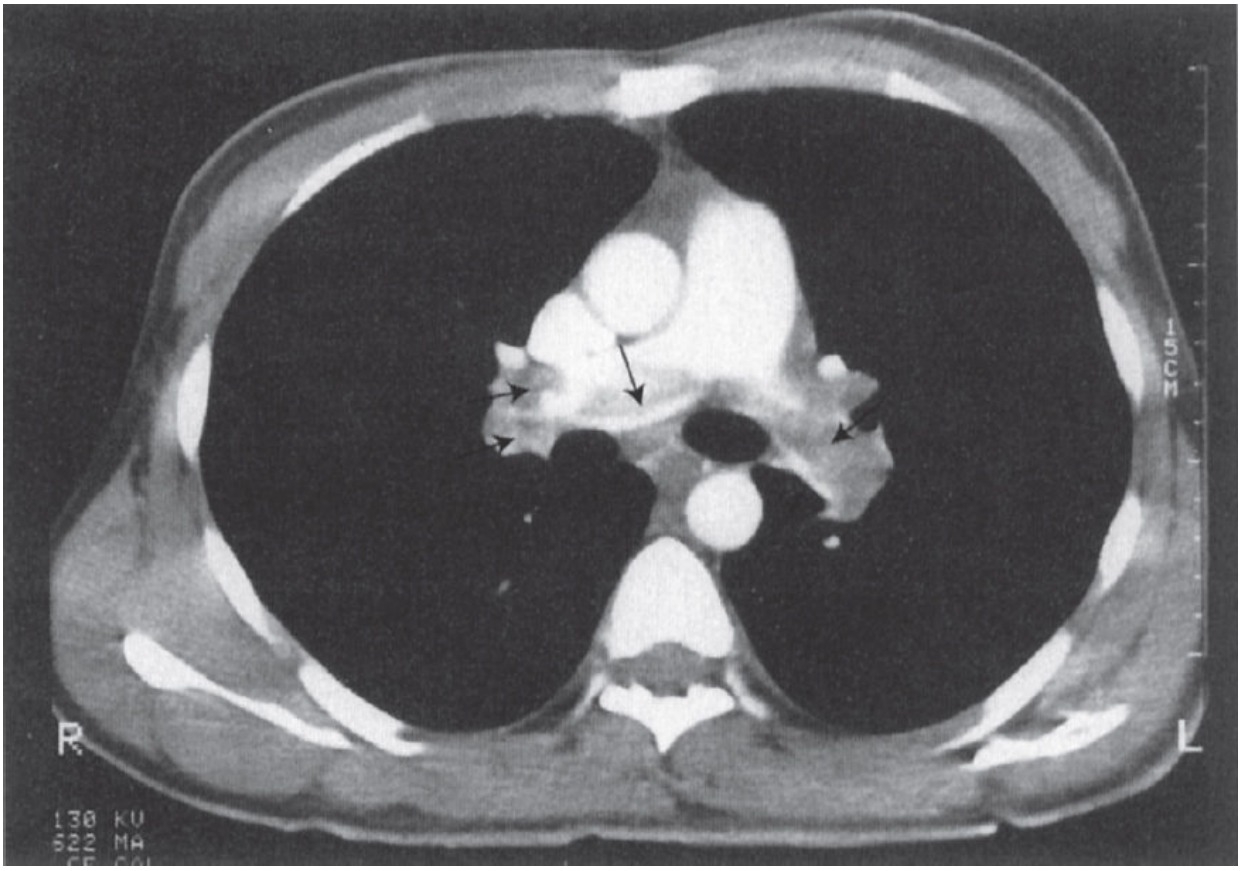
11 Bilateral pleural effusions (curved arrows) (lateral). (*Radiology* 101, 3rd ed, 2009.)



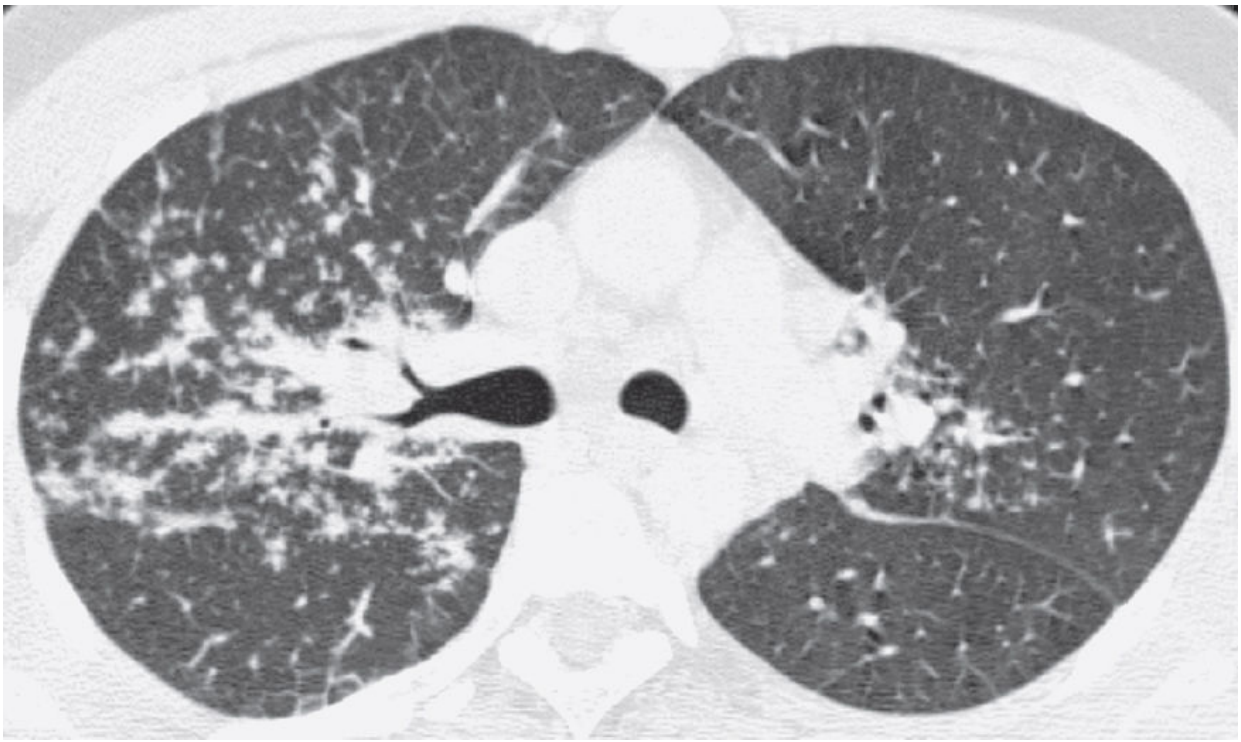
12 Pneumothorax. (*Radiology* 101, 3rd ed, 2009.)



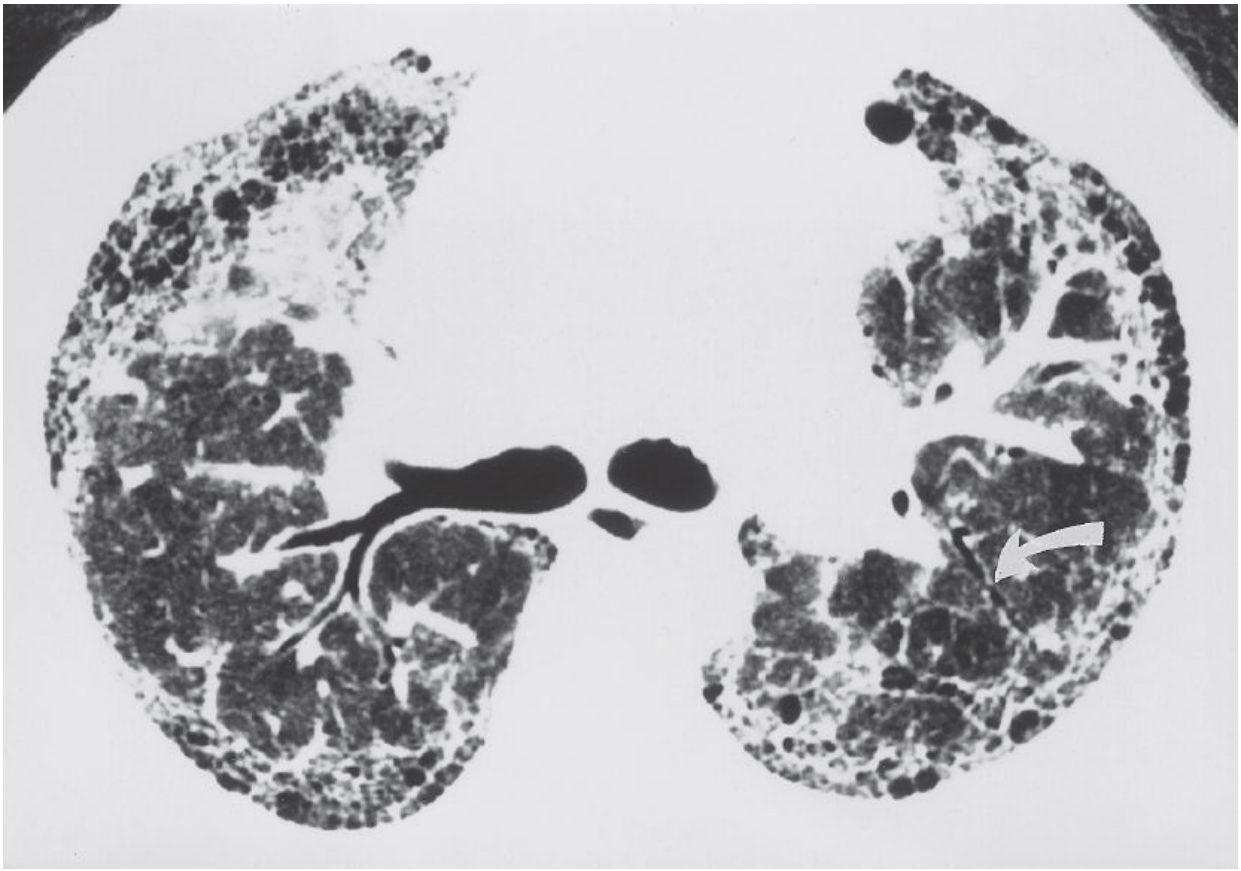
13 Normal chest CT at level of pulmonary arteries (parenchymal windows). (*Radiology* 101, 3rd ed, 2009.)



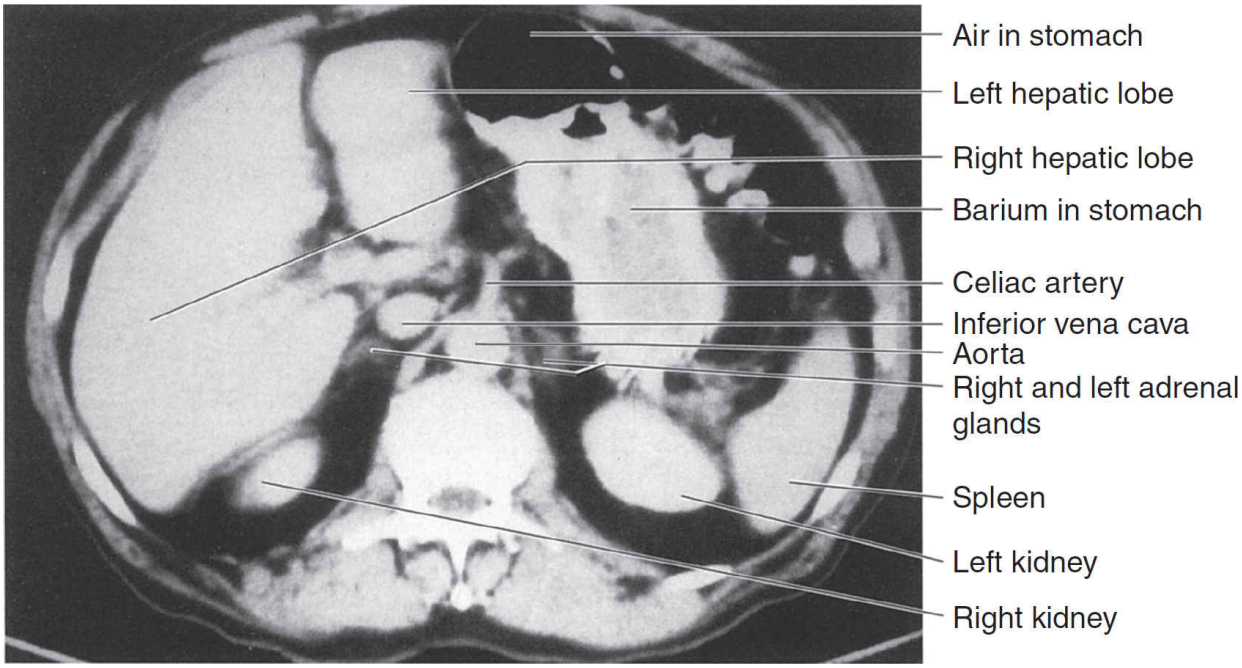
14 Bilateral PE (mediastinal windows). (*Radiology* 101, 3rd ed, 2009.)



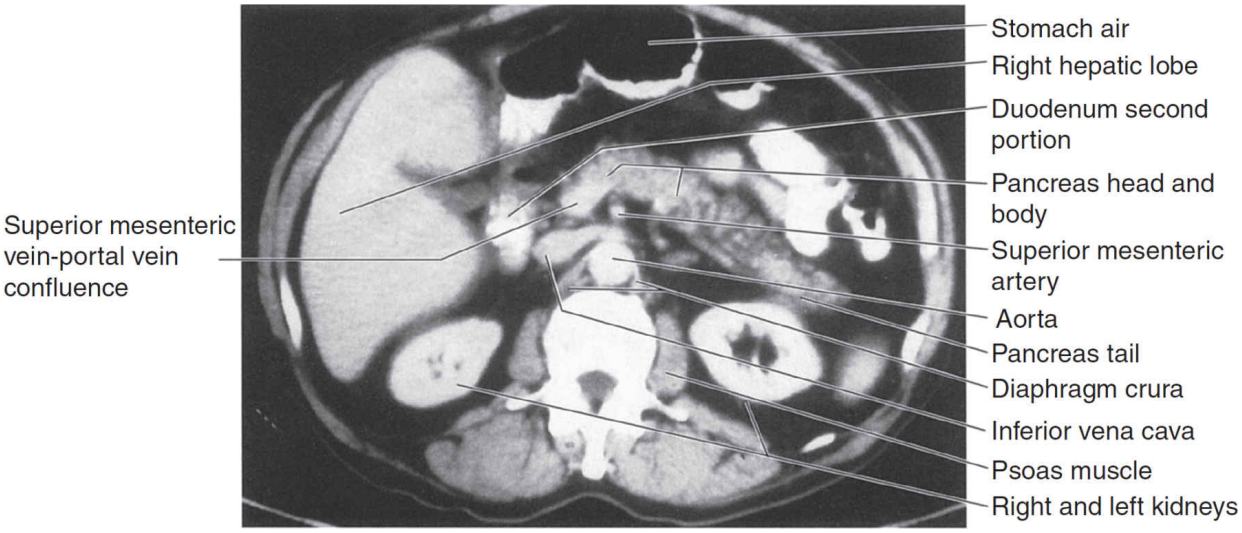
15 Sarcoidosis with perilymphatic nodules. (*Fund. Diag. Radiology,* 3rd ed, 2006.)



16 Idiopathic pulmonary fibrosis. (*Fund. Diag. Radiology,* 3rd ed, 2006.)

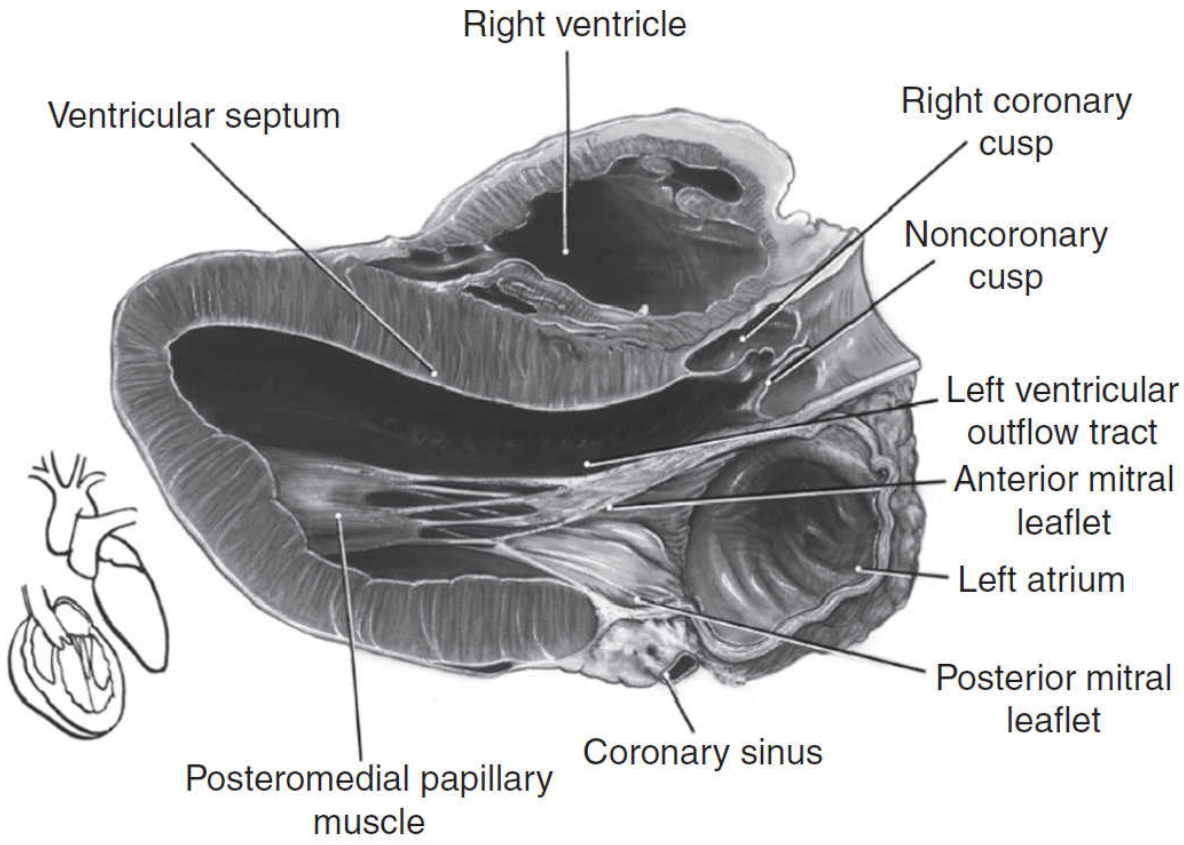


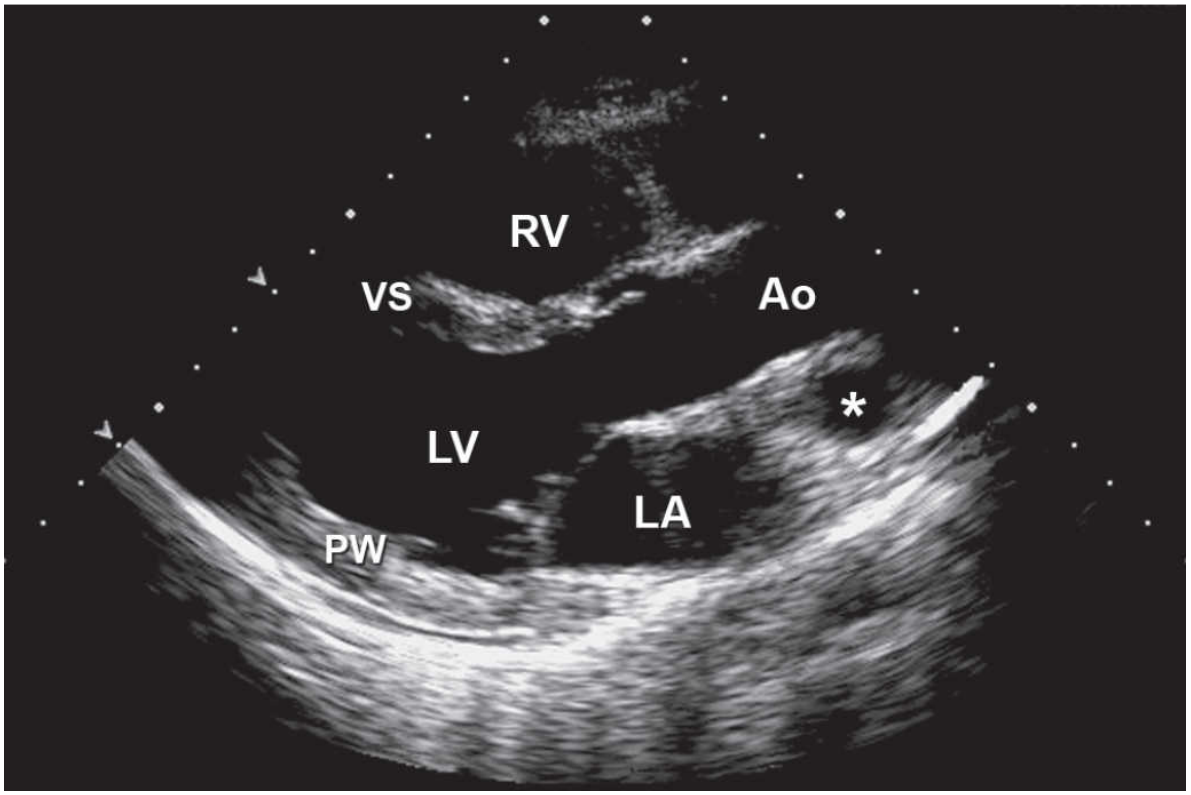
17 Normal abdomen CT at level of liver & spleen. (*Radiology* 101, 3rd ed, 2009.)



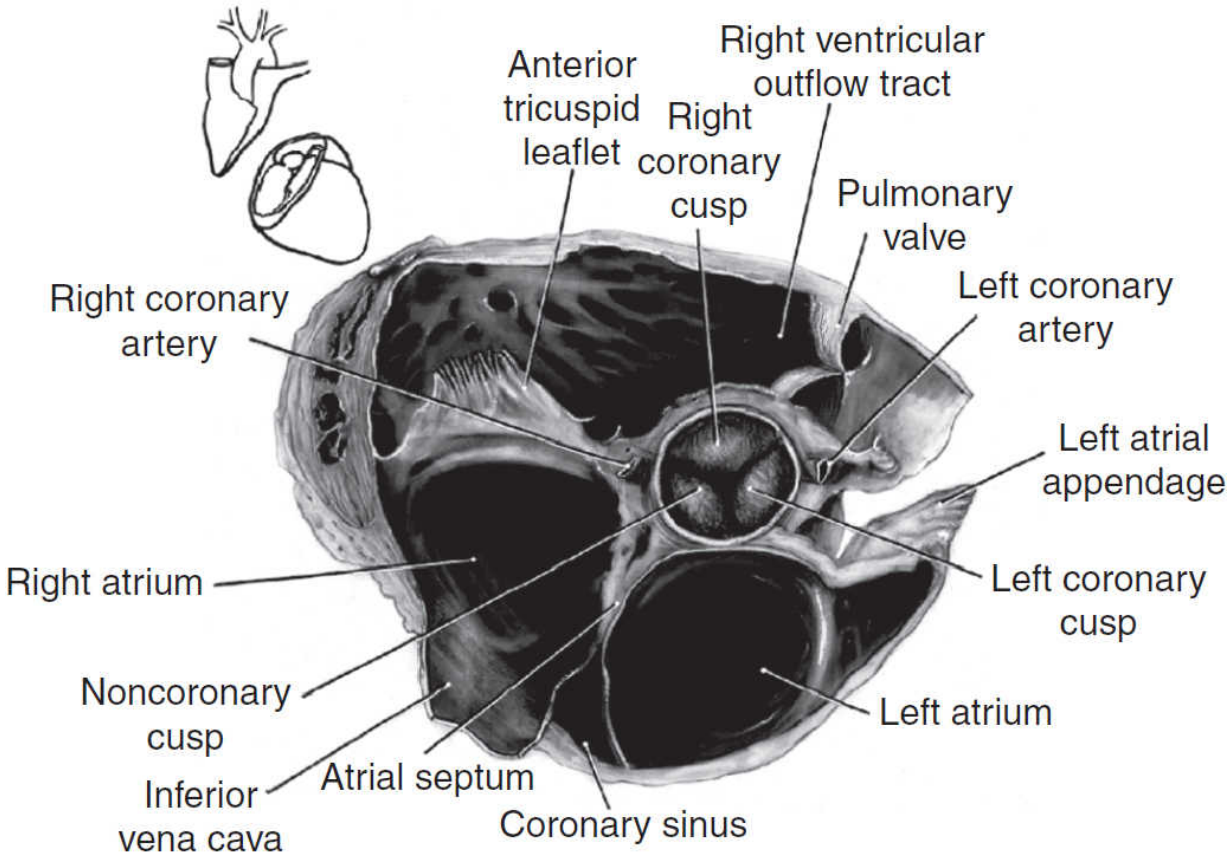
18 Normal abdomen CT at level of pancreas. (*Radiology* 101, 3rd ed, 2009.)

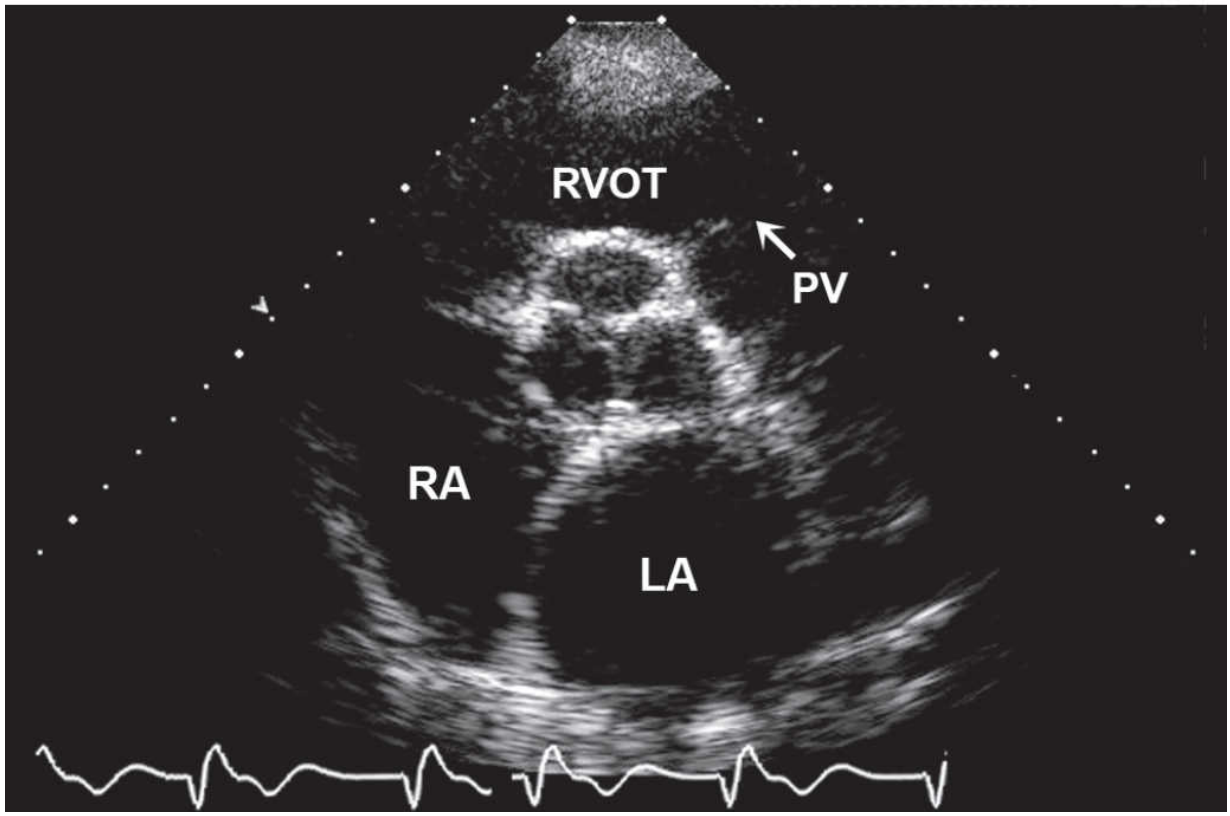
Echocardiography


Right ventricle
Ventricular septum
Right coronary cusp
Noncoronary cusp
Left ventricular outflow tract
Anterior mitral leaflet
Left atrium
Posterior mitral leaflet
Coronary sinus
Posteromedial papillary muscle

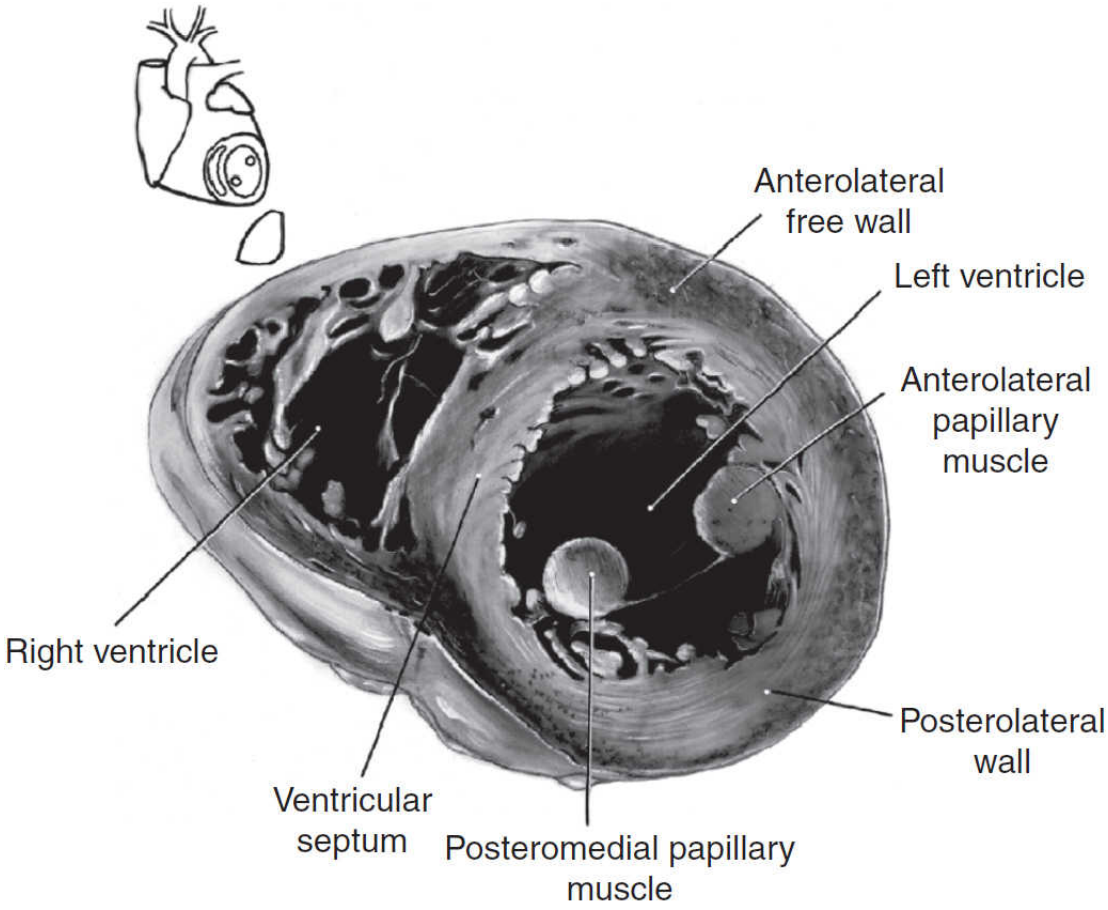

RV
VS
Ao
*
LV
LA
PW

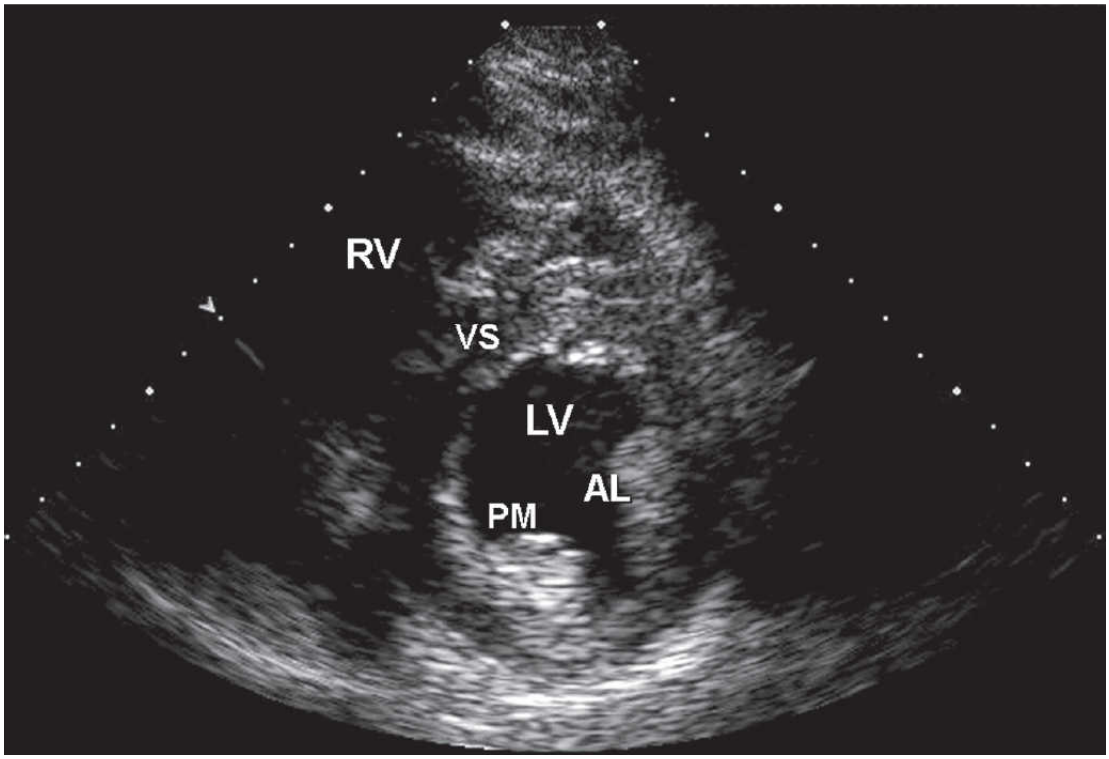
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ventricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: From Mayo Clinic Proceedings [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006.)


Anterior tricuspid leaflet
Right ventricular outflow tract
Right coronary cusp
Pulmonary valve
Right coronary artery
Left coronary artery
Left atrial appendage
Right atrium
Left coronary cusp
Noncoronary cusp
Left atrium
Inferior vena cava
Atrial septum
Coronary sinus

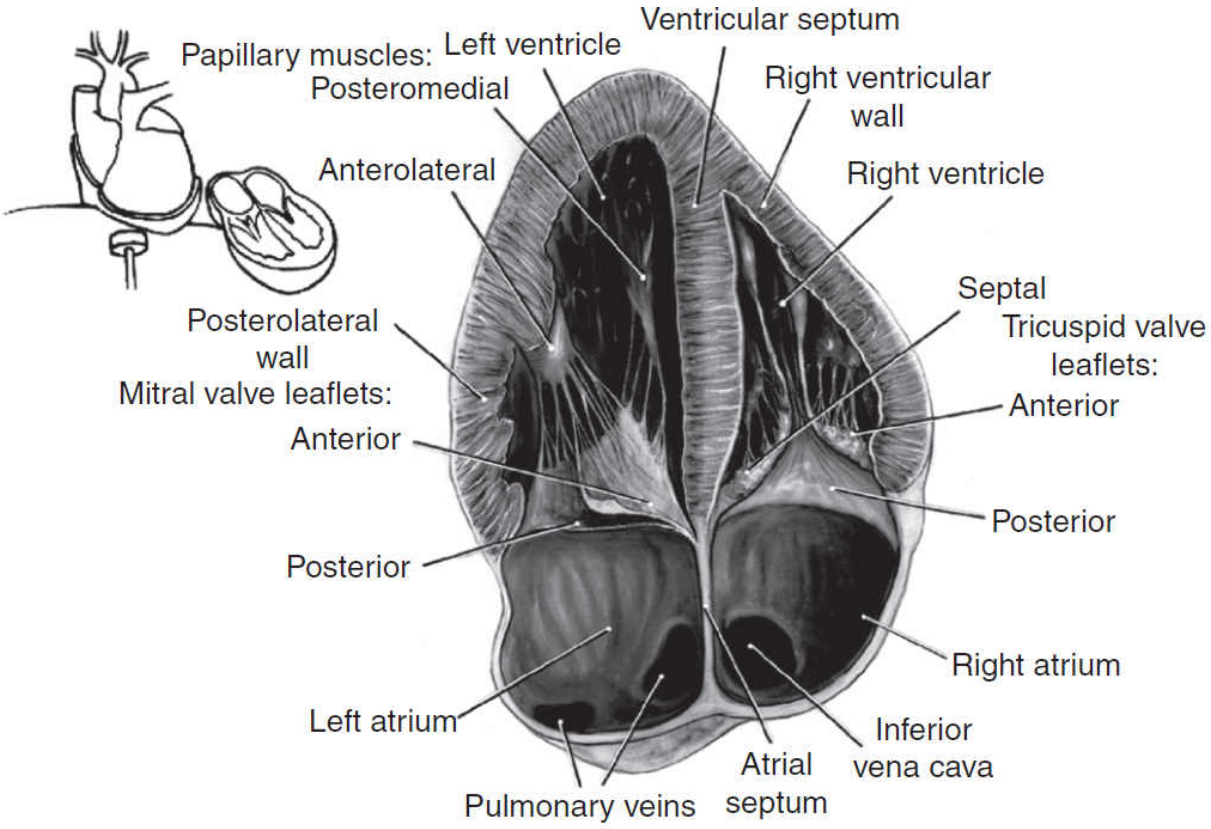

RVOT
PV
RA
LA

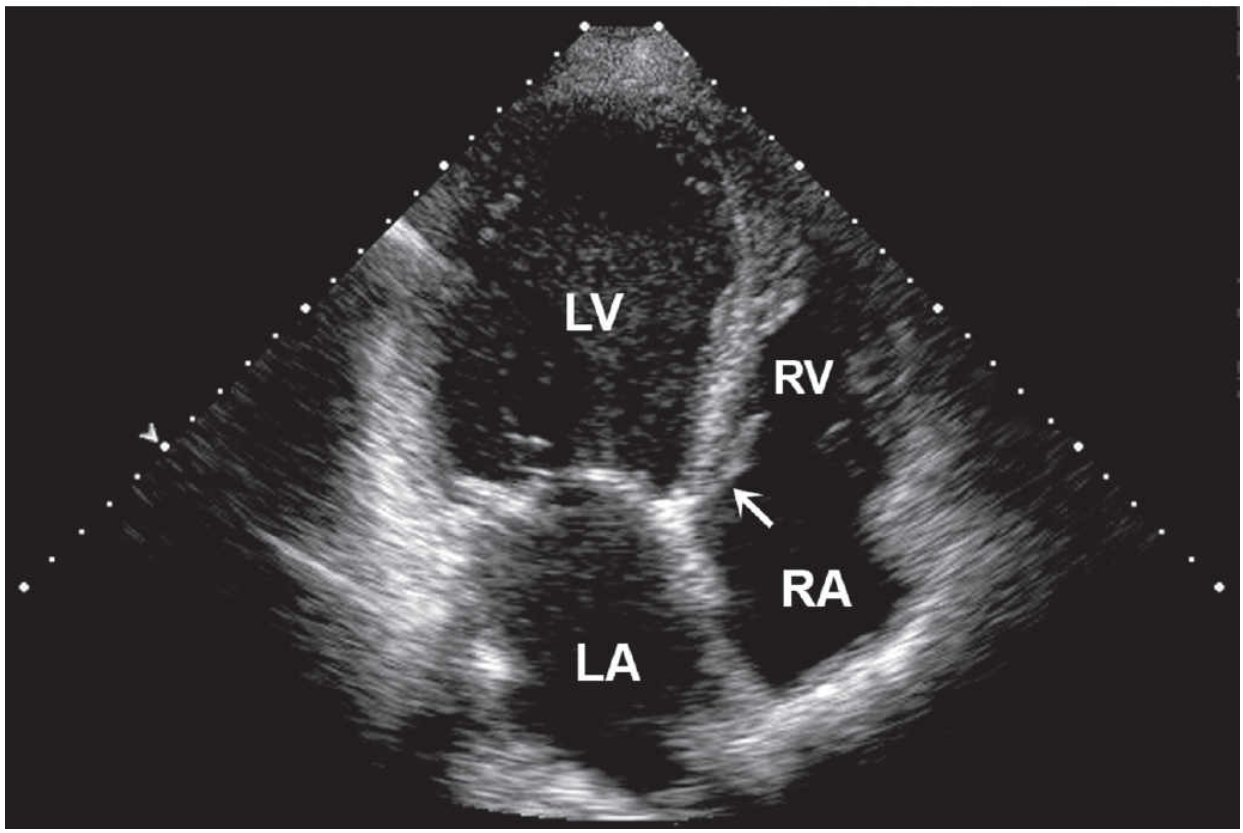
2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: From Mayo Clinic Proceedings [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings,* 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual, 3rd ed.* Philadelphia: Lippincott Williams & Wilkins, 2006.)


Anterolateral free wall
Left ventricle
Anterolateral papillary muscle
Right ventricle
Posterolateral wall
Ventricular septum
Posteromedial papillary muscle


RV
VS
LV
AL
PM

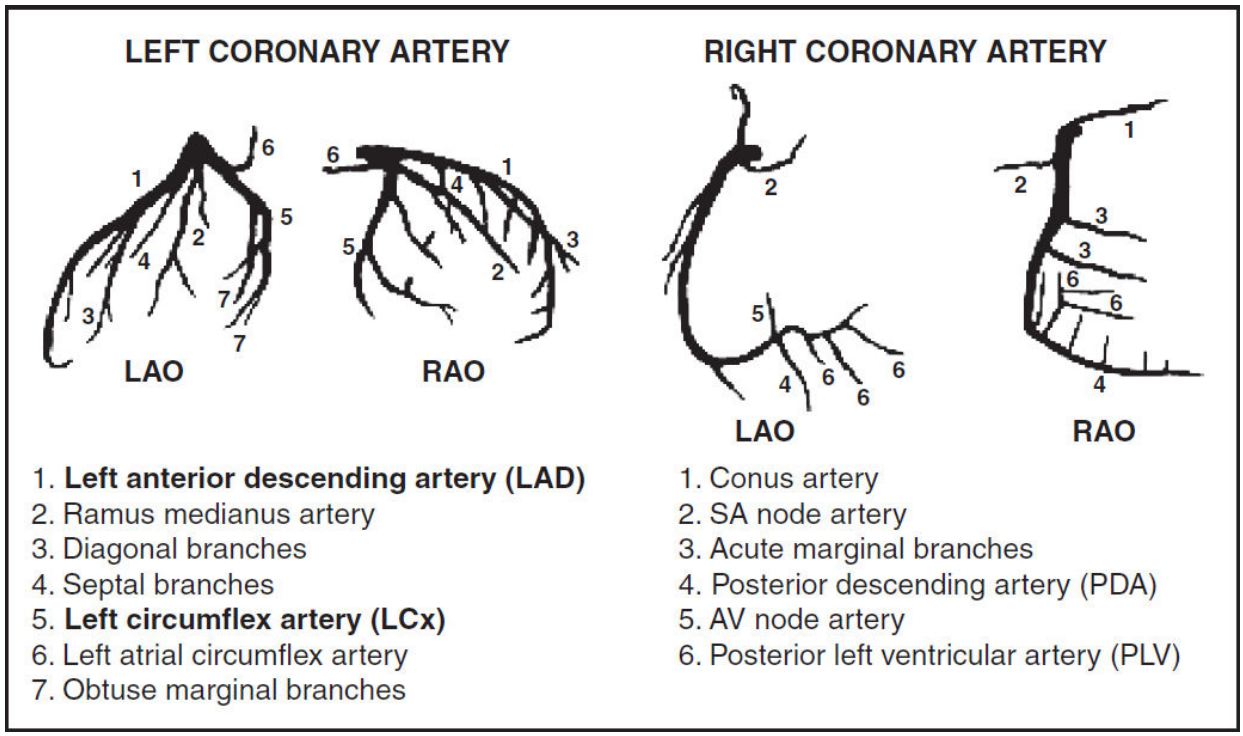
3 Parasternal short-axis view at the level of the papillary muscles: AL, anterolateral papillary muscle; LV, left ventricle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum. (Top: From *Mayo Clinic Proceedings* [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual, 3rd ed.* Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


Papillary muscles:
Posteromedial
Anterolateral
Left ventricle
Ventricular septum
Right ventricular wall
Right ventricle
Septal
Tricuspid valve leaflets:
Anterior
Posterior
Posterolateral wall
Mitral valve leaflets:
Anterior
Posterior
Left atrium
Pulmonary veins
Atrial septum
Inferior vena cava
Right atrium


LV
RV
RA
LA

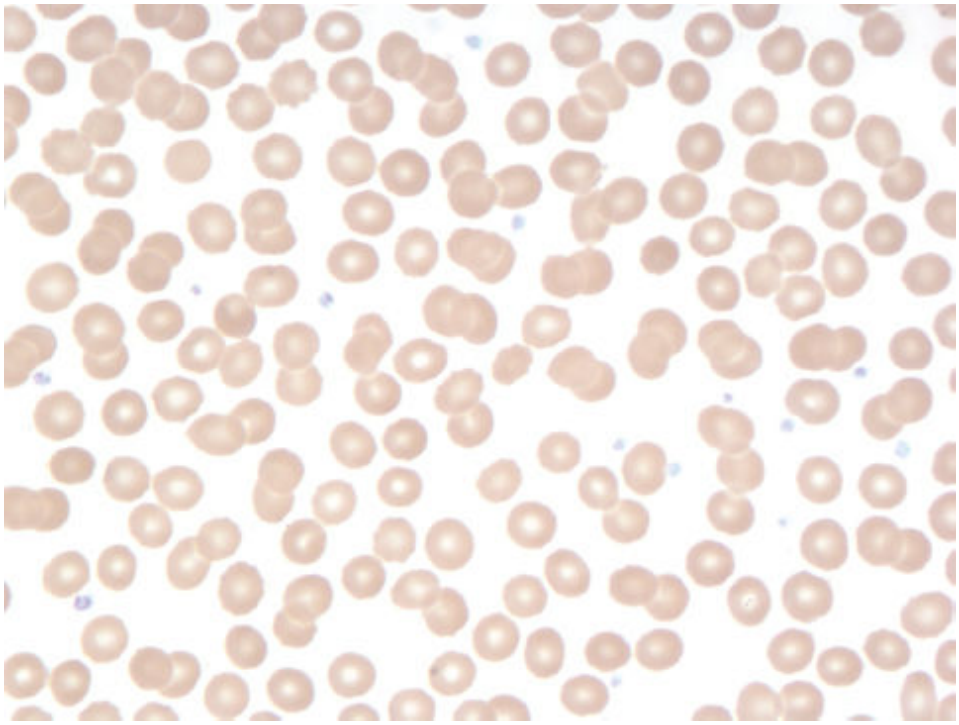
4 Apical four-chamber view: Note that at some institutions the image is re- versed so that the left side of the heart appears on the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: From *Mayo Clinic Proceedings* [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Coronary Angiography

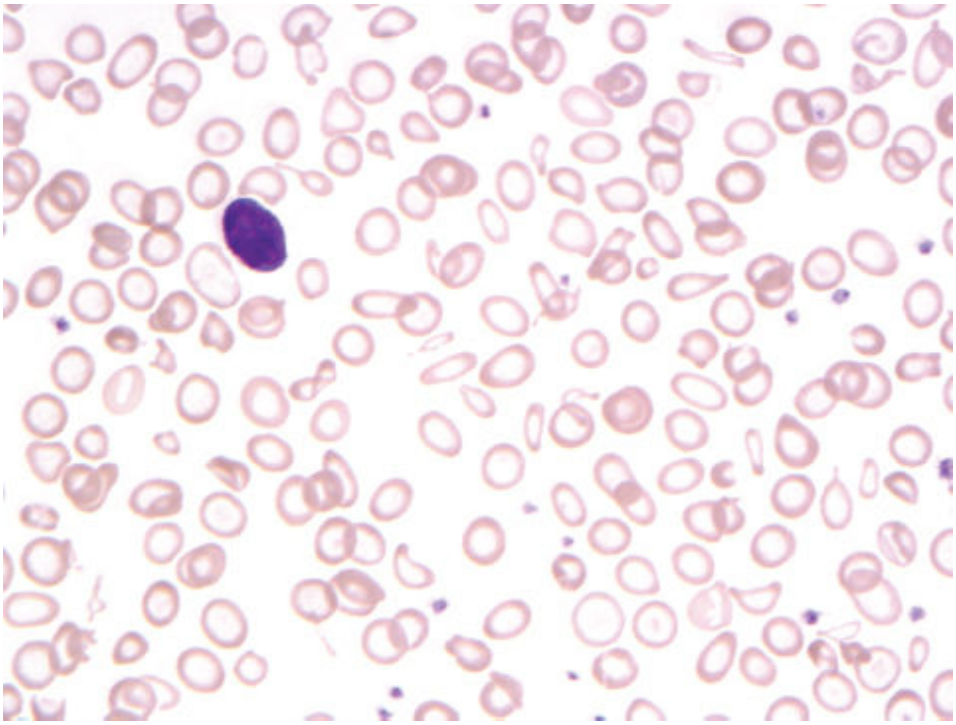


Coronary arteries. (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

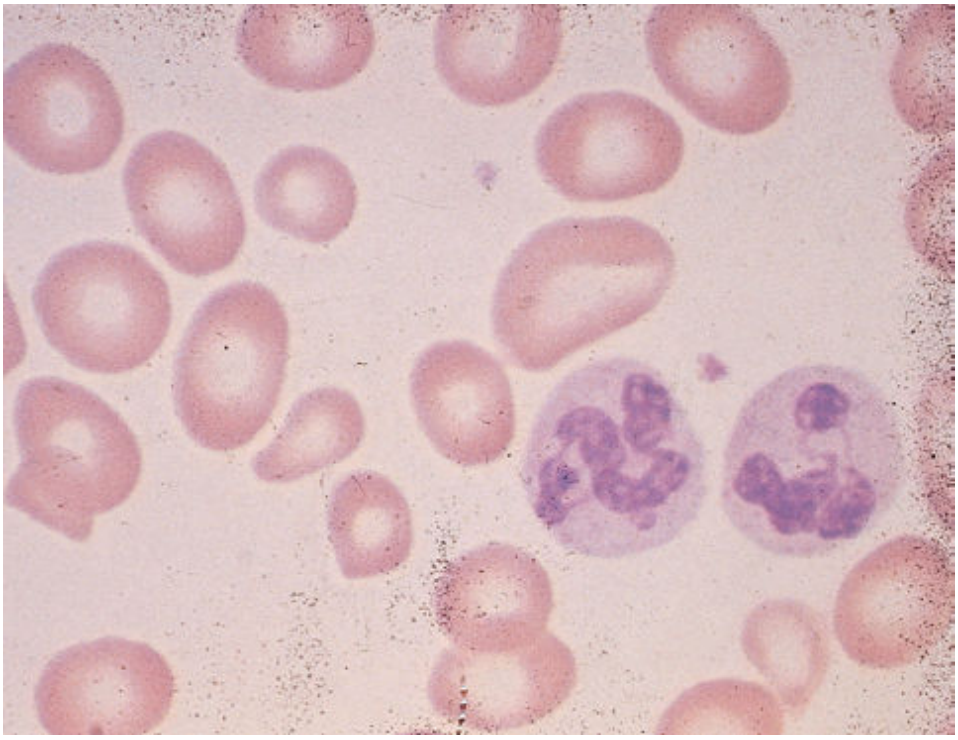
Peripheral Blood Smears



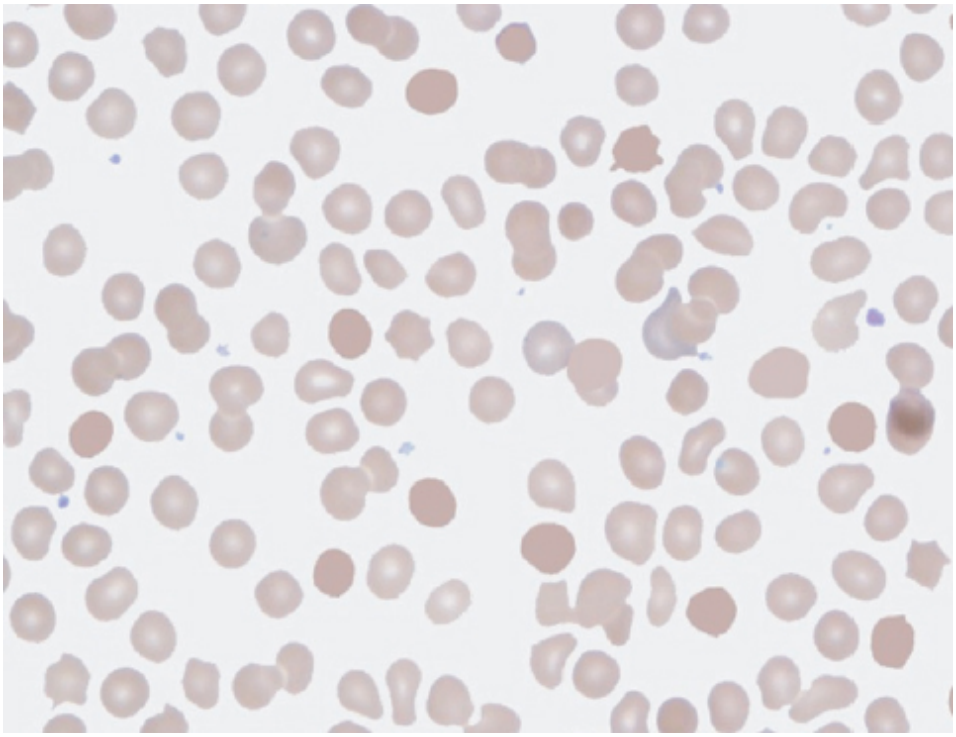
1 Normal smear.



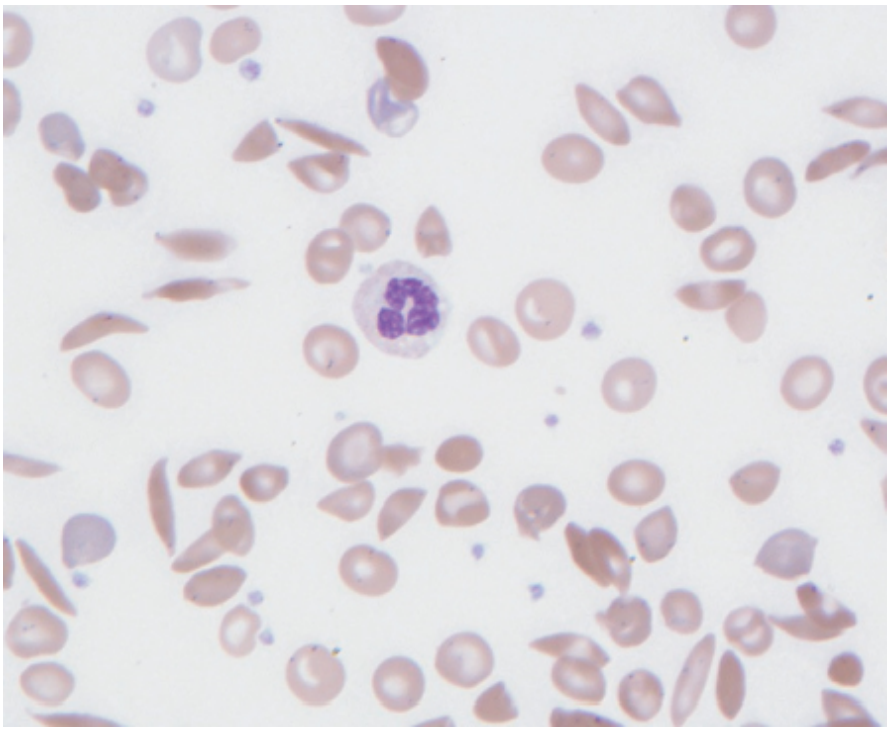
2 Hypochromic, microcytic anemia due to iron-deficiency.



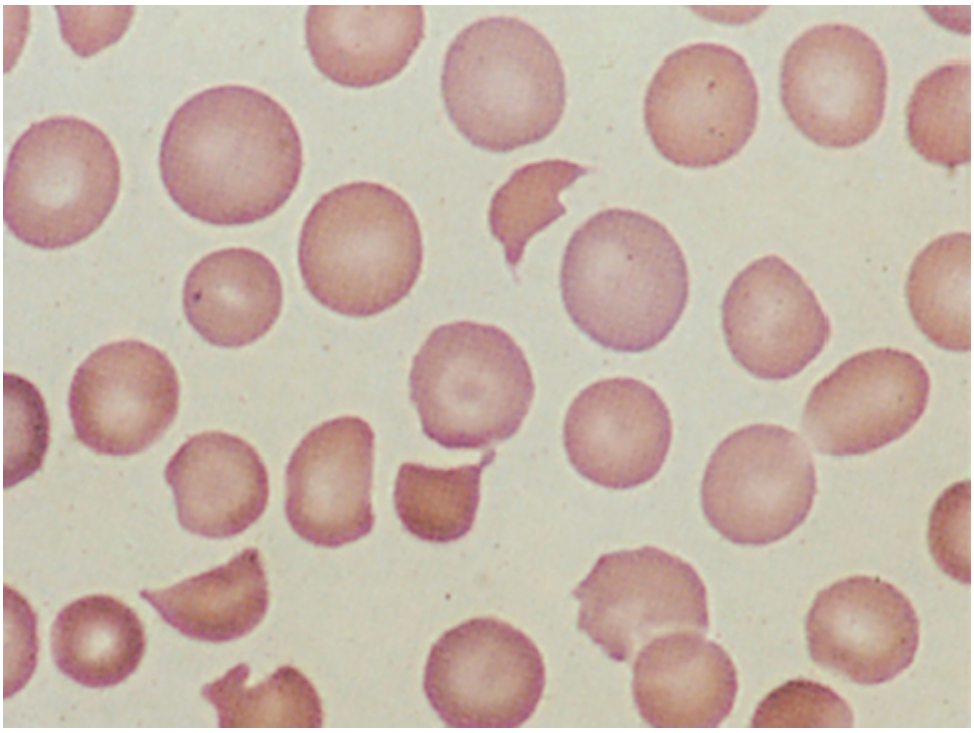
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



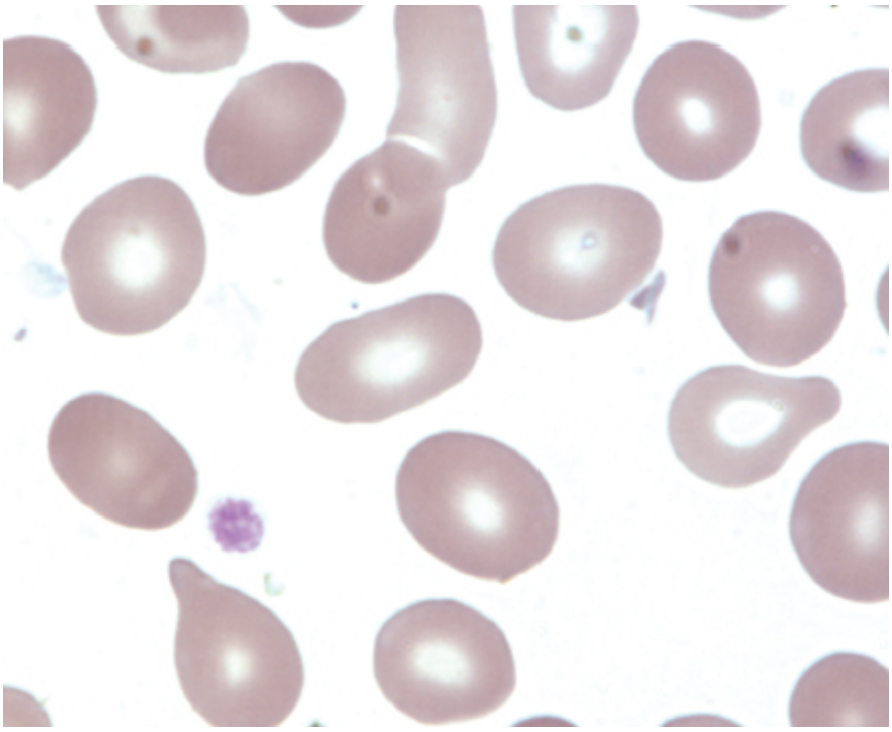
4 Spherocytes due to autoimmune hemolytic anemia.



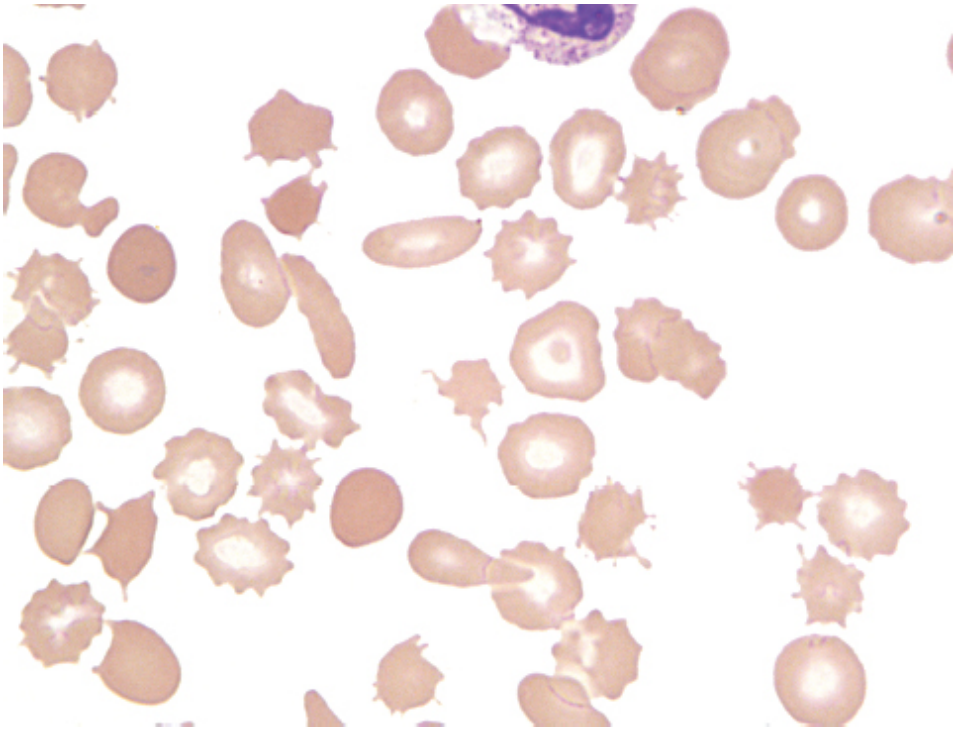
5 Sickle cell anemia.



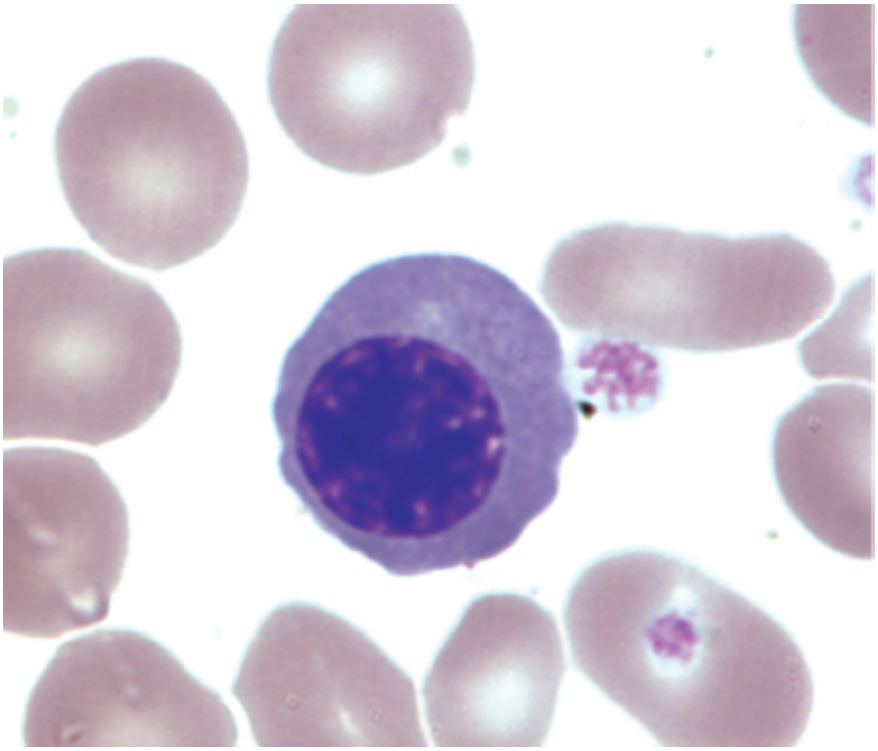
6 Schistocytes.



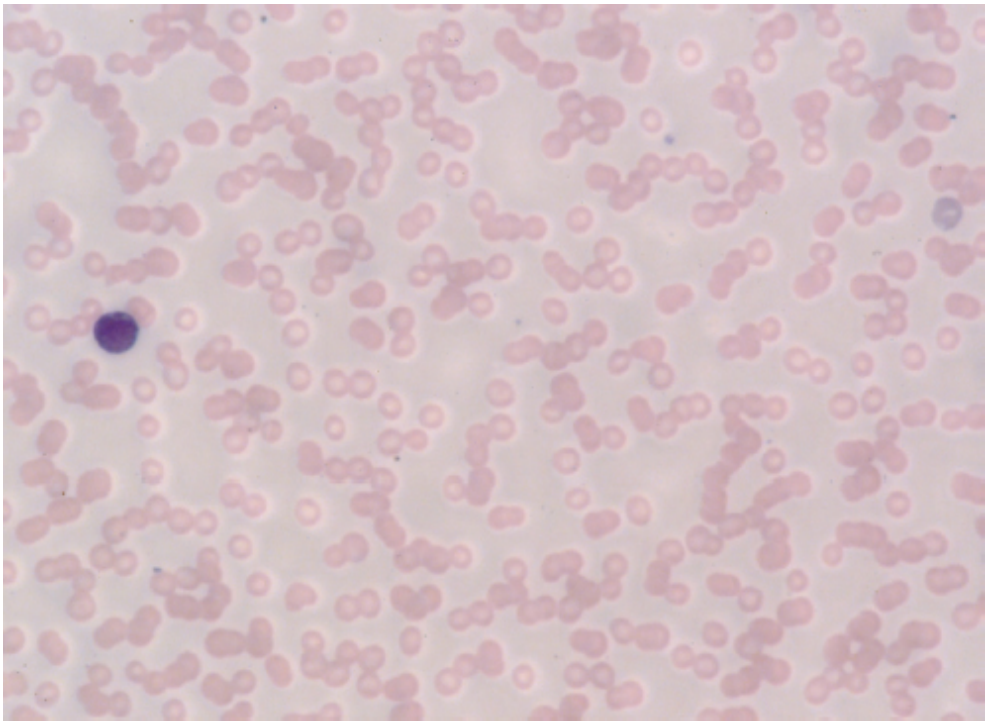
7 Teardrop shaped RBC (dacrocyte).



8 Acanthocytes.

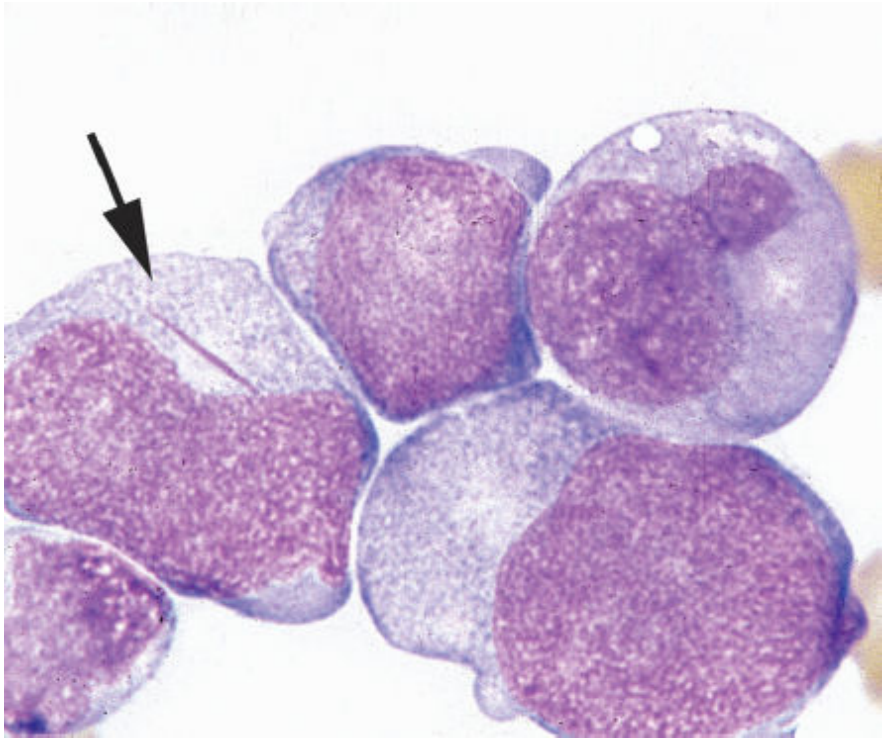


9 Nucleated RBC.

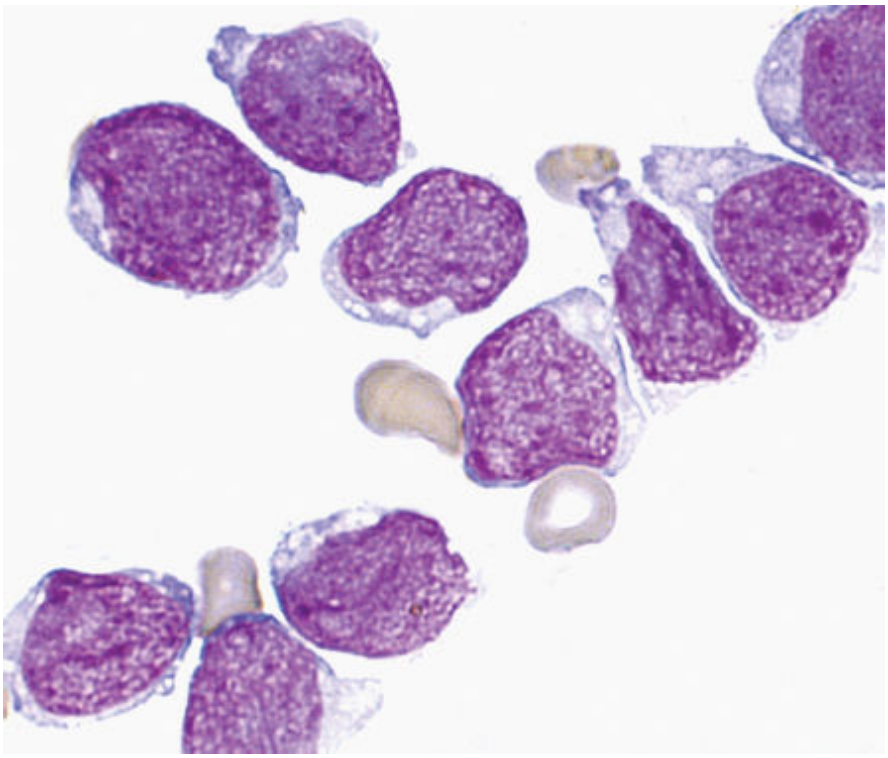


10 Rouleaux.

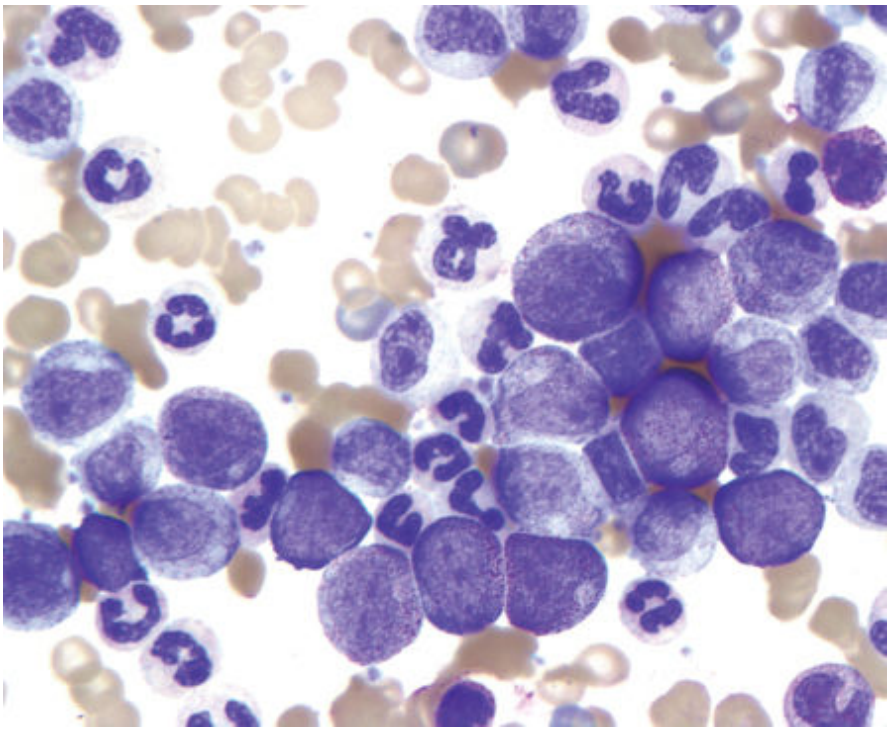
Leukemias



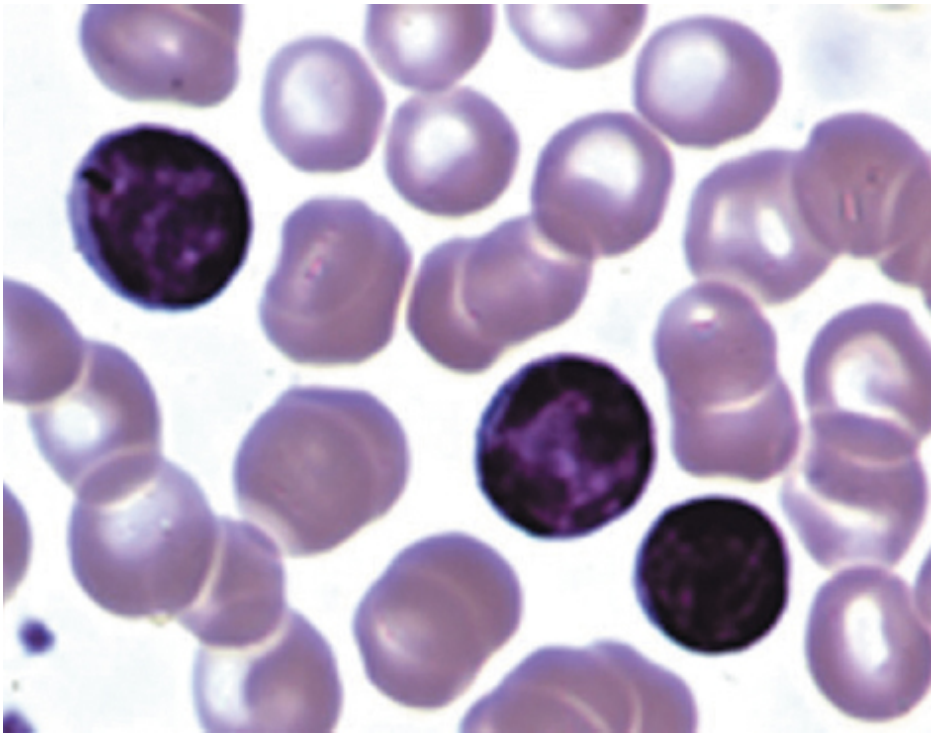
1 AML with Auer rod.



2 ALL.

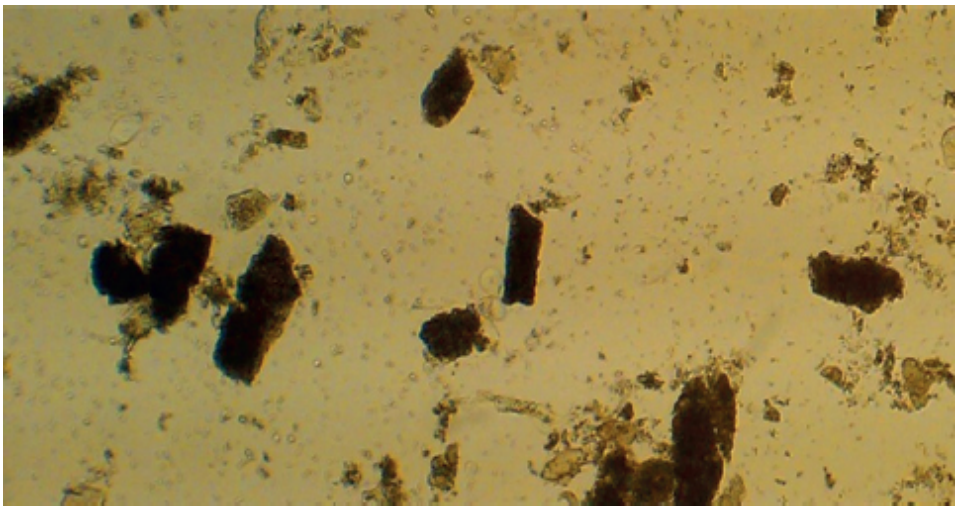


3 CML.

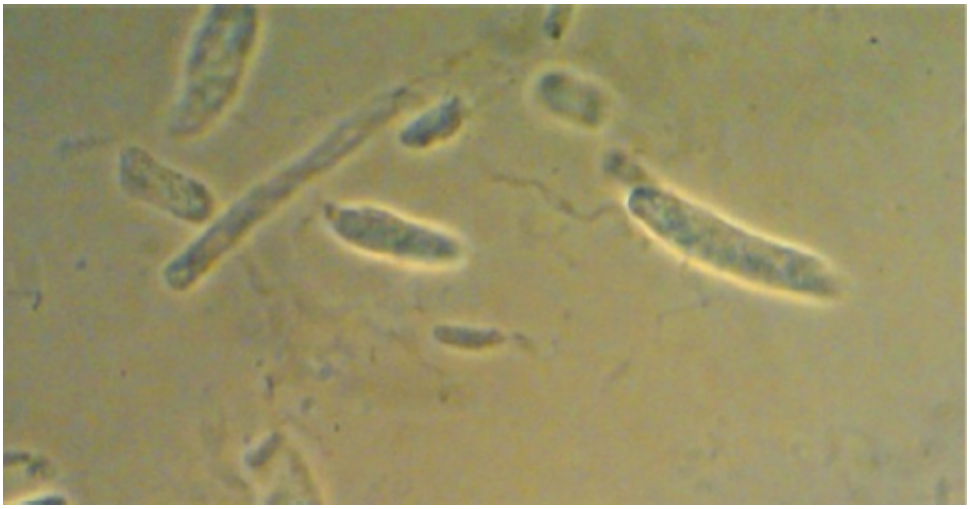


4 CLL.

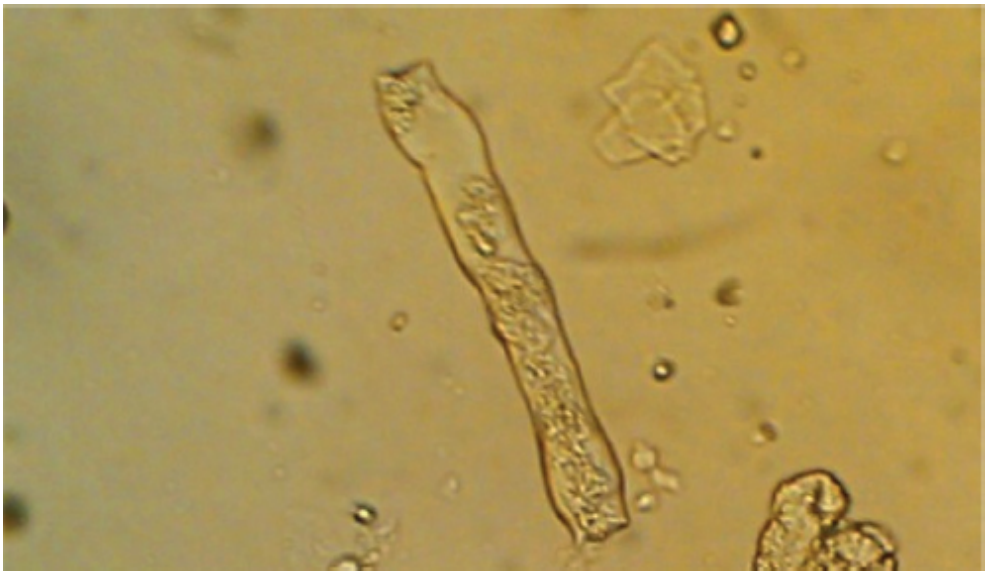
All photos excluding Leukemias Fig. 4: From Wintrobe's *Clin. Hematol*. 12th ed, 2009: Leukemias. Fig. 4: From Devita, Hellman, and Rosenberg's *Cancer: Princip. & Prac. of Oncol*. 8th ed, 2008.



1 “Muddy brown” or granular cast (courtesy Nicholas Zwang, MD)

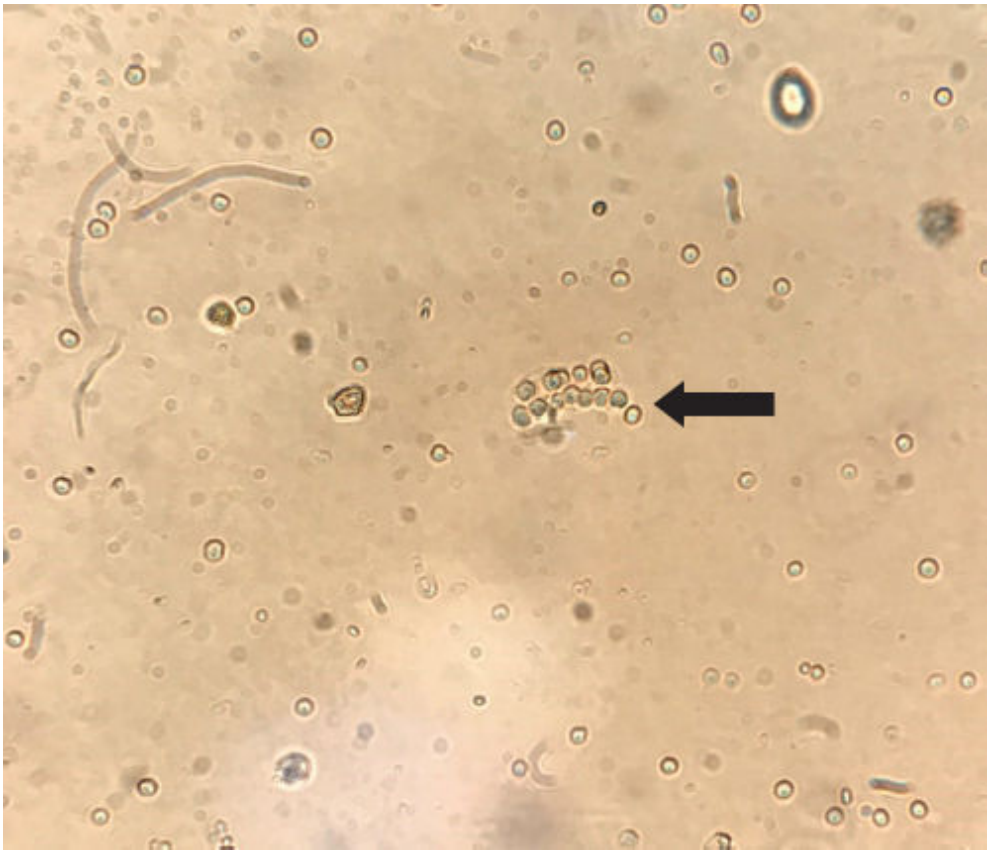


2 Hyaline cast (courtesy Nicholas Zwang, MD)

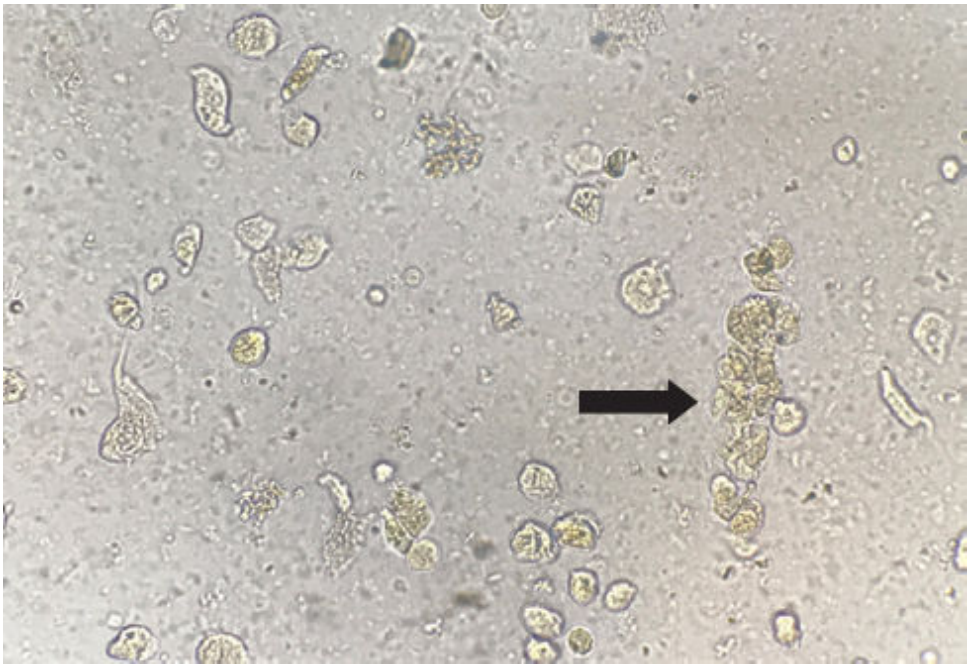


3 “Waxy broad” cast (courtesy Nicholas Zwang, MD)

4 Renal tubular epithelial cell (courtesy Nicholas Zwang, MD)

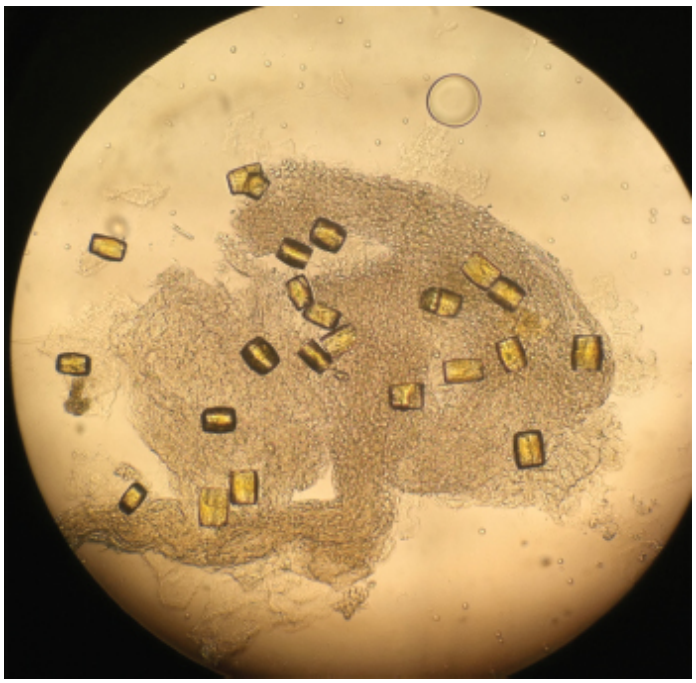


5 RBC cast (courtesy Harish Seethapathy, MBBS)

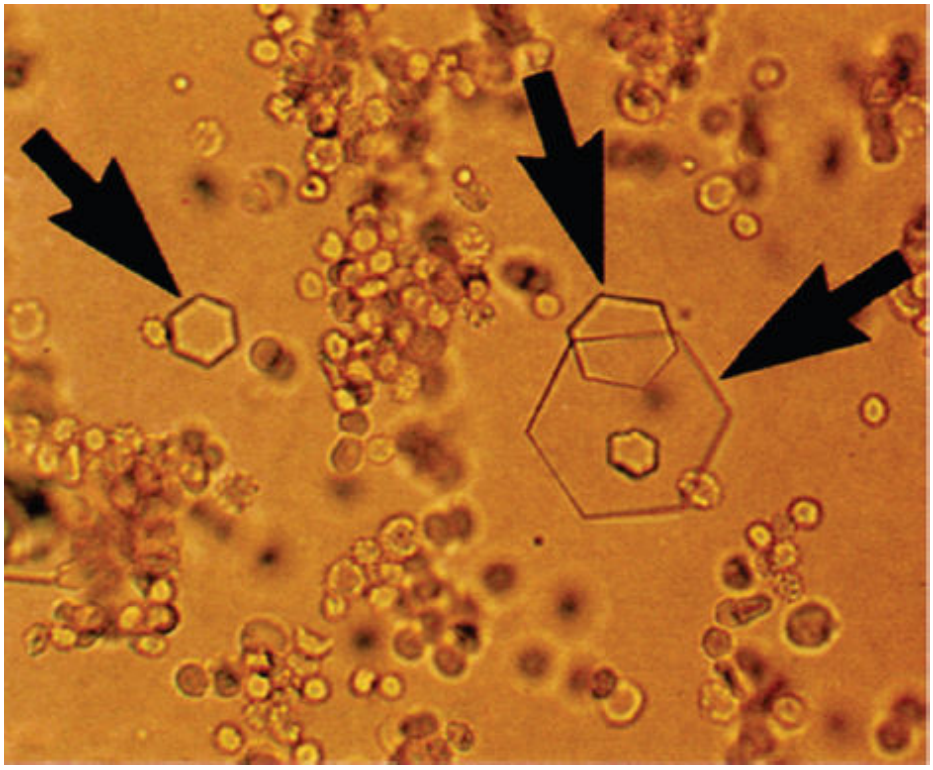


6 WBC cast (courtesy Harish Seethapathy, MBBS)

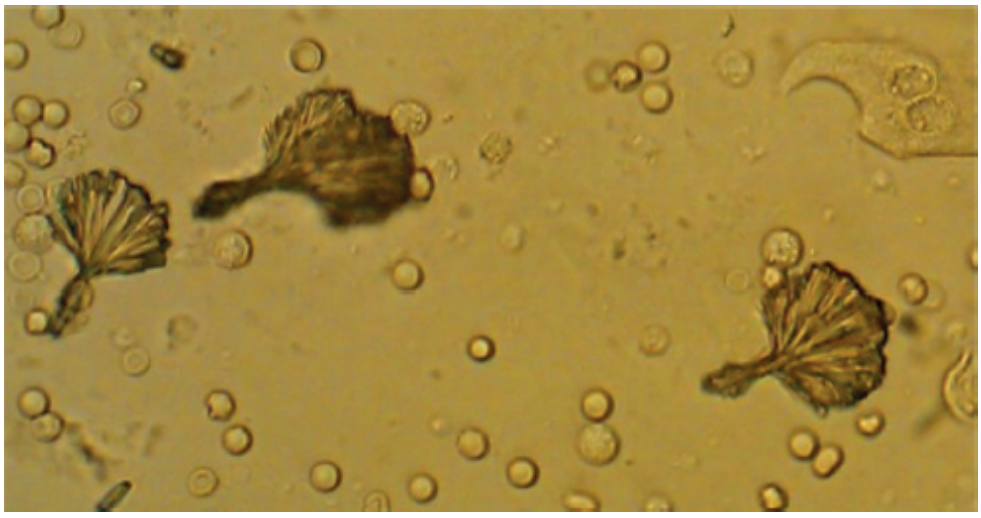
7 Calcium oxalate crystals (courtesy Mallika Mendu, MD). Calcium dihydrate (arrow), calcium monohydrate (dashed arrow), and amorphous calcium crystals (arrow-head)



8 “Struvite” magnesium ammonia phosphate crystals (courtesy Brett Carroll, MD)

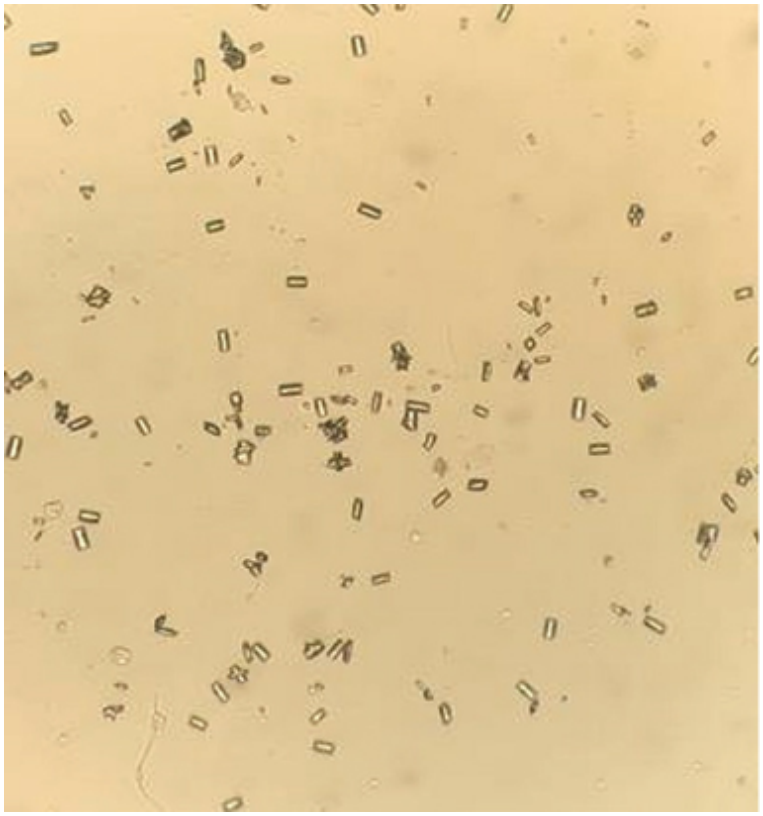


9 Cystine crystals (*Clin. Lab. Medicine*, 1994.)

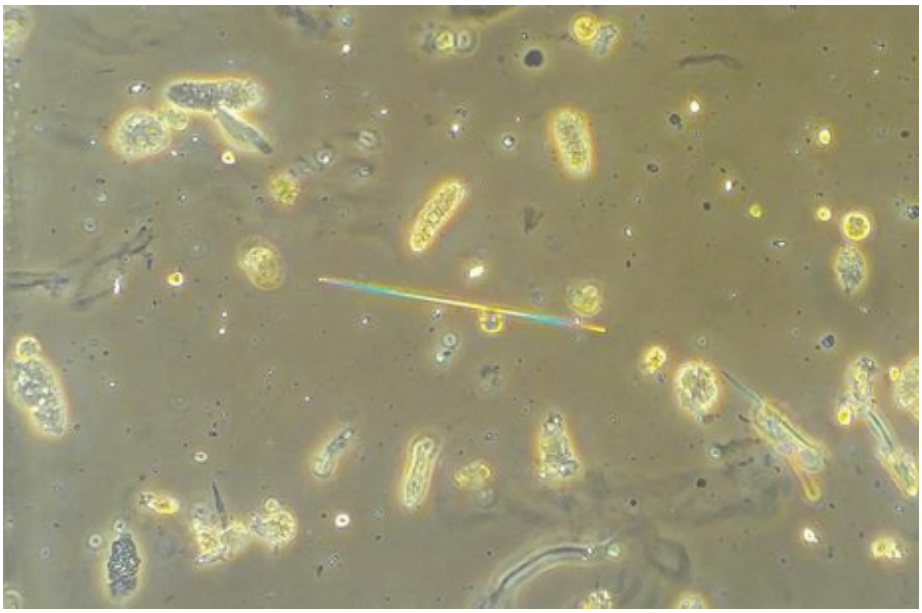


10 Sulfadiazine "shock of wheat" crystals (courtesy Nicholas Zwang, MD)

11a Uric acid crystals under polarized light (courtesy Harish Seethapathy, MBBS)



11b Uric acid crystals under normal light (courtesy Harish Seethapathy, MBBS)

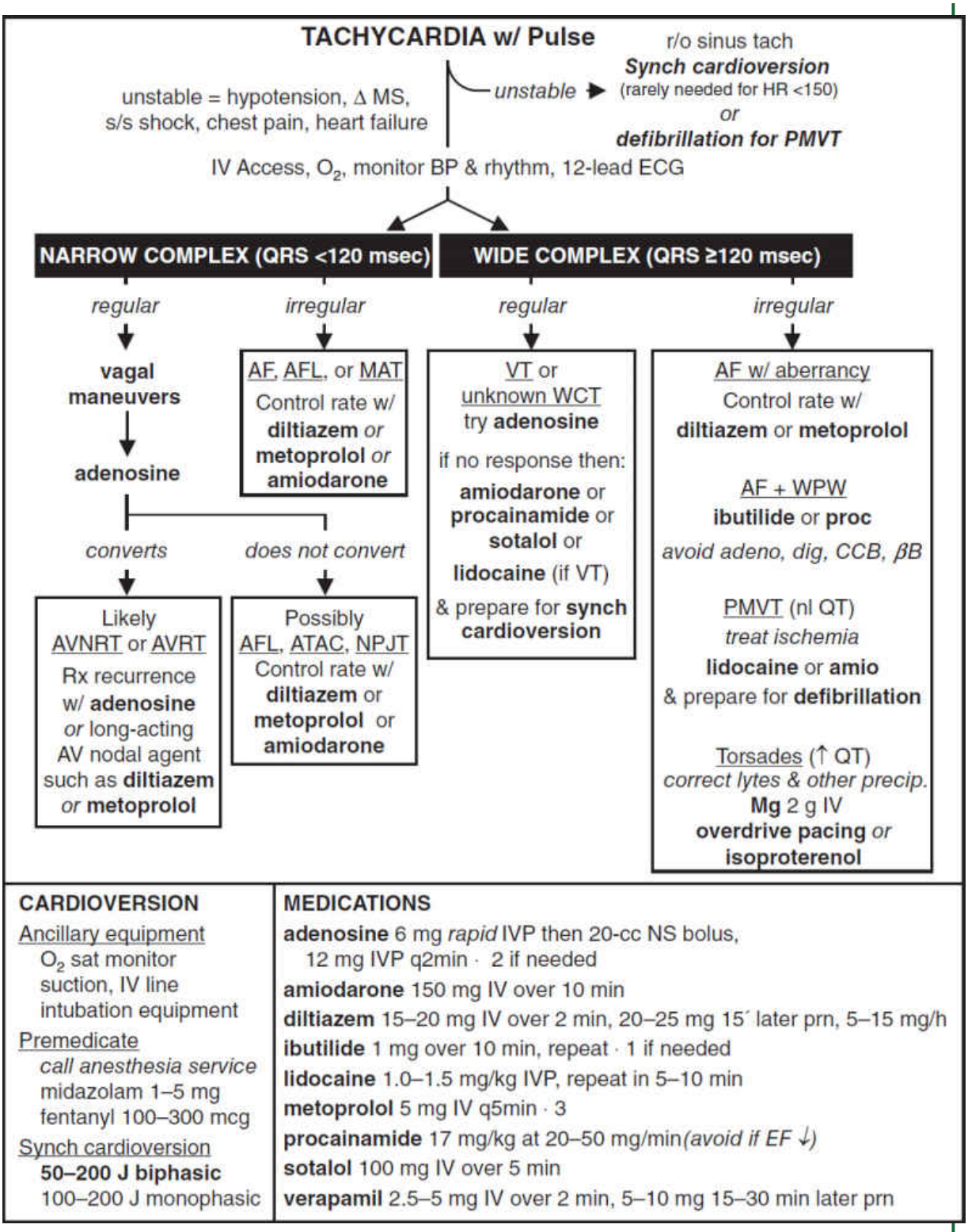


12 Acyclovir needle crystals (courtesy Yuvaram Reddy, MBBS)

NOTES

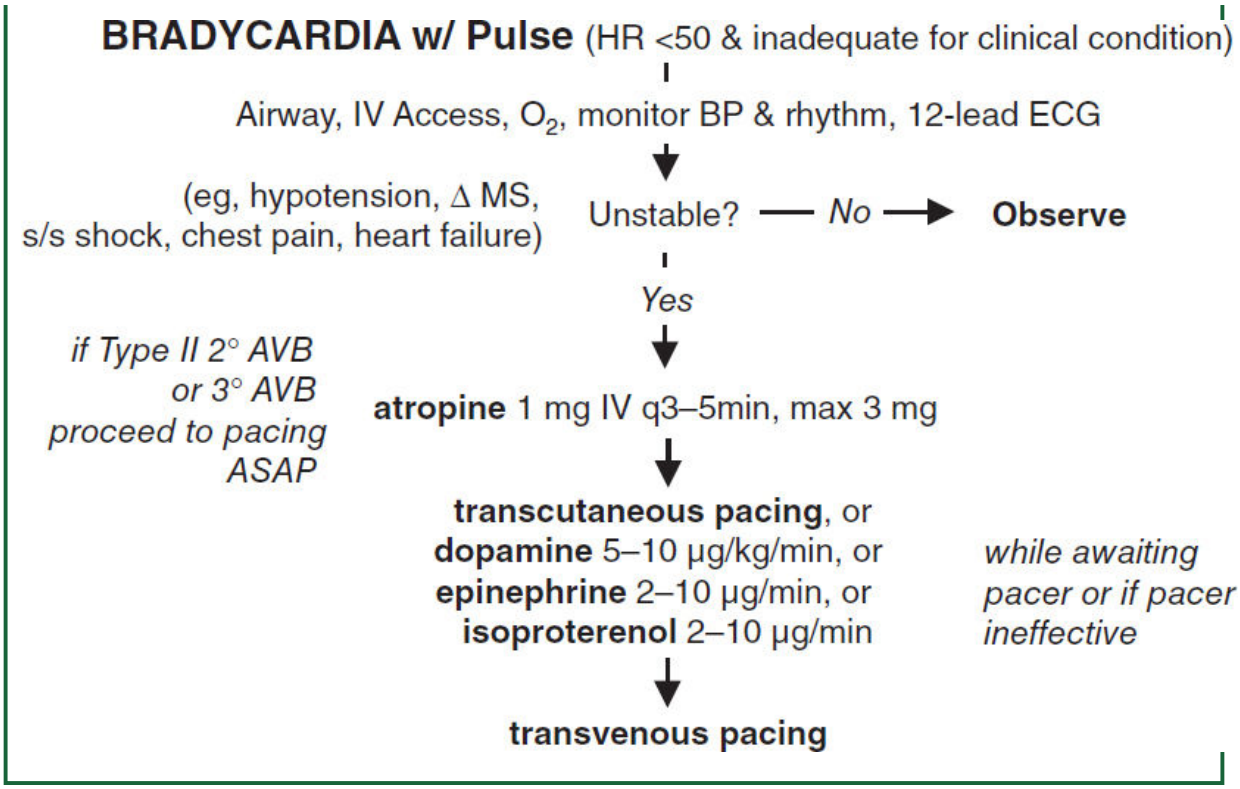
ACLS ALGORITHMS

Figure ACLS-1 ACLS Tachycardia Algorithm



(Adapted from ACLS 2020 Guidelines, *Circ* 2020;142(Suppl 2):S366)

Figure ACLS-2 ACLS Bradycardia Algorithm



(Adapted from ACLS 2020 Guidelines, *Circ* 2020;142(Suppl 2):S366)

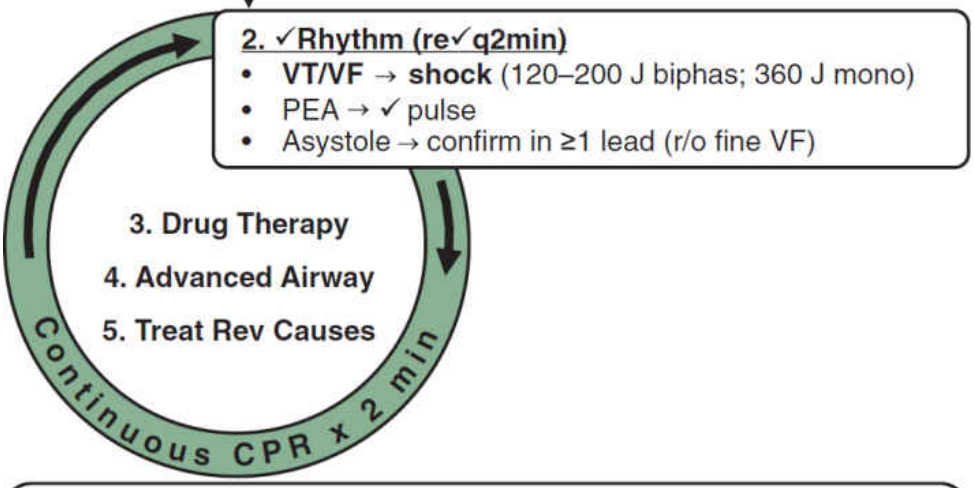
Figure ACLS-3 VF/Pulseless VT, Asystole, & PEA Algorithms

PULSELESS ARREST

1. CPR

- **C**ompressions
  - **Push hard (2–2.4 inches) & fast (100–120/min)**
  - Minimize interruptions; rotate compressor q2min
- **A**irway: open airway (eg, head tilt-chin lift)
- **B**reathing: 10 breaths/min; 2 breaths q 30 compressions
  - Bag–mask acceptable; supplemental O_2

Attach monitor/defibrillator ASAP



3. Drug Therapy

- Establish IV/IO access *(do not interrupt CPR)*
- **Epinephrine 1 mg IV q3–5min** (or 2 mg via ETT)
- **Amiodarone 300 mg IVB;** 2nd dose 150 mg
- **Lidocaine 1–1.5 mg/kg IVB (~100 mg);** 2nd dose 0.5–0.75 mg/kg
- Magnesium 1–2 g IV only for TdP

4. Consider Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Clinical assessment: bilat. chest expansion & breath sounds
- Device to ✓ tube placement
  - Continuous waveform capnography (~100% Se & Sp)
  - Colorimetric exhaled CO_2 detection (≈clinical assess.); false neg w/ ineffective CPR, PE, pulm. edema, etc.
- 10 breaths per min w/ continuous compressions

5. Treat Reversible Causes

- Hypovolemia: volume
- Hypoxia: oxygenate
- H^+ ions (acidosis): $NaHCO_3$
- Hypo/hyper K: KCl/Ca et al.
- Hypothermia: warm
- Tension PTX: needle decomp.
- Tamponade: pericardiocent.
- Toxins: med-specific
- Thromb. (PE): lysis, thrombect.
- Thromb. (ACS): PCI or lysis

(Adapted from ACLS 2020 Guidelines, *Circ* 2020;142(Suppl 2):S366)