POCKET NOTEBOOK

POCKET MEDICINE

SEVENTH EDITION

Marc S. Sabatine

The Massachusetts General Hospital Handbook of Internal Medicine

Wolters Kluwer

POCKET NOTEBOOK

Pocket MEDICINE

Seventh Edition

Edited by

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The Massachusetts General Hospital Handbook of Internal Medicine

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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.

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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 a 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 seventh edition come several major improvements. We have updated every topic thoroughly. In particular, we have included the newest diagnostic algorithms and pharmacotherapy for acute coronary syndromes, the revolutionary data for transcatheter aortic valve replacement (TAVR), and distilled the most recent guidelines for the classification and treatment of hypertension. We have added a dedicated section for the management of cystic fibrosis and updated the treatment of sepsis and shock. We continue to revise the approach to malignancies based on molecular classification and the corresponding biologic therapies, including dedicated sections on immunotherapy. We have incorporated the paradigm-shifting data for diabetes medications that lower cardiovascular risk and cover the newest classes of lipid-lowering therapies. 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.

This edition builds on the work of the many contributors to prior editions of *Pocket Medicine*. In addition, we appreciate the advice on specific topics from additional attendings including Dr. Adam Sperling.

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 judgement 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 Melinda Cuerda and Abby Cange, my academic coordinators. They 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.

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.

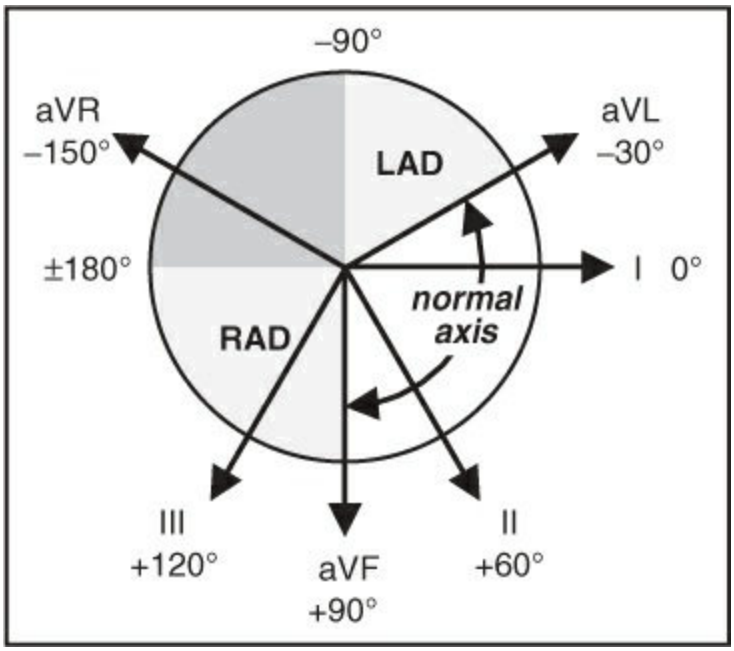
MARC S. SABATINE, MD, MPH

ELECTROCARDIOGRAPHY

Approach (a systematic approach is vital)

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

Figure 1-1 QRS axis

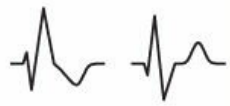


Left axis deviation (LAD)

- 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

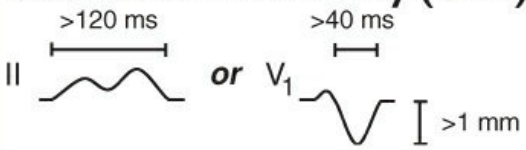
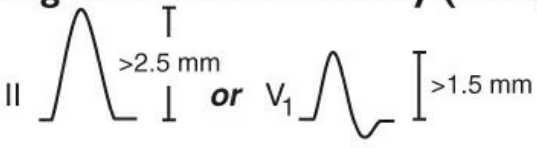
Bundle Branch Blocks (*Circ* 2009;119:e235)		
Normal		Initial depol. left to right across septum (r in V_1 & q in V_6; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB).
RBBB		1. QRS ≥120 msec (110–119 msec = IVCD or "incomplete") 2. rSR' 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 from start of QRS to end of Tw (use longest QT, often V2-V3, omit U wave)
- 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

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
- Myocardial injury: 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
- Possible etiologies (nonspecific):

  old anteroseptal MI (usually 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, $S_IS_{II}S_{III}$ 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 peak of notch 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)

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)

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, pericard./pleural effusion, myxedema, ↑ BMI, amyloid, 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 incl. LVH, RVH, early repol
- Evaluate if: arrhythmias, HR <30, prolonged 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
	Cardiac Causes
ACS (15–25% 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, 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. (*JAMA* 2002;287:2262)
	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.
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.
	GI Causes
Esophageal reflux	Substernal burning, acid taste in mouth, water brash. ↑ by meals, recumbency; ↓ by antacids. EGD, manometry, pH monitoring.
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; ↑ LFTs.
Pancreatitis	Epigastric/back discomfort. ↑ amylase & lipase; abd 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*, 11th ed, 2018; *JAMA* 2015;314:1955)

Initial approach

- 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) to ✔ for posterior STEMI if: hx c/w ACS but stnd ECG unrevealing; ST ↓ V_1–V_3 (ant ischemia vs. post STEMI) w/ refractory angina; or R/S >1 in V_1–V_2
- CXR; other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing
- Troponin: *>99th %ile w/ rise and/or fall in approp. setting is dx of AMI* (*Circ* 2018;138:e618)
  Detectable 1–6 h after injury, peaks 24 h, may be elevated for 7–14 d in STEMI ✔ at presentation & 3–6 h later; repeat if clinical or ECG Δs; ? sex-specific cutpoints If high-sens Tn (hsTn) assay, can ✔ at presentation & 1 h later; assess level & Δ
- Causes for ↑ Tn other than plaque rupture (= "type 1 MI"): (1) Supply-demand mismatch not due to Δ in CAD (= "type 2 MI"; eg, ↑↑ HR, shock, HTN crisis, spasm, severe AS), (2) non-ischemic injury (myocarditis/toxic CMP, cardioversion, cardiac contusion) or (3) multifactorial (PE, sepsis, severe HF, renal failure, Takotsubo, infilt dis.)
- CK-MB: less Se & Sp than Tn (other sources: skel. muscle, intestine, etc.); CK-MB/CK ratio >2.5 → cardiac source. Limited utility: ? higher bar for post-revasc MI; early reMI.

Early noninvasive imaging

- Low prob of ACS (eg, ⊖ ECG & Tn) & stable → outPt or inPt noninv. fxnal or imaging test (qv)
- CCTA w/ high NPV, low PPV. ↓ LOS c/w fxnal testing (*NEJM* 2012;366:1393). In stable outPt w/ CP, CCTA added to standard of care ↑ early but not overall angiography/revasc; ↑ use of preventive med Rx, and ↓ coronary death/MI at 5 y (*NEJM* 2018;379:924).
- "Triple r/o" CT angiogram sometimes performed to r/o CAD, PE, AoD if dx unclear

NONINVASIVE EVALUATION OF CAD

Stress testing (*JACC* 2012;60:1828; *J Nucl Cardiol* 2016; 23:606)

- Indications: dx obstructive CAD, evaluate Δ in clinical status in Pt w/ known CAD, risk stratify after ACS, 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, myopericarditis, acute aortic dissection
  - Relative (discuss with stress lab): left main CAD, mod symptomatic valvular stenosis, severe HTN, HCMP, 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 "coronary steal" from vessels w/ fixed epicardial dis. 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 ~85%, Sp ~85%; no radiation; operator dependent
- Cardiac MRI (w/ pharmacologic stress) another option with excellent Se & Sp

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* 2008;117:103; *Eur Heart J* 2011;31:2984 & 2011;32:810)

- Goal: identify hibernating myocardium that could regain fxn after revascularization
- Options: MRI (Se ~85%, Sp ~75%), PET (Se ~90%, Sp ~65%), dobutamine stress echo (Se ~80%, Sp ~80%); SPECT/rest-redistribution (Se ~85%, Sp ~60%)
  In Pts w/ LV dysfxn, viabil. doesn't predict ↑ CABG benefit vs. med Rx (*NEJM* 2011;364:1617)

Coronary CT/MR angio (*NEJM* 2008;359:2324; *Circ* 2010;121:2509; *Lancet* 2012;379:453)

- Pts w/ CP: CCTA 100% Se, 54% Sp for ACS, ∴ NPV 100%, PPV 17% (*JACC* 2009;53:1642). ↓ LOS, but ↑ cath/PCI, radiation vs. fxnal study (*NEJM* 2012;367:299; *JACC* 2013;61:880).
- Sx outPt: CCTA vs. fxnal testing → ↑ radiation, cath/PCI early; by 5 y, ↓ CHD death/MI w/ similar rates of cath/PCI (*NEJM* 2018;379:924)
- Unlike CCTA, MR does not require iodinated contrast or radiation, and can assess LV fxn

Coronary artery calcium score (*NEJM* 2012;366:294; *JAMA* 2012;308:788)

- 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
- May provide incremental value to clinical scores for risk stratification (*JAMA* 2004;291:210). ACC/AHA guidelines note CAC assessment is reasonable in asx Pts w/ intermed risk (7.5– <20% 10-y risk) and selected borderline risk (5– <7.5% 10-y risk) (*Circ* 2019;139:e1082).

CORONARY ANGIOGRAPHY AND REVASCULARIZATION

Indications for coronary angiography in stable CAD, asx Pts, and others

- CCS class III–IV angina despite med Rx, angina + systolic dysfxn, or unexplained low EF
- High-risk stress test findings (qv) or uncertain dx after noninv testing (& info will Δ mgmt)
- Occupational need for definitive dx (eg, pilot) or inability to undergo noninvasive testing
- Survivor of SCD, polymorphic VT, sustained monomorphic VT
- Suspected spasm; nonathero cause of ischemia (eg, anomalous coronary; CCTA preferred)
- Preop workup in select Pts undergoing organ transplant eval (CCTA reasonable)

Precath checklist & periprocedural pharmacotherapy

- Peripheral arterial exam (radial, femoral, DP, PT pulses; bruits); ✔ palmar arch intact (eg, w/ pulse oximetry & plethysmography). ✔ can lie flat, NPO >6 h.
- ✔CBC, PT, Cr; hold ACEI/ARB if renal dysfxn (see "CIAKI"). Blood bank sample.
- ASA 325 mg × 1. Timing of $P2Y_{12}$ inhib debated. ASAP for STEMI. ? preRx NSTEACS if clopi (*JAMA* 2012;308:2507) or ticagrelor, not prasugrel. Cangrelor (IV $P2Y_{12}$ inhib) ↓ peri-
  PCI events vs. clopi w/o PreRx (*NEJM* 2013;368:1303). ? statin preRx (*Circ* 2011;123:1622).

Coronary revascularization in stable CAD (*NEJM* 2016;374:1167; *JACC* 2017;69:2212)

- Optimal med Rx (OMT): preferred 1st line if stable disease w/o critical anatomy & w/ nl EF
- PCI: ↓ angina; no Δ exercise time (*Lancet* 2018;391:31) or D/MI (*NEJM* 2015;373:1204);
  if ≥1 stenosis w/ FFR (qv) ≤0.8, ↓ urg revasc & MI c/w OMT (*NEJM* 2018;379:250)
- CABG (*NEJM* 2016;374:1954): in older studies, ↓ mort. c/w OMT if 3VD, LM, 2VD w/ crit. prox LAD, esp. if ↓ EF; recently confirmed if multivessel dis. & EF <35% (*NEJM* 2016;374:1511); radial artery ↑ patency & ↓ MACE vs. saphenous vein grafts (*NEJM* 2018;378:2069); less complete revasc & possibly ↑ mort. w/ off vs. on-pump (*NEJM* 2016;375:2359 & 377:623)
- If revasc deemed necessary, *PCI* if limited # of discrete lesions, nl EF, no DM, poor operative candidate; *CABG* if extensive or diffuse disease, ↓ EF, DM or valvular disease; SYNTAX score II: ID Pts w/ ↑ benefit w/ CABG (*Lancet* 2013;381:639); if multivessel disease w/ high complexity or DM, CABG ↓ mortality (*Lancet* 2018;391:939); if LM disease, PCI ≈ CABG, but ↑ repeat revasc w/ PCI (*JAMA Cardiol.* 2017;2:1079)

PCI and peri-PCI interventions

- Access: radial ↓ bleed/vasc comp (? ↓ death in ACS) vs. fem (*Circ CV Interv* 2018;11:e000035)
- 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)

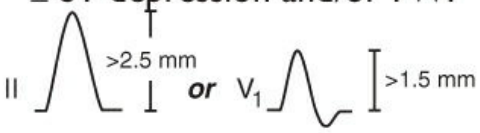
similar to FFR, doesn't require vasodilator; iFR threshold ≤0.89 (*NEJM* 2017;376:1813 & 1824).

- Balloon angioplasty by itself rare b/c elastic recoil; reserved for lesions too narrow to stent
- Bare metal stents (BMS): ↓ restenosis & repeat revasc c/w angioplasty alone
- Drug-eluting stents (DES): latest DES ↓ cardiac death or MI, repeat revasc, and stent thrombosis vs. BMS (*Lancet* 2019;393:2503)
- 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 for just 1 mo, followed by $P2Y_{12}$ inhib for 11 mo (*Lancet* 2018;392:940; *JAMA* 2019;321:2414 & 2428).
- If need long-term oral anticoag, consider clopi+DOAC and consider stopping ASA (? after ~1 wk) as ↓ bleed, but trend small ↑ ischemic risk (*Lancet* 2013;381:1107 & *NEJM* 2019;380:1509)

Post-PCI complications (*NEJM* 2017;377:1513)

- Postprocedure ✔ vascular access site, distal pulses, ECG, CBC, Cr
- Bleeding: if hematoma/overt bleeding → manual compression, reverse/stop anticoag.
  Retroperitoneal bleed: may p/w ↓ Hct ± back pain; ↑ HR & ↓ BP late; Dx w/ abd/pelvic CT (I^-); Rx: reverse/stop anticoag (d/w interventionalist), IVF/PRBC/plts as required.
- Vascular damage (~1% of dx angio, ~5% of transfemoral PCI; *Circ* 2007;115:2666)
  Pseudoaneurysm: triad of pain, expansile mass, systolic bruit; Dx: U/S; Rx (if pain or >2 cm): manual or U/S-directed compression, thrombin injection, or surgical repair
  AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair if large or sx
  LE ischemia (emboli, dissection, clot): cool, mottled extremity, ↓ distal pulses; Dx: pulse volume recording (PVR), angio; Rx: percutaneous or surgical repair
- Peri-PCI MI: >5× ULN of Tn/CK-MB + either sx or ECG/angio Δs; Qw MI in <1%
- Contrast-induced AKI: w/in 48 h, peak 3–5 d; pre-hydration reasonable (see "CIAKI")
- Cholesterol emboli syndrome (typically in middle-aged & elderly and w/ Ao atheroma)
  renal failure (late and progressive, ± eos in urine); mesenteric ischemia (abd pain, LGIB, pancreatitis); intact distal pulses but livedo pattern and toe necrosis
- Stent thrombosis: mins-yrs after PCI, typically p/w AMI. Due to mech prob. (stent underexpansion or unrecognized dissection, typically presents early) or d/c of antiplt Rx; espec if d/c both ASA & $P2Y_{12}$ inhib (*JAMA* 2005;293:2126).
- In-stent restenosis: mos after PCI, typically p/w gradual ↑ angina (10% p/w ACS).
  Due to combination of elastic recoil and neointimal hyperplasia; ↓ w/ DES vs. BMS.

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)

- 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)
- Ischemia w/o plaque rupture ("type 2" MI): ↑ demand (eg, ↑ HR), ↓ supply (eg, HoTN)
- Direct myocardial injury: myocarditis; Takotsubo/stress CMP; toxic CMP; cardiac contusion

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

- Typical angina: retrosternal pressure/pain/tightness ± radiation to neck, jaw, arms; precip. by exertion, relieved by rest/ NTG. In ACS: new-onset, crescendo or at rest.
- Associated symptoms: dyspnea, diaphoresis, N/V, palpitations or light-headedness
- Many MIs (~20% in older series) are initially unrecognized b/c silent or atypical sx
- Atypical sxs (incl N/V & epig pain) ? more common in ♀, elderly, diabetes, inferior ischemia

Physical exam

- Signs of ischemia: S_4, new MR murmur 2° pap. muscle dysfxn, paradoxical S_2, diaphoresis
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ 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 w/ old LBBB: ≥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%)

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 to assess distal LCX/RCA territory. ✔ R-sided precordial leads in IMI to help 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 or prox LAD occlusion or diffuse ischemia.

- Cardiac biomarkers: ✔ Tn (pref. over CK-MB) at presentation & 3–6 h (? 1hr if hsTn); repeat if clinical or ECG Δs; >99th %ile w/ rise and/or fall in appropriate clinical setting dx of AMI (see "Chest Pain"); in CKD, ↑ Tn still portends poor prognosis (*NEJM* 2002;346:2047)
- If low prob, stress test, 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

Likelihood of ACS (*Circ* 2007;116:e148)			
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

Approach to triage

- If hx, initial ECG & Tn non-dx, repeat ECG q15–30min × 1 h & Tn 3–6 h (? 1hr if hs) later
- If remain nl and low likelihood of ACS, search for alternative causes of chest pain
- If remain nl, have ruled out MI, *but* if high suspicion for ACS based on hx, then still need to r/o UA w/ stress test to assess for inducible ischemia (or CTA to r/o epicardial CAD);
  if low risk (eg, age ≤70; ∅ prior CAD, CVD, PAD; ∅ rest angina) can do before d/c from ED or as outPt w/in 72 h (0% mortality, <0.5% MI; *Ann Emerg Med* 2006;47:427)
  if not low risk, admit and initiate Rx for possible ACS and consider stress test or cath

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 ↑ cardiogenic shock early (espec if signs of HF) (*Lancet* 2005;366:1622). *Contraindic.* PR >0.24 sec, HR <60, 2°/3° AVB, severe bron-chospasm, 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 for resp distress or to keep S_aO_2 >90%; no mortality benefit if 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;372:1500)

- ACEI/ARB: start once hemodynamics and renal function stable
  - Strong indication for ACEI 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)
  - ARB appear ≈ ACEI (*NEJM* 2003;349:20); give if contraindic to ACEI
- IABP: can be used for refractory angina when PCI not available

NSTE-ACS (*CIRC* 2014;130:e344)

Key issues are antithrombotic regimen and invasive vs. conservative strategy

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. Some data for upstream clopidogrel (*JAMA* 2012;308:2507). See below for specific recommendations.	
• 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). Use only with ASA <100 mg qd	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 if undergoing PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery	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) Contraindic. if h/o TIA/CVA; ? avoid if >75 y
• Clopidogrel* 300–600 mg × 1 → 75 mg qd Requires ~6 h to steady state	ASA+clopi → 20% ↓ CVD/MI/stroke vs. ASA alone ↑ benefit if given hrs *prior* to PCI (*JAMA* 2012;308:2507), but if require CABG, need to wait >5 d after d/c clopi
• 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 $P2Y_{12}$ inhibition during 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.

*~30% pop has ↓ fxn *CYP2C19* → ↑ CV events if PCI on clopi (*NEJM* 2009;360:354)

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	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

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

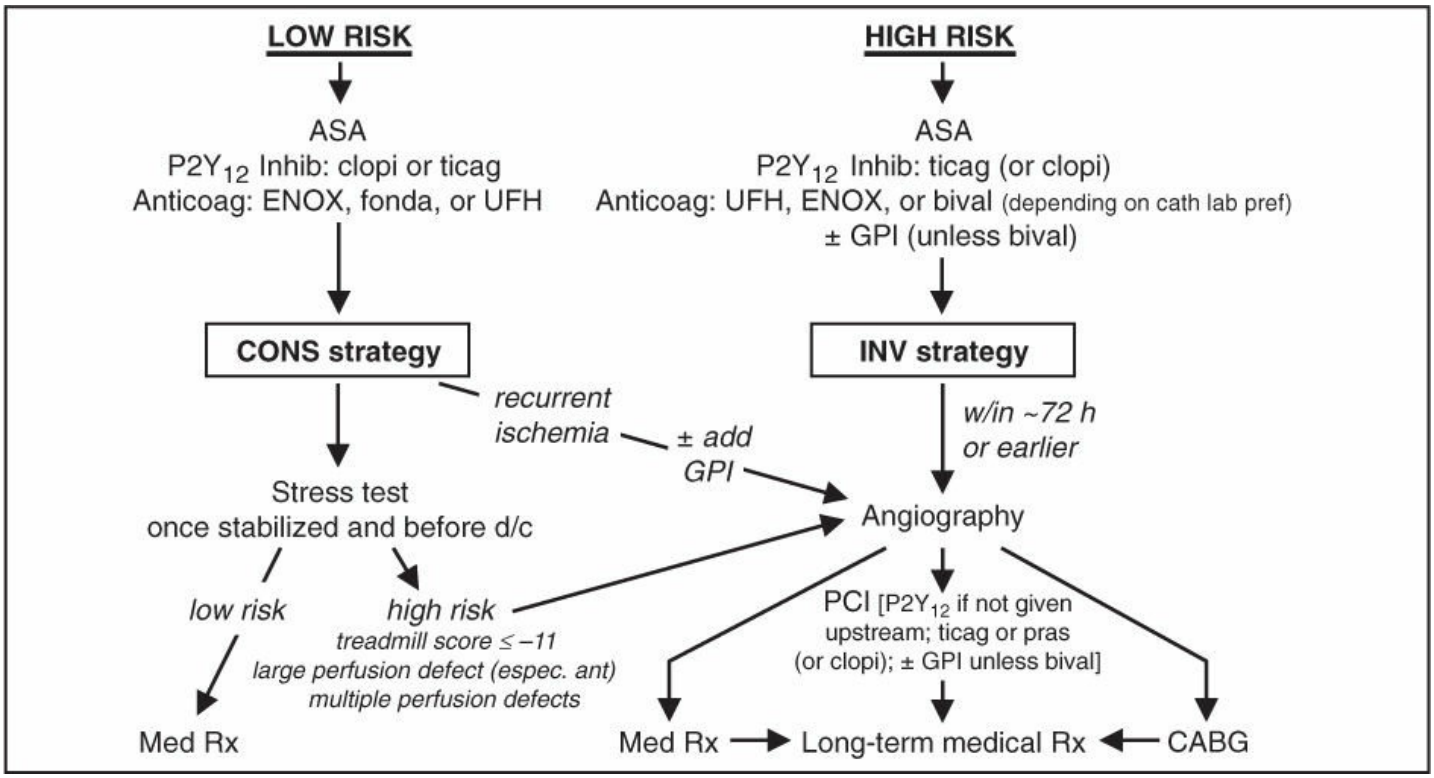
Coronary angiography (*Circ* 2014;130:e344)

- Immediate/urgent coronary angiography (w/in 2 h) if refractory/recurrent angina or hemodynamic or electrical instability
- Invasive (INV) strategy = routine angiography w/in 72 h
  - *Early (w/in 24 h) if:* ⊕ Tn, ST Δ, GRACE risk score (www.outcomes-massmed.org/grace) >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 mortality c/w cons. (*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.
- Conservative (CONS) strategy = selective angio. 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)**		

Figure 1-2 Approach to UA/NSTEMI



STEMI

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
- Routine thrombus aspiration: no benefit, ↑ stroke (*Lancet* 2015;387:127; 2015;372:1389)
- Consider PCI of non-culprit lesions at time of primary PCI or planned staged procedure because appears to ↓ MACE vs. culprit alone (*NEJM* 2013;369:1115; *JACC* 2015;65:963); but 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.	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 ⌀ 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 hi-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	*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 *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)
GP IIb/IIIa inhibitors	*Lysis:* no indication (*Lancet* 2001;357:1905)

abciximab, eptifibatide, tirofiban	*Peri-PCI:* 60% ↓ D/MI/UR (*NEJM* 2001;344:1895)

Adapted from ACC/AHA 2013 STEMI Guidelines Update (*Circ* 2013;127:529); *Lancet* 2013;382:633

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)
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 (*Lancet* 2014;384:599; *NEJM* 2017;377:1132)

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 ~$^1/_2$ 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 VT (<100 bpm), often seen after successful reperfusion; typically asx, self-terminates, 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)	Anticoagulate × 3–6 mo
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

Prognosis

- In registries, in-hospital mortality is 6% w/ reperfusion Rx (lytic or PCI) and ~20% w/o
- TIMI Risk Score for STEMI (includes age, time to Rx, anterior MI or LBBB, Killip class, tachycardia, HoTN) defines 30-d mortality after STEMI (*JAMA* 2001;286:1356)

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)

Medications (barring contraindications)

- Aspirin: 81 mg daily (no clear benefit to higher doses)
- $P2Y_{12}$ inhib (ticagrelor or prasugrel preferred over clopi): treat for *at least* 12 mo

  Prolonged Rx >12 mo → ↓ MACE & CV death, ↑ in bleeding, but no ↑ ICH. Beyond 1st 12 mo, ticag 60 bid preferred to 90, b/c better tolerability (*NEJM* 2015;372:1791; *EHJ* 2016;37:390).

  PPIs ↓ GI complic; some PPIs ↓ antiplt effect, but no clear ↑ in CV risk (*NEJM* 2010;363:1909)

- **β**-blocker: 23% ↓ mortality after MI
- LDL-C management: benefit with lowering LDL-C to <<40 mg/dl (*Lancet* 2017;390:1962)
  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)
- ACEI: lifelong if HF, ↓ EF, HTN, DM; 4–6 wk or at least until hosp. d/c in all STEMI
  ? long-term benefit in CAD w/o HF (*NEJM* 2000;342:145 & 2004;351:2058; *Lancet* 2003;362:782)
- 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)
- Oral anticoag: if needed (eg, AF, LV thrombus), consider DOAC instead of warfarin; some data for reduced-dose DOAC but unclear if ischemic stroke prevention adeq. (*NEJM* 2016; 375:2423 & 2017;377:1513). Clopi (not ticag or pras). Stopping ASA (? after ~1 wk) ↓ bleed risk by 40–50%, but trend small ↑ MI & stent thromb. (*Lancet* 2013;381:1107; *NEJM* 2019;379:1509).
- 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)

ICD (*NEJM* 2008;359:2245; *Circ* 2014;130:94)

- 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)

Risk factors and lifestyle modifications (*Circ* 2014;129(Suppl 2):S1 & S76)

- Low chol. (<200 mg/d) & fat (<7% saturated) diet; ? Ω-3 FA.
- LDL-C at least <70 mg/dl (& ≥50% ↓ in LDL-C) (*Circ* 2019;139:e1082)
- BP <130/80 (*JACC* 2018;71:e127); quit smoking
- If diabetic, tailor HbA1c goal based on Pt (avoid TZDs and saxa if HF); GLP1-RA & SGLT2i ↓ MACE & SGLT2i ↓ hospitalization for HF (*Lancet* 2019;393:31 & *Circ* 2019;139:2022)
- 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 (*JAMA* 2013;310:1711; *NEJM* 2018;378:345); ✔ for depression

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 (*Circ* 2009;119:e391; *NEJM* 2013;369:e35)

- 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* 2006;113:1020)
  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, sepsis, ARDS
- No benefit in decompensated HF (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ~$^1/_2$ 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 internal jugular or L subclavian veins for "anatomic" flotation into PA
- Inflate balloon (max 1.5 mL) when advancing and to measure PCWP
- Use resistance to inflation and pressure tracing to avoid overinflation & risk of PA rupture
- 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 ~1/2 PEEP (× ¾ to convert cm H_2O to mmHg).
- PCWP: LV preload best estimated at *a* wave; risk of pulmonary edema from avg PCWP

Cardiac output

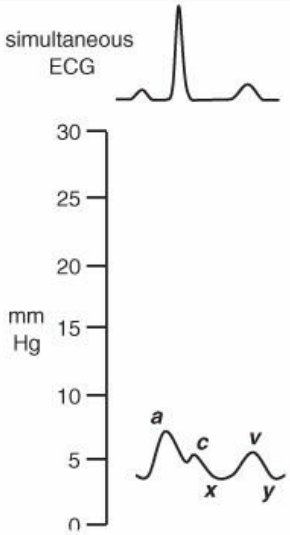
- Thermodilution: saline injected in RA or prox thermal filament. Δ in temp over time measured at thermistor (in PA) used to calc CO. Inaccurate if ↓ CO, sev TR, or shunt.
- Fick method: O_2 consumption $\dot{V}O_2$ (L/min) = CO (L/min) × Δ arteriovenous O_2 content

  ∴ 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), ↑↑ 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)
hepatic and renal congestion when CVP/RAP >15 mmHg

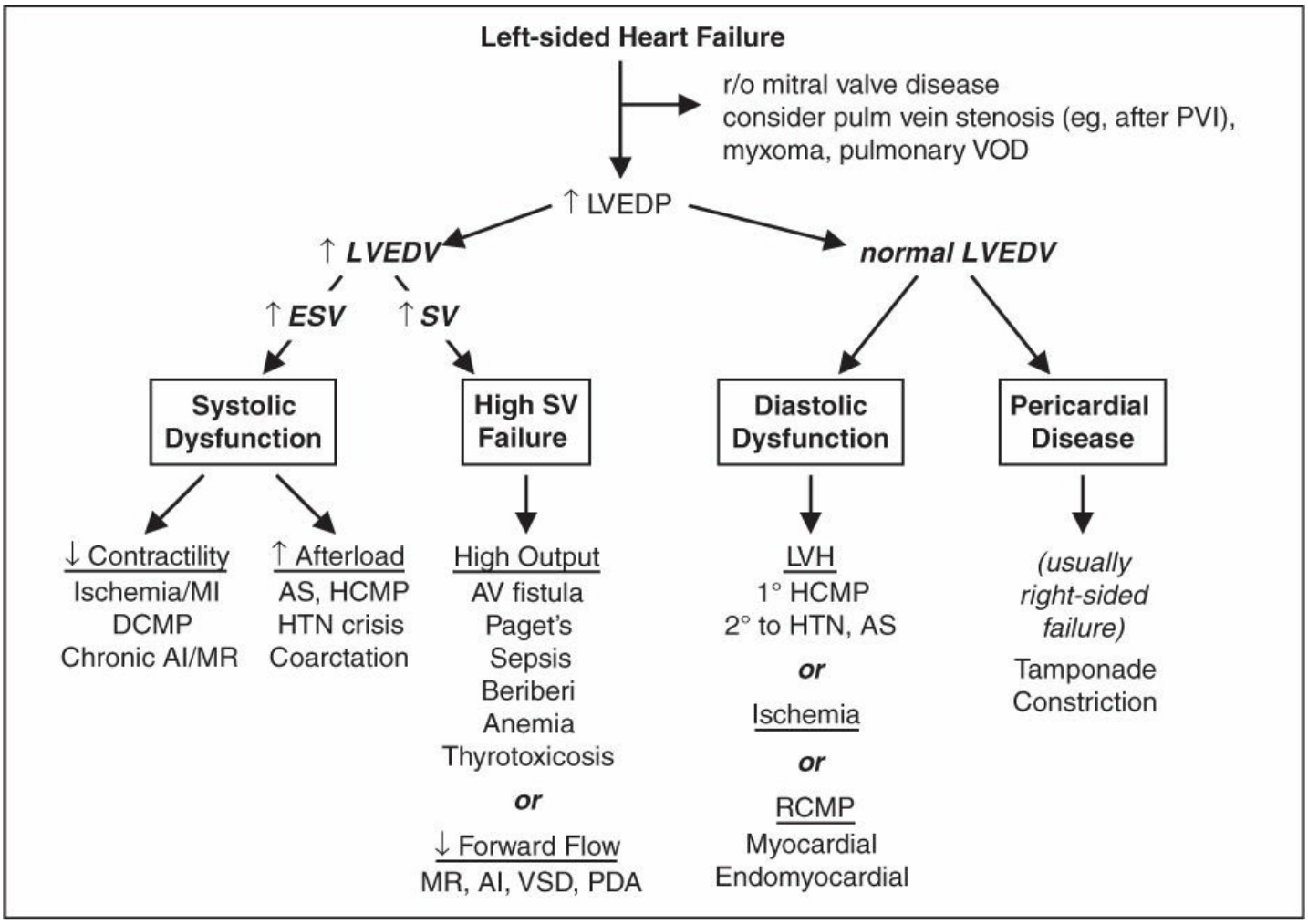
- Optimize preload = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (*NEJM* 1973;289:1263)
  goal PCWP ~14–18 in acute MI, ≤14 in acute decompensated HF
  optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve
  ↑ by giving NS (albumin w/o clinical benefit over NS; PRBC if significant anemia)
  ↓ by diuresis (qv), ultrafiltration or dialysis if refractory to diuretics
- 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 ↑ (& ∴ CO ↓): temporize w/ pressors until can ↑ CO (see below)
  MAP <60 & SVR low/nl (& ∴ inappropriate vasoplegia): vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [α] or vasopressin [V_1] if refractory); 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 (2–5), TandemHeart (5), VAD (L-sided, R-sided or both; temp or perm; 10) or ECMO (6) (*JACC* 2015;65:e7 & 2542)

HEART FAILURE

Definitions (*Braunwald's Heart Disease*, 11th ed., 2019)

- 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%), mid-range (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: ≥4 cm ↑ in JVP for ≥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)

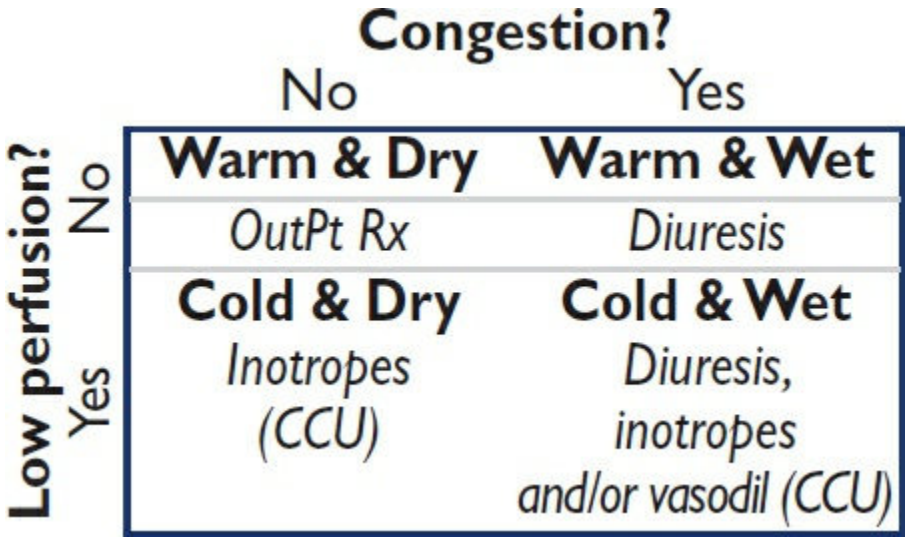
Evaluation for the potential causes of heart failure

- ECG: evidence for CAD, LVH, LAE, heart block or low voltage (? infiltrative CMP/DCMP)
- 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 degree of congestion & adequacy of perfusion
- For congestion: "LMNOP"
  - Lasix IV; total daily dose 2.5× usual daily PO dose → ↑ UOP, but transient ↑ in Cr vs. 1× usual dose; ∅ clear diff between contin. gtt vs. q12h (*NEJM* 2011;364:797)
  - Morphine (↓ sx, venodilator, ↓ afterload)
  - Nitrates (venodilator)
  - Oxygen ± noninvasive vent (↓ sx, ↑ P_aO_2; no Δ mortality; see "Mechanical Ventilation")
  - Position (sitting up & legs dangling over side of bed → ↓ preload)
- For low perfusion, see below
- Adjustment of oral meds
  - ACEI/ARB: hold if HoTN, consider Δ to hydralazine & nitrates if renal decompensation
  - βB: reduce dose by at least $^1/_2$ if mod HF, d/c if severe HF and/or need inotropes

Treatment of acute advanced heart failure (*Circ* 2009;119:e391)

- Consider PAC if not resp to Rx, unsure re: vol status, HoTN, ↑ Cr, 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; +2.5–5 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). Fully magnetically levitated centrifugal flow pump (HeartMate 3) ↓ stroke or re-op vs. axial flow HeartMate II (*NEJM* 2019;380:1618); HeartWare LVAD another centrifugal option (*NEJM* 2017;376:451).
- Cardiac transplantation: ~2500/yr in U.S. 10% mort. in 1st y, median survival ~10 y

Recommended Chronic Therapy by HF Stage (*Circ* 2009;119:e391)		
Stage (not NYHA Class)		Therapy
A	At risk for HF (eg, HTN, FHx CMP); but asx & w/o struct. heart 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: ACEI, ARB or ARNI; βB; aldo antag; ICD; ? CRT; nitrate/hydral; dig.
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 NYHA III → ~33% ↓ risk of hosp (*Lancet* 2016;387:453)

Treatment of Chronic HF with Reduced EF (*JACC* 2017;70:776)	
Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
BP	Goal <130/80 (*JACC* 2018;71:127)
ACEI	↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20–30% in asx but ↓ EF (*NEJM* 1992;327:685; *Lancet* 2000;355:1575) High-dose more effic. than low. Watch for ↑ Cr, ↑ K (ameliorate by low-K diet, diuretics, K binders), cough, angioedema.
ATII receptor blockers (ARBs)	*Consider as alternative if cannot tolerate ACEI (eg, b/c cough)* Noninferior to ACEI (*Lancet* 2000;355:1582 & 2003;362:772) As with ACEI, higher doses more efficacious (*Lancet* 2009;379:1840)

	Adding to ACEI → ↑ risk of ↑ K and ↑ Cr (*BMJ* 2013;346:f360)
ARNI (ARB + neprilysin inhib) *(do not use w/ ACEI, allow 36-h washout)*	*Preferred RAAS inhib 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.
Hydralazine + nitrates	*Consider if cannot tolerate ACEI/ARB or in blacks 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)
β-blocker (data for carvedilol, metoprolol, bisoprolol)	*EF will transiently ↓, then ↑. Contraindic. in decompensated HF.* 35% ↓ mort. & 40% ↓ rehosp. in NYHA II–IV (*JAMA* 2002;287:883) 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	*Consider if adeq. renal fxn and w/o hyperkalemia; watch for ↑ K* 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)
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)
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
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)
Ivabradine (I_f blocker w/o ⊖ ino)	*Consider if EF ≤35%, NYHA II or III, HR ≥70, NSR on max βB.* 18% ↓ CV mort or HF hosp (*Lancet* 2010;376:875)
Iron supplementation	*? IV (not PO) if NYHA II/III, EF ≤40%, Fe-defic* (ferritin <100 or 100–300 & TSAT <20%). ↑ QoL independent of Hct (*NEJM* 2009;361:2436).
Anticoagulation	*If AF, VTE, LV thrombus*, ± *if large akinetic LV segments.* In SR w/ rEF, ↓ isch stroke, but ↑ bleed (*NEJM* 2012;366:1859 & 2018;379:1332).
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)
Other	SGLT2i ↓ death/HF hosp in DM (*Lancet* 2019;393:31)
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") (*NEJM* 2016;375:1868)

- Epidemiology: ~$^1/_2$ of Pts w/ HF have normal or only min. impaired systolic fxn (EF ≥40%); risk factors for HFpEF incl ↑ age, ♀, DM, AF. Mortality ≈ to those w/ systolic dysfxn.
- 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 even modest ↑ 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: abnl MV inflow (E/A reversal and Δs in E wave deceleration time) & ↓

myocardial relax. (↑ isovol relax. time & ↓ early diastole tissue Doppler vel)
(2) exercise-induced ↑ PCWP (± ↓ response chronotropic & vasodilator reserve)

- Treatment: diuresis for vol overload, BP control, prevention of tachycardia and ischemia; no benefit to: ACEI/ARB (*NEJM* 2008;359:2456) or PDE5 inhib (*JAMA* 2013;309:1268); spironolactone ? ↓ CV death & HF hosp (at least in Americas) (*NEJM* 2014;370:1383); ARNi (*JACC Heart Fail* 2017;5:471) under study; transcatheter interatrial shunt reduces PCWP during exercise, ? whether improves sx/outcomes (*Circ* 2017;137:364)

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

DILATED CARDIOMYOPATHY (DCM)

Definition and epidemiology (*Circ* 2013;128:e240; *JACC* 2013;62:2046)

- Ventricular dilatation and ↓ contractility ± ↓ wall thickness *in the absence of myocardial disease caused by ischemia/infarct, valvular disease or hypertension*
- Incidence: 5–8/100,000/y; prevalence: 1/2500. Most common reason for heart transplant.

Etiologies (*JACC* 2011;57:1641; *Circ Res* 2012;111:131)

- Familial (~35%): Pt & ≥2 closely related family members w/ otherwise unexplained DCM; ~30 genes identified to date, encoding structural & nuclear proteins
- Idiopathic (<20%): ? undiagnosed infectious, alcoholic, or genetic cause
- Infectious myocarditis (10–15%; *Lancet* 2012;379:738; *JACC* 2012;59:779)
  - Viruses (parvoB19 & HHV6 > Coxsackie, adeno, echo, CMV, HCV): from subacute (dilated LV, mild–mod dysfxn) to fulminant (nondil., thick, edematous LV, sev dysfxn)
  - Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB)
  - HIV: ~8% of asx HIV ⊕; due to HIV, other virus *or* antiretrovirals; also premature CAD
  - Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (*Lancet* 2018;391:82)
- 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), cyclophosphamide, trastuzumab
- Infiltrative (5%): often mix of DCMP + RCMP (qv) with thickened wall
  amyloidosis, sarcoidosis, hemochromatosis, tumor
- Autoimmune: *collagen vasc. dis.* (3%): PM, SLE, scleroderma, PAN, RA, GPA;
  peripartum (last month → 5 mo postpartum; *EHJ* 2015;36:1090): ~1:3000 preg. ↑ risk w/ multiparity, ↑ age, Afr Am; stnd HF Rx (if preg, no ACEi or spironolact.); ? bromocriptine to ↓ prolactin; 72% normalize EF (*JACC* 2015;66:905); ~30% recur w/ next preg
  - 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)
- 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).
- Arrhythmogenic right ventricular cardiomyopathy (ACM/ARVC): fibrofatty

replacement of RV → dilation (dx w/ MRI); ECG: ± RBBB, TWI V_1–V_3, ε wave; risk VT (*NEJM* 2017;376:61)
- Tachycardia: likelihood ∝ rate/duration; often resolves w/ rate cntl (*Circ* 2005;112:1092)
- 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
- Chest pain can be seen w/ some etiologies (eg, myocarditis)

Diagnostic studies and workup (*JACC* 2016;67:2996)
- CXR: moderate to marked cardiomegaly, ± pulmonary edema & pleural effusions
- 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: up to 76% Se, 96% Sp for myocarditis or infiltrative dis. (*JACC Imaging* 2014;7:254); extent of midwall fibrosis correlated w/ mortality in niCMP (*JAMA* 2013;309:896) and may identify Pts w/ EF >40% who benefit from ICD (*Circ* 2017;135:2106)
- 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)
- Stress test: useful to r/o ischemia (low false ⊖ rate), high false ⊕ rate, even w/ imaging
- Coronary angiography to r/o CAD if risk factors, h/o angina, Qw MI on ECG, equivocal ETT; consider CT angiography (*JACC* 2007;49:2044)
- ? Endomyocardial biopsy (*JACC* 2007;50:1914): yield 10%; of these, 75% myocarditis (for which no proven Rx) & 25% systemic disease; 40% false ⊖ rate (patchy dis.) & false ⊕ (necrosis → inflammation); ∴ biopsy if: acute & hemodyn compromise (r/o GCM, ANEM); arrhythmia or RCMP features (r/o infiltrative); or suspect toxic, allergic, tumor

Treatment (see "Heart Failure" for standard HF Rx)
- Possibility of reversibility of CMP may temper implantation of devices
- Immunosuppression: for giant cell myocarditis (prednisone + AZA), collagen vascular disease, peripartum (? IVIg), & eosinophilic; no proven benefit for viral myocarditis
- Prognosis differs by etiology (*NEJM* 2000;342:1077): postpartum (best), ischemic/GCM (worst)

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Definition and epidemiology
- LV (usually ≥15 mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Prevalence: 1/500; 50% sporadic, 50% familial, most asymptomatic

- Ddx: LVH 2° to HTN, AS, elite athletes (wall usually <13 mm & symmetric and nl/↑ rates tissue Doppler diastolic relaxation; *Circ* 2011;123:2723), Fabry dis. (↑ Cr, skin findings)

Pathology

- Autosomal dominant mutations in cardiac sarcomere genes (eg, β-myosin heavy chain)
- Myocardial fiber disarray with hypertrophy, which creates arrhythmogenic substrate
- Many morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical

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
- Syncope: Δs in load-dependent CO, arrhythmias

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 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)

- CXR: cardiomegaly (LV and LA)
- 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
- ? Genotyping for family screening, but pathogenic mutation ID'd in <$^1/_2$ (*Circ* 2011;124:2761)

Treatment (*EHJ* 2014;35:2733; *NEJM* 2018;379:655)

- Heart failure
  - ⊖ inotropes/chronotropes: β-blockers, 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* physiology (∇ ≥50 mmHg):

(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.

No clear benefit of dual-chamber pacing (*JACC* 1997;29:435; *Circ* 1999;99:2927)

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. Consider for SCD prevention if: NSVT, ⊕ FHx SCD, unexplained syncope, LV wall ≥30 mm, failure of SBP to ↑ or fall from peak ≥20 mmHg w/ exercise, ? extensive MRI delayed enhancement. EPS *not* useful. HCM Risk-SCD Score (*EHJ* 2014;35:2010): consider ICD if high risk (≥6%/y), may consider if intermediate (4–<6%/y).
- Counsel to avoid dehydration, extreme exertion
- Endocarditis prophylaxis not recommended (*Circ* 2007;16:1736)
- 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 CARDIOMYOPATHY (RCM)

Definition (*Circ* 2006;113:1807)

- Impaired ventricular filling with ↓ compliance in nonhypertrophied, nondilated ventricles; normal or ↓ diastolic volumes, normal or near-normal EF; must r/o pericardial disease

Etiology (*JACC* 2010;55:1769 & 2016;68:411)

- Myocardial processes

Autoimmune (scleroderma, polymyositis-dermatomyositis)

Infiltrative diseases (see primary entries for extracardiac manifestations, Dx, Rx)

Amyloidosis (*Circ* 2011;124:1079): age at presentation ~60 y; ♂:♀ = 3:2

AL (eg, MM, etc.); familial (transthyretin, ATTR); AA/senile (dep. of TTR, ANP)

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

Nl voltage/septal thickness has NPV ~90%

Labs: ✔ SPEP/UPEP, serum free light chain ratio (<0.25 or >1.65 κ-to-λ ratio)

MRI: distinct late gadolinium enhancement pattern (*JACC* 2008;51:1022)

Sarcoidosis (can also be DCM): presents at age ~30 y; ↑'d in blacks, N. Europe, ♀ 5% w/ systemic sarcoid have overt cardiac involvement; 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
Gallium or FDG uptake at areas of inflam.; sestaMIBI w/ non-cor. perfusion defects
Cardiac MRI: T2 early gad (edema); fibrosis/scar in basal septum; LGE prognostic
Cardiac bx low-yield b/c patchy
Hemochromatosis: in middle-aged men (espec N. European); 15% p/w cardiac sx
Diabetes; storage diseases: Gaucher's, Fabry, Hurler's, glycogen storage diseases

- Endomyocardial processes
  Chronic eosinophilic: Löffler's endocarditis (temperate climates; ↑ eos; mural thrombi that embolize); endomyocardial fibrosis (tropical climates; var. eos; mural thrombi)
  Toxins: radiation (also p/w constrictive pericarditis, valvular dis, ostial CAD), anthracyclines
  Serotonin: carcinoid, serotonin agonists, ergot alkaloids. Metastatic cancer.

Pathology & pathophysiology

- Path: normal or ↑ wall thickness ± infiltration or abnormal deposition
- ↓ myocardial compliance → nl EDV but ↑ EDP → ↑ systemic & pulm. venous pressures
- ↓ ventricular cavity size → ↓ SV and ↓ CO

Clinical manifestations (*Circ* 2000;101:2490)

- 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, ↓ decel. time
- Cardiac MRI/PET: may reveal inflammation or evidence of infiltration (but nonspecific)
- 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 during respiratory cycle (vs. discordance in constrictive pericarditis; *Circ* 1996;93:2007)
- Endomyocardial biopsy if suspect infiltrative process; fat pad bx for amyloid
- 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
- Tafamidis (TTR binder) ↓ death and CV hosp for TTR amyloid CM (*NEJM* 2018;379:1007)

VALVULAR HEART DISEASE

AORTIC STENOSIS (AS)

Etiology

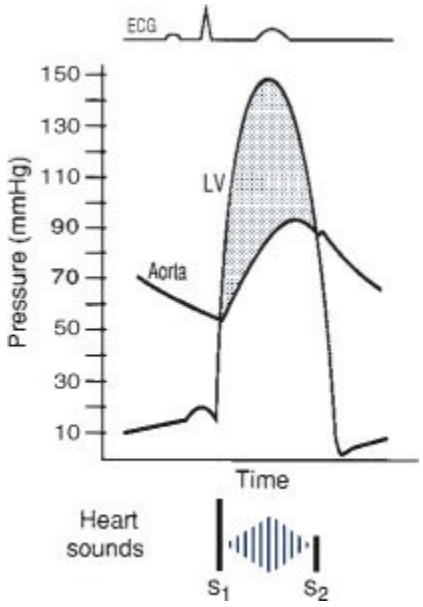
- Calcific: predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- Congenital (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- Rheumatic heart disease (AS usually accompanied by AR and MV disease)
- AS mimickers: subvalvular (HCMP, subAo membrane) or supravalvular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

Clinical manifestations (usually indicates AVA <1 cm2 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., 6th ed., 2015, 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 morphology, jet velocity, estim pressure gradient (∇) & calculate AVA, LVEF
- Cardiac cath: usually to *r/o CAD* (in ~$^1/_2$ 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* 2014;129:e521)						
Stage	**Sx**	**Severity**	**Max Jet Vel (m/s)**	**Mean Grad (mmHg)**	**AVA (cm^2)[a]**	**LVEF**
n/a	N	Normal	1	0	3–4	nl
A	N	At risk	<2	<10	3–4	nl
B	N	Mild	2–2.9	<20	>1.5	nl
		Moderate	3–3.9	20–39	1–1.5	nl
C1	N	Severe	≥4	≥40	≤1.0	nl
		Very severe	≥5	≥60	≤0.8	nl
C2		Severe + ↓ EF	≥4	≥40	≤1.0	↓
D1	Y	Severe	≥4	≥40	≤1.0	nl
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; [b]DSE → max jet vel ≥4 & AVA ≤1.0; [c]small LV w/ ↓ stroke vol.

Treatment (*Circ* 2014;129:e521; *Lancet* 2016;387:1312; *JACC* 2017; 69:1313)

- Based on *symptoms:* once they develop, AVR needed.
- AVR: indicated in sx (stage D1); asx severe + EF <50% (stage C2); or severe (stage C1) *and* undergoing other cardiac surgery.
  Reasonable if:
  Asx severe (stage C1) *but* either sx or ↓ BP w/ exercise (can *carefully* exercise asx AS to uncover sx; do *not* exercise sx AS) or very severe
  Sx severe w/ low flow/∇ w/ low EF & response to dobuta (stage D2) or normal EF but AS felt to be cause of sx (stage D3)
  Asx moderate AS (stage B) *and* undergoing cardiac surgery
- Transcatheter AoV replacement (TAVR, 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: ↑ AVA, *but* risk of stroke/AR & restenosis; ∴ bridge to AVR or palliation

TAVR (transcatheter AoV replacement) (*JACC* 2017;135:e1159)

- Valves: balloon-expandable or self-expanding. Most commonly deployed retrograde via perc. transfemoral access (best outcomes); also retrograde via axillary art. or ascend. Ao (via small sternotomy & aortotomy). Alternatively, antegrade transapical via small thoracotomy & LV puncture (if narrow iliofemoral artery or calcified Ao).
- Peri- & postprocedural complic.: low CO; annular rupture or coronary occlusion (both rare); stroke; local vascular; paravalvular leaks; CHB (? higher w/ self-expanding valve).
- Post op: lifelong ASA 75–100 mg + clopidogrel 3–6 mo

- Outcomes w/ TAVR. In *nonoperative Pts* (ie, vs. med Rx): 44% ↓ mortality but still ~20% annual mortality in TAVR group (*NEJM* 2012;366:1696; *JACC* 2014;63:1972).
  High-risk Pts (STS predicted 30d surg. mort. >8%) vs. surgical AVR (SAVR): ≈ mortality & ↑ early risk of stroke w/ balloon-expand.; 20–30% ↓ in death or stroke w/ self-expand. (*Lancet* 2015;385:2477; *JACC* 2016;67:2565)
  Medium-risk Pts (predicted 30d-mort. ~4–8%): ≈ death/stroke (? ↓ w/ balloon-expandable via transfemoral) (*NEJM* 2016;374:1609 & 2017;376:1321)
  Low-risk Pts (predicted 30d-mort. <4%): ↓ death or stroke (*NEJM* 2019;380:1695 & 1706)
  TAVR w/ ↑ vasc. complic. but ↓ bleeding, AKI, AF; need for PPM in ~25% w/ self-expand.
  Mod/severe paravalvular AI in 5–10% at 2 y, ~14% at 5 y (may be lower in lower risk Pts). Repositionable valve has rate <1% at 1 y, but ~40% rate of PPM (*JAMA* 2018;319:27).

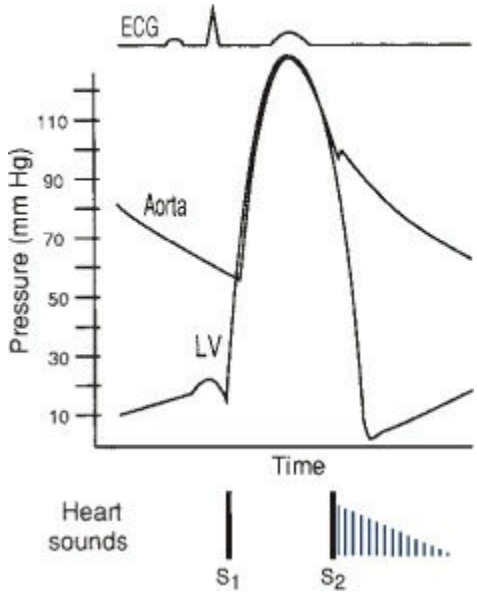
AORTIC REGURGITATION (AR)

Etiology (*Circ* 2006;114:422)

- Valve disease (43%): rheumatic heart disease (usually mixed AS/AR + MV disease); bicuspid AoV (natural hx: $^1/_3$ → normal, $^1/_3$ → AS, $^1/_6$ → AR, $^1/_6$ → 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 LUSB (RUSB 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 (*Circ* 2014;129:e521; *Lancet* 2016;387:1312)

- 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)
- Surgery (AVR, replacement or repair if possible):
  Severe and sx (if equivocal, consider stress test)
  Asx *and* either EF ≤50% or LV dilation [LVESD >50 mm or LVESDi (indexed to BSA) ≥20 or 25 mm/m^2 (*JACC* 2019;73:1741)] or undergoing cardiac surg
- Transcatheter AoV replacement (TAVR) 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; no clear benefit in asx severe AR w/ mild LV dilation & nl LV fxn (*NEJM* 2005;353:1342)

MITRAL REGURGITATION (MR)

Etiology (*Lancet* 2009;373:1382; *NEJM* 2010;363:156)

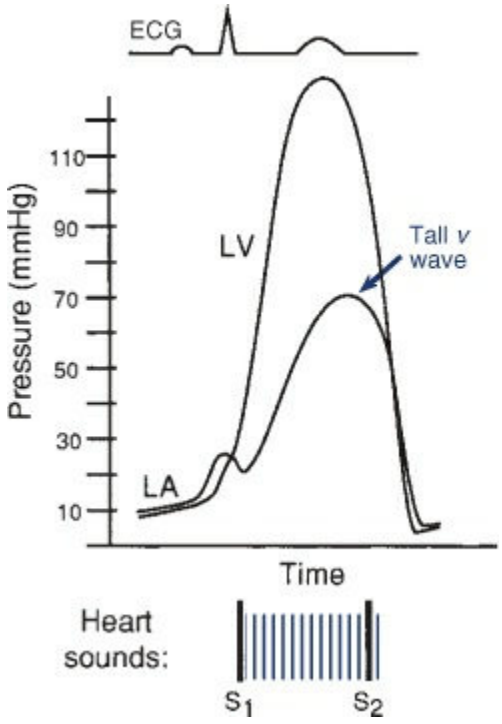
- Primary (degeneration of valve apparatus)
  Leaflet abnl: myxomatous (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs (phen-fen), XRT
  Chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma
  Papillary muscle dysfxn b/c of ischemia 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%) (*NEJM* 1988;318:1572)
  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 (*NEJM* 2005;352:875)

- 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

Classification of Primary Mitral Regurgitation

Severity	Regurg. Fraction	Jet Area (% of LA)	Jet Width (cm)	ERO (cm^2)	Angio*
Mild	<30%	<20	<0.3	<0.2	1+
Moderate	30–49%	20–40	0.3–0.69	0.2–0.39	2+
Severe†	≥50%	>40	≥0.70	≥0.40	3/4+

*1+ = LA clears w/ each beat; 2+ = LA does not clear, faintly opac. after several beats; 3+ = LA & LV opac. equal.

†For secondary MR, because ERO underestimated & likely progressive LV dysfxn, ERO ≥0.20 is severe

Treatment (*Lancet* 2016;387:1324; *Circ* 2017;135:e1159; *JACC* 2017;70:2421)

- 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 & EF >30%; asx & either EF 30–60% or LVESD ≥40 mm; ? asx, EF >60%, LVESD

<40, but EF ↓ or LVESD ↑; MV repair reasonable if asx & either EF >60% + LVESD <40 mm or new AF or PHT; if AF, concomitant surgical ablation ↓ AF recurrence, ∅ Δ stroke; consider for sx cntl or if planning no anticoag (*NEJM* 2015;372:1399)

- *Secondary MR:* if mod-sev MR (ideally ERO ≥0.40), EF 20–50%, sx despite optimized GDMT, transcatheter MV repair w/ edge-to-edge clips appears to ↓ mortality and HF hosp (*NEJM* 2018:379;2297 & 2307)
- For primary (degenerative) MR, surgery superior to percutaneous repair (*NEJM* 2011;364:1395)
- Balloon-expandable bioprosthetic valve in severe MR w/ severe mitral annular calcification under study (*JACC* 2018;71:1841)
- If sx & EF<60% but not operative candidate: HF Rx (βB, ACEI, ± aldo antag); ↓ preload w/ diuretics, NTG (espec. if ischemic MR) for sx relief ± ↓ ERO; maintain SR
- Asymptomatic: ∅ 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

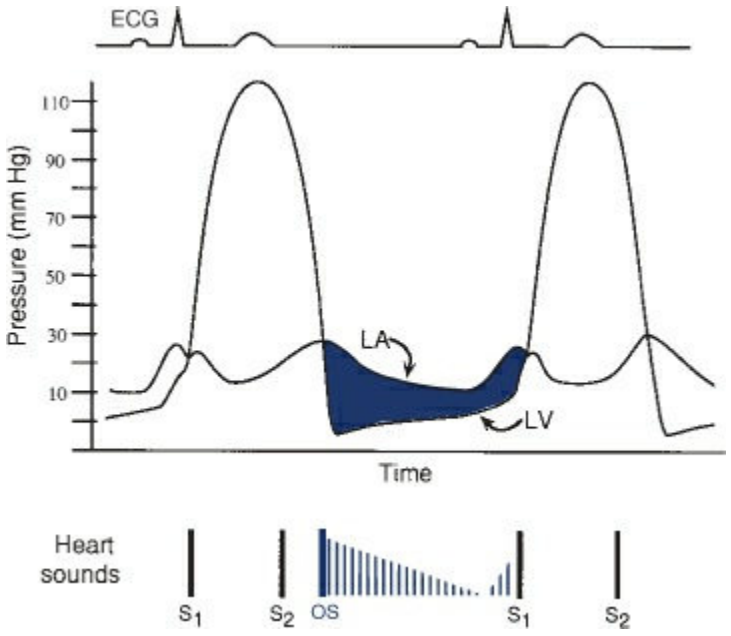
MITRAL STENOSIS (MS)

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 today
- Mitral annular calcification: encroachment upon leaflets → fxnal MS; espec in ESRD
- 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

Classification of Mitral Stenosis

Stage	Mean ∇ (mmHg)	Pressure 1/2 Time	MVA (cm^2)	PA sys (mmHg)
Normal	0		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 (*Circ* 2014;129:e521; *Lancet* 2016;387:1324)

- 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: AF; prior embolism; LA clot; ? LA >55 mm or large LA w/ spont contrast
- Mechanical intervention indicated if heart failure sx w/ MVA ≤1.5; reasonable if asx but very severe (MVA ≤1) and morphology favorable for PMBC; may consider PMBC if MVA >1.5 but hemodyn signif w/ exercise, or if asx but MVA ≤1.5 and new-onset AF
- Percutaneous mitral balloon commissurotomy (PMBC): preferred Rx if RHD; MVA doubles, ∇ ↓ by 50%; ≈ MVR *if* valvuloplasty score <8, ∅ if mod-severe MR or LA clot
- Surgical (MV repair if possible, o/w replacement): consider in sx Pts w/ MVA ≤1.5 if PMBC unavailable/failed/contraindicated or valve morphology unsuitable
- 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)

- 1° etiol: rheumatic, CTD, XRT, IE, Ebstein's, carcinoid, tumors, pacemaker leads
- Fxnl etiol (most common): RV and/or PHT (may be 2° to L-sided dis.), RV dilation ± MI
- Holosystolic murmur, 3rd/4th ICS, ↑ w/ insp (Carvallo's sign); S_3; prominent *cv* wave in JVP
- Consider repair or replacement for sx severe TR (eg, ERO ≥0.40 cm^2); emerging transcatheter Rx under study: coaptation, caval implants, orthotopic valve (*JACC* 2018;71:2935)

PROSTHETIC HEART VALVES

Mechanical (60%)

- 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 (40%)

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Less durable, but min. thrombogenic; consider if >~70 y, lifespan <20 y, or ∅ anticoag
- If 50–69 y, 2× reop but $^1/_2$ 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 for surgical valves (*Circ* 2017;135:e1159)

- *High-risk features:* prior thromboembolism, AF, EF <30–35%, hypercoagulable
- Warfarin (ØNOACs): mech MVR or high-risk mech AVR: INR 3. Low-risk mech AVR or high-risk bio MVR/AVR: INR 2.5. Consider in bio MVR/AVR for 3–6 mo if low bleed risk.
- + ASA (≤100 mg): all prosth. valves unless hx GIB, uncontrolled HTN, erratic INR, or >80 y
- If thrombosis, ↑ intensity (eg, INR 2–3 → 2.5–3.5; 2.5–3.5 → 3.5–4.5; add ASA if not on)
- For TAVR, dual antiplatelet therapy (see TAVR section in "Aortic Stenosis")

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* 2014;129:e521)

- Risk from major bleeding must be weighed against risk of valve thrombosis
- Not bleeding: if INR 5–10, withhold warfarin; if INR >10 also give vit K 1–2.5 mg PO
- Bleeding: FFP or PCC ± low-dose (1 mg) vit K IV

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 L-sided valve & either severe sx or large (≥1 cm or 0.8 cm^2); o/w UFH × days; if persists, consider lytic (eg, tPA 10 mg IVB → 90 mg over 2 hrs or 25 mg over 6 hrs repeating prn *JACC CV Imaging* 2013;6:206), success in ~80%, but ~10% risk of death, stroke or major bleed; lytic reasonable for R-sided
- 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

PERICARDITIS AND PERICARDIAL EFFUSION

Anatomy

- Tissue sac surrounding heart & proximal great vessels; 2 layers (parietal & visceral)

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

PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Acute Pericarditis (*JAMA* 2015;314:1498; *EHJ* 2015;36:2873)	
Idiopathic (>80%)	Most presumed to be undiagnosed viral etiologies
Infectious (<5% can be confirmed infectious)	Viral: Coxsackie, echo, adeno, EBV, VZV, CMV, parvo, HIV, flu Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): *S. pneumo, Neisseria, Coxiella, S. aureus, Borrelia* (Lyme); TB Fungi: *Histo, Coccidio, Candida;* Parasite: *Entamoeba, Echino, Toxo*
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); ascending AoD; chest trauma; postpericardiotomy; procedural complic. (ie, PCI, PPM)
Radiation	>40 Gy to mediastinum; acute or delayed; may be transudative
Effusion w/o pericarditis	CHF, cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis. Transudative.

Clinical manifestations (*NEJM* 2014;371:2410)

- 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 ~2/3 of Pts w/ pericarditis; ranges from asx to tamponade

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)

- 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: pericardial effusions (often appear larger by CT than by echo) ± calcifications
- MRI: may reveal pericardial thickening/inflammation, as well as myocardial involvement
- CK-MB or troponin (⊕ in ~30%; *JACC* 2003;42:2144) if myopericarditis. Consider CRP/ESR.

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, meds, relevant malignancy evaluation
- 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 (*JAMA* 2015;314:1498; *EHJ* 2015;36:2921)

- 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, uremic, preg., NSAIDs contraindicated, or refractory idiopathic disease. Appear to ↑ rate of pericarditis recurrence (*Circ* 2008;118:667). If due to TB, steroids ↓ risk of constriction (*NEJM* 2014;371:1121).
- 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 ≥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, large effusion/tamponade, T >38°C, no NSAID response after 7 d. Treatment: colchicine 0.6 mg bid × 6 mo (*Annals* 2011;155:409; *Lancet* 2014;383:2232). Nb drug-drug interactions (noted above).
- 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, ↑ JVP, hypotension
- ↑ JVP (76%) w/ blunted *y* descent
- Reflex tachycardia (77%), hypotension (26%; occasionally hypertensive), 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 (~$^1/_3$), RV infarct
  ? absent if pre-existing ↑ LVEDP, irregular rhythm, severe AI, ASD, regional tamponade
- Distant heart sounds (28%), ± pericardial friction rub (30%)
- 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), myocard. 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 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)

Treatment

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

Constrictive Pericarditis vs. Restrictive Cardiomyopathy		
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 95%, Sp 96%; *HF Rev* 2013;18:255) 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)

HYPERTENSION

JNC 8 Classification		
Category	Systolic	Diastolic
Normal	<120	<80
Pre-HTN	120–139	80–89
Stage 1 HTN*	140–159	90–99
Stage 2 HTN	≥160	≥100

2017 AHA/ACC BP Classification		
Category	Systolic	Diastolic
Normal	<120	<80
Elevated BP	120–129	<80
Stage 1HTN	130–139	80–89
Stage 2 HTN	≥140	≥90

BP in mmHg. Average ≥2 measurements >1–2 min apart. Confirm stage 1 w/in 1–4 wk; can Rx stage 2 immediately. (*J Clin HTN* 2014;16:14; *Circ* 2018;138:e426)

Epidemiology (*JAMA* 2014;311:1424; *Circ* 2018;138:e426)

- Prevalence ~30% in U.S. adults, ≥44% in African-Americans; M = F
- Of those with HTN, ~3/4 were treated, ~1/2 achieve target BP, ~1/6 were unaware of dx

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 <30 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 "Renal Failure"
RENAL	**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"
ENDO	Pheochromocytoma (<1%)	Paroxysmal HTN, H/A, palp.	
ENDO	Myxedema (<1%)	See "Thyroid Disorders"	TFTs
ENDO	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	iCa
OTHER	**Obstructive sleep apnea** (qv); alcohol		
OTHER	**Medications:** OCP, steroids, licorice; NSAIDs (espec COX-2); Epo; cyclosporine		
OTHER	Aortic coarctation: ↓ LE pulses, systolic murmur, radial-femoral delay; abnl TTE, CXR		
OTHER	Polycythemia vera: ↑ Hct		

Standard workup

- 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 ↓ 10 mmHg → 20% ↓ MACE, 28% ↓ HF, 13% ↓ mort. (*Lancet* 2016;387:957)

- ACC/AHA: initiate BP med if BP ≥130/80 & *either* clinical CVD (ischemic heart disease, HF, stroke) *or* 10-y ASCVD risk ≥10%; otherwise if BP ≥140/90
- JNC8: target <140/90 if <60 y or DM or CKD, <150/90 if ≥60 y w/o DM or CKD
- In high CV risk w/o DM, SBP target of <120 (via unattended automated cuff) ↓ MACE & mortality vs. target of <140, but w/ ↑ HoTN, AKI, syncope, electrolyte abnl (*NEJM* 2015;373:2103). Same pattern in subgp ≥75 y (*JAMA* 2016;315:2673).
- 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; enhance K intake (3.5–5 g/d)
  limit alcohol: ≤2 drinks/d in men; ≤1 drink/d in women & lighter-wt Pts; avoid NSAIDs
- 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*
  Uncomplicated: CCB, ARB/ACEI, or thiazide (chlorthalidone preferred) are 1st line; βB not
  For black, elderly, and ? obese Pts: reasonable to start with CCB or thiazide
  + CAD (*Circ* 2015;131:e435): ACEI or ARB (*NEJM* 2008;358:1547); 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: ACEI/ARB/ARNi, βB, diuretics, aldosterone antagonist (see "Heart Failure")
  + prior stroke: ACEI ± thiazide (*Lancet* 2001;358:1033)
  + diabetes mellitus: consider ACEI or ARB; can also consider thiazide or CCB
  + chronic kidney disease: ACEI or ARB (*NEJM* 1993;329:1456 & 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 $^1/_2$ max dose; after 1 mo, uptitrate or add drug
- Pregnancy: methyldopa, labetalol, & nifed pref. Hydral OK; avoid diuretics; ∅ 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 labetalol, carvedilol, or nebivolol), α-blocker, or direct vasodilator

HYPERTENSIVE CRISES

- Hypertensive emergency: SBP >180 or DBP >120 w/ 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 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 Emergency (*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
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
Enalaprilat	1.25–5 mg q6h	

*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 aneurysm (≥50% dilation of all 3 layers of aorta) vs. false (rupture within 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: ♂:♀ 2:1; ~60% root/ascending; 40% desc.
- AAA: ~4–8% prev in those >60 y; 5× more common in ♂; mostly infrarenal

Pathophysiology & risk factors (*NEJM* 2009;361:1114; *Nat Med* 2009;15:649)

- 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
- Classic clinical risk factors: HTN, atherosclerosis, smoking, age, ♂
- CTD (Marfan, Ehlers-Danlos type IV, Loeys-Dietz); congenital (bicuspid AoV, Turner's) aortitis (Takayasu's GCA, spondyloarthritis, IgG4, syphilis); trauma

Screening (*Circ* 2010;121:e266 & 2011;124:2020; *Annals* 2014;161:281; *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 (*Circ* 2010;121:e266 & 2011;124:2020)

- 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* 2008;117:1883 & 2010;121:e266 & 2016;133:680; *NEJM* 2014;371:2101)

- Goal is to prevent rupture (50% mortality prior to hospital) by modifying risk factors
- Risk factor modification: smoking cessation; LDL-C <70–100 mg/dl
- BP control: **β**B (↓ dP/dt) ↓ aneurysm growth (*NEJM* 1994;330:1335); 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 surgery (individualized based on FHx, body size, gender, 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

Endovascular repair (EVAR) (*NEJM* 2008;358:494; *Circ* 2011;124:2020 & 2015;131:1291)

- 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 (*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
- AAA: <4 cm q2–3y; 4–5.4 cm q6–12mo; more often if rate of expansion >0.5 cm in 6 mo
- TAA: 6 mo after dx to ensure stable, and if stable, then annually (*Circ* 2005;111:816)
- Screen for CAD, PAD, and aneurysms elsewhere, espec popliteal. About 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 twice as common as distal)

- 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 or acquired predisposition: *CTD* (Marfan, Loeys-Dietz, Ehlers-Danlos type IV); *congenital anomaly* (bicuspid AoV, coarct [eg, Tuner's syndrome], PCKD); *aortitis* (Takayasu's, GCA, Behçet's, syphilis); *preg.* (typically 3rd trim.); fluoroquinolone exposure
- 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%
AI 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; *JACC CV Img* 2014;7:406)

- 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 ($^2/_3$ 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; *JACC* 2013;61:1661; *Lancet* 2015;385:800)

- ↓ 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 **β**B (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy in response to vasodilators; verap/dilt if **β**B contraindic; *then* ↓ *SBP w/* IV vasodilators (eg, nitroprusside)
- If HoTN: urgent surgical consult, IVF to achieve euvolemia, pressors to keep (MAP 70 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), however pre-emptive endovascular intervention may ↓ late complications, mort (*JACC* 2013;61:1661; *Circ Cardiovasc Int* 2013;6:407)

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) *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: ~1%/h × 48 h for acute prox AoD w/ 10–35% at 30 d; ↑ mort. if HTN or HoTN
- 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) (*NEJM* 2000;342:703)

- 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*

Sick sinus syndrome (SSS)

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

AV Block	
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"). Due to AV node abnl: 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 Due to His-Purkinje abnl: ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation/AoV surgery/TAVR. 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)

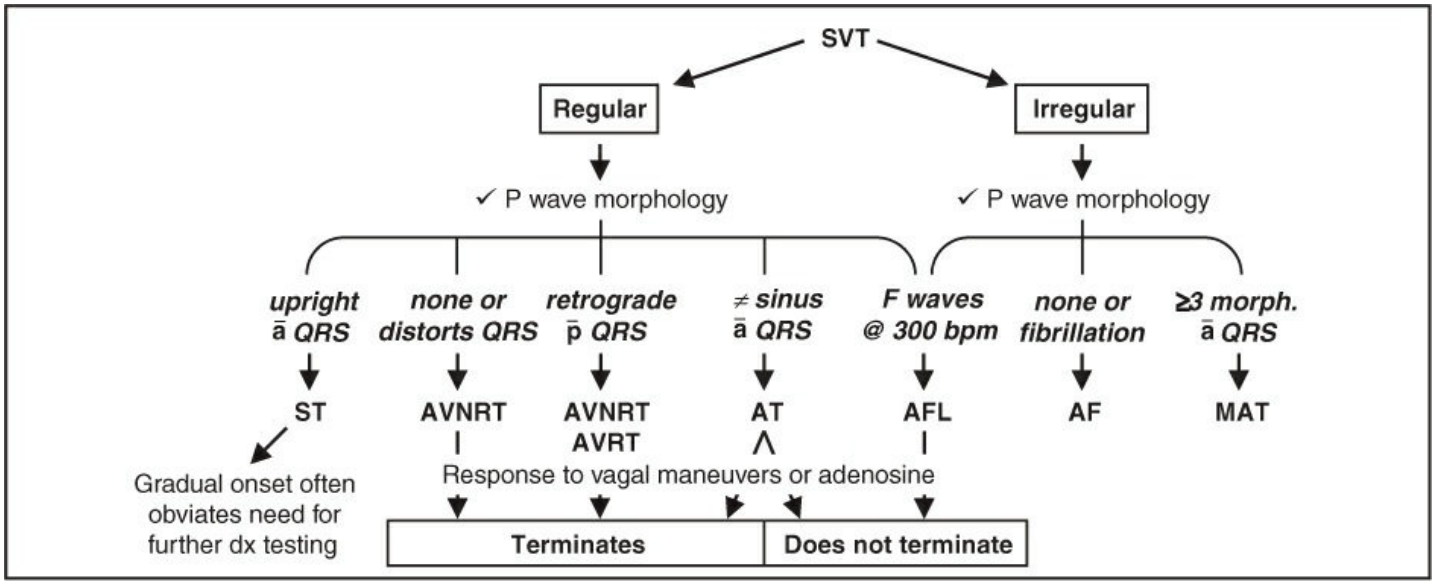
SUPRAVENTRICULAR TACHYCARDIAS (SVTS)

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 (see below).
	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) After QRS (ie, short RP) & inverted in inf. leads → *retrograde* atrial activ. AVNRT: buried in or distort terminal portion of QRS (pseudo RSR′ in V_1) AVRT: slightly after QRS (RP interval >100 ms favors AVRT vs. AVNRT) NPJT: either no P wave or retrograde P wave similar to AVNRT *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

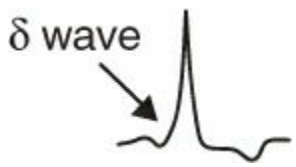
*Avoid adenosine & nodal agents if accessory pathway + pre-excited tachycardia, see below (*JACC* 2003;42:1493)

- *Catheter ablation:* high overall success rate (AFL/AVNRT ~95%, AVRT ~90%, AF ~70%)
  complications: stroke, MI, bleeding, perforation, conduction block (*JAMA* 2007;290:2768)

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* 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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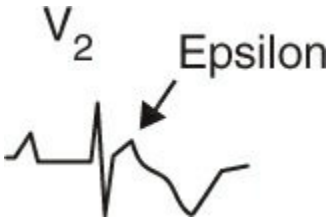
WIDE-COMPLEX TACHYCARDIAS (WCTS)

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 structurally *abnormal* heart: prior MI (scar); CMP; myocarditis

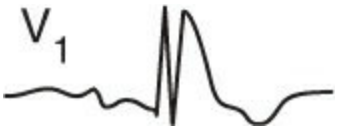


arrhythmogenic RV CMP (ARVC): incomplete RBBB,
ε wave (terminal notch in QRS) & TWI in V_1–V_3 on resting ECG
LBBB-type VT, dx w/ MRI (*Lancet* 2009;373:1289)

- In structurally *normal* heart (w/ normal resting ECG):
  RVOT VT: LBBB-type VT or PVCs w/ inferior axis; typically ablate
  Idiopathic LV 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
    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 >60–100 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* 2016;133:1715; *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 inducibility
- ICD: 2° prevention after documented VT/VF arrest (unless due to reversible cause). 1° prev. if high risk, eg, EF <30–35%, ? 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, verapamil if idiopathic LV VT, or AAD (eg, amio, mexiletine) to suppress VT
- If med a/w TdP → QT >500 ± VPBs: d/c med, replete K, give Mg, ± pacing (*JACC* 2010;55:934)
- RFA if isolated VT focus or if recurrent VT triggering ICD firing (↓ VT storm by 34%; *NEJM* 2016;375:111); ablation before ICD implantation ↓ discharge rate by 40% (*Lancet* 2010;375:31). Non-invasive radioablation (15-min ablation time) under investigation (*Circ* 2019;139:313).

ATRIAL FIBRILLATION

Classification (*Circ* 2014;130:e199)

- Paroxysmal (self-terminating, usually <48 h, often triggered in pulm veins) vs. persistent (>7 d) vs. long-standing persistent (>1 y) vs. permanent (no plan for SR)
- Nonvalvular (AF absent rheumatic MS, prosthetic valve, or mitral valve repair) vs. valvular

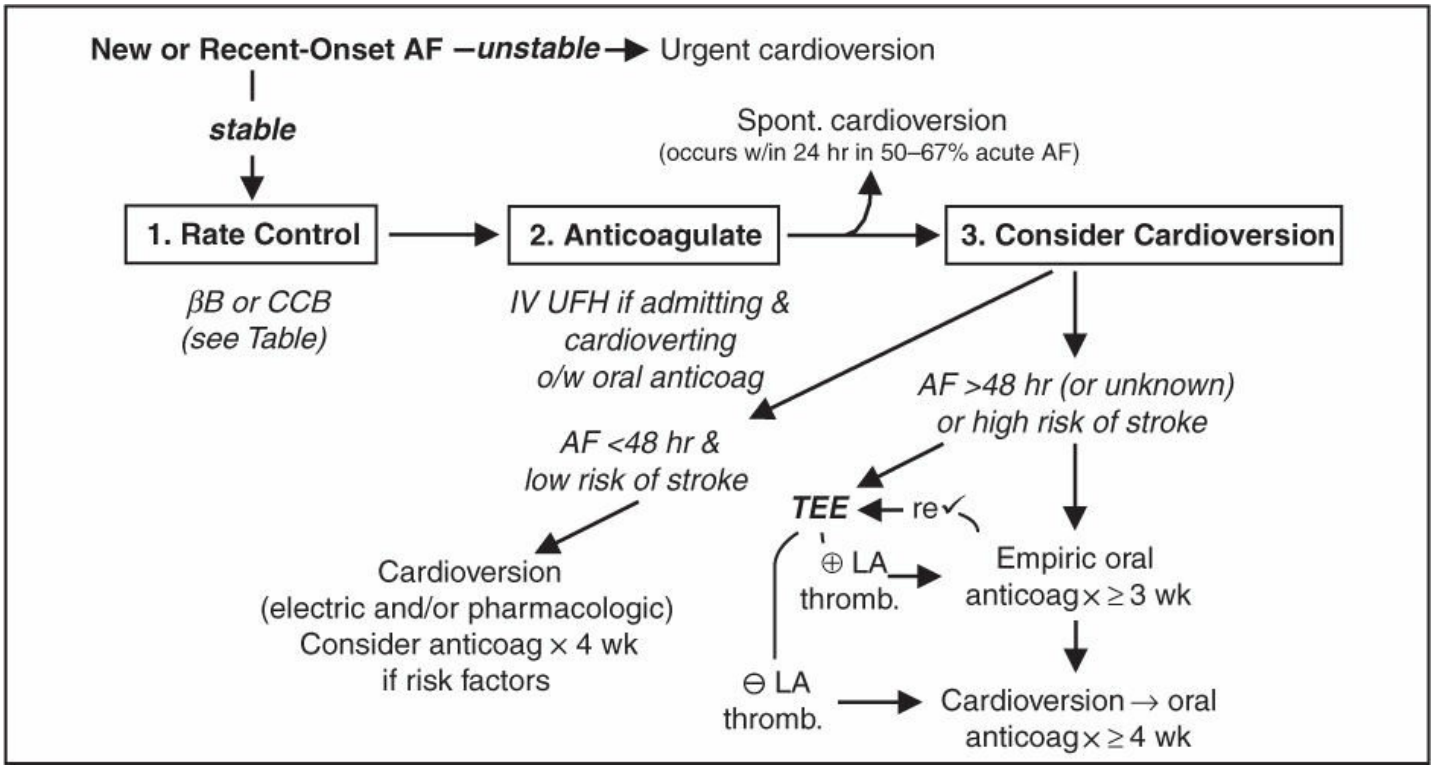
Epidemiology and etiologies (*Circ* 2011;124:1982; *Nat Rev* 2016;2:1)

- 1–2% of pop. has AF (10% of those age ≥80); M > F; lifetime risk ~25%
- 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, theophylline, caffeine, smoking, ibrutinib
  - Neurogenic: subarachnoid hemorrhage, ischemic stroke
- Chronic: ↑ age, HTN, ischemia, valve dis. (MV, TV, AoV), CMP, hyperthyroidism, obesity

Evaluation

- H&P, ECG, CXR, TTE (LA size, thrombus, valves, LV fxn, pericardium), K, Mg, Cr, FOBT before anticoag, TFTs; r/o MI not necessary unless other ischemic sx
- 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)		0.25 mg q2h 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)
- 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)

- No ↓ mortality or stroke vs rate control (*NEJM* 2002;347:1825 & 2008;358:2667 & 2016;374:1911)
- Consider if *sx* w/ rate control (eg, HF), difficult to control rate, or tachycardia-mediated CMP

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. ∅ *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

- Pulm vein isolation (radiofreq or cryo; *NEJM* 2016;374:2235): ~70% success; no need to interrupt anticoag; superior to AAD (*JAMA* 2014;311:692) & ↑ 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;139:epub; *EHJ* 2018;39:1330)

- *All valvular AF* (ie, rheum MS, valve prosthesis or repair), because stroke risk very high
- Nonvalvular AF (NVAF): stroke risk ~4.5%/y
- CHA_2DS_2-VASc to guide Rx: CHF (1 point); HTN (1); Age ≥75 y (2); DM (1), Stroke/TIA (2); Vascular disease (eg, MI, PAD, Ao plaque) (1); Age 65–74 (1); ♀ Sex category (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 → anticoagulate; score 1 → consider anticoag. or ASA (? latter reasonable

if risk factor 65–74 y, vasc dz or ♀) 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 (some data for reduced dose but unclear if ischemic stroke prevention adequate), clopi (not ticag or prasugrel), and consider stopping ASA (? after ~1 wk) (*Lancet* 2013;381:1107; *NEJM* 2016;375:2423 & 2017;377:1513 & 2019;380:1509).
- 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, else no (*JACC* 2017;69:735).

Direct Oral Anticoagulants (DOACs) for NVAF (*Lancet* 2014;383:955)		
Anticoag	Dosing	Efficacy & Safety vs. Warfarin
Dabigatran (Direct thromb inhib)	150 mg bid (110 not avail in U.S.) (75 mg bid if CrCl 15–30)	150 mg: ↓ ischemic stroke & ICH, but ↑ GIB 110 mg: ≈ ischemic stroke & ↓ major bleed/ICH Risks: GI side effects, ↑ MI c/w warfarin
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
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.
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.
Onset w/in hrs. Reversal: idarucizumab for dabi; andexanet for FXa; 4F-PCC.		

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

- If contraindic. to long-term OAC, consider perc. left atrial appendage (LAA) occlusion (*JACC* 2017;70:2964). Nb, ideally warfarin + ASA × 45 d → DAPT out to 6 mo → ASA.
- Consider perc. epicardial LAA ligation or surgical resection if undergoing other card surg

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)

- Neurocardiogenic (a.k.a. vasovagal, ~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] (*NEJM* 2008;358:615)
- 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, migraine
- 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* (*Archives* 2009;169:1299)
- *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 neurologic dis.; no CV disease at baseline → 5% cardiac, 25% vasovagal; CV disease → 20% cardiac, 10% vasovagal (*NEJM* 2002;347:878)
- 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; FOBT
- ECG (abnormal in ~50%, but only definitively identifies cause of syncope in <10%)
  Conduction: SB, sinus pauses/sinus arrhythmia, AVB, BBB/IVCD
  Arrhythmia: ectopy, ↑ or ↓ QT, preexcitation (WPW), Brugada, ε wave (ARVC), 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)

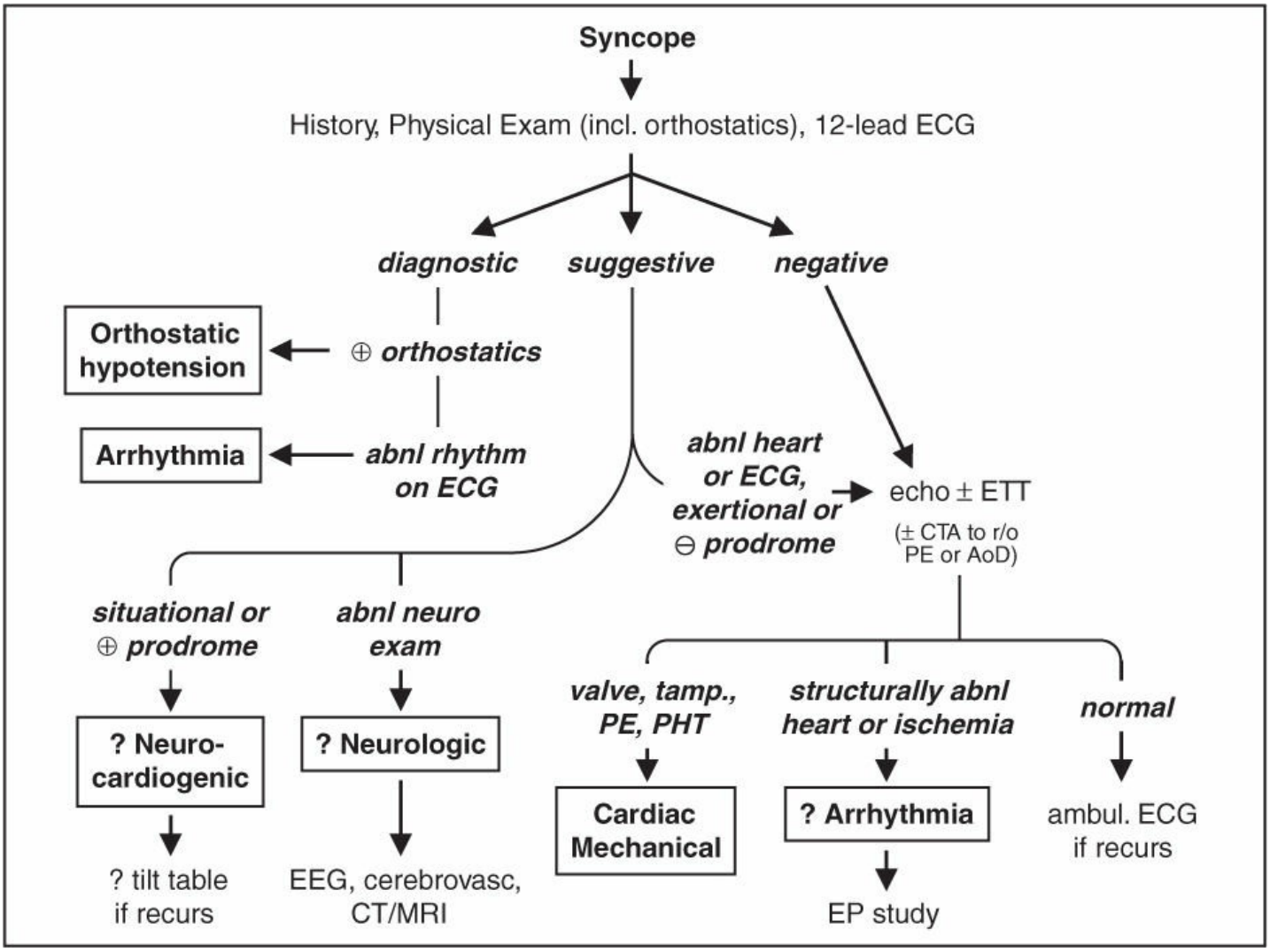
Other diagnostic studies (consider based on results of H&P and ECG)

- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope
  Holter monitoring (continuous ECG 24–72 h): useful if *frequent* events arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)
  Event recorder (activated by Pt to record rhythm strip): limited role in syncope because only useful if established prodrome (because must be Pt activated)
  External loop recorders (continuously saves rhythm, ∴ can be activated *after* an event): useful for episodes (including w/o prodrome) likely to occur w/in 1 mo; can be coupled w/ mobile cardiac telemetry than can be auto-triggered for specific rhythms
  Implantable loop recorders (SC; can record 2–3 y; can be triggered): useful if episodes

<1/mo; dx in 55% of cases; rec 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 neurocardiogenic, 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 (lack of prodrome, exertional, resultant 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 (*EHJ* 2018;39:1883)

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder, ? ICD if Brugada pattern, sarcoid, ARVC, early repol + syncope
- Neurocardiogenic: consider fludrocortisone or midodrine (*JACC* 2016;68:1; *Neuro* 2014;83:1170); ? βB or SSRI (*Circ A&E* 2012; 5:920)
  consider dual-chamber PPM if rec episodes + prolonged pauses (*Circ* 2012;125:2566)
- Orthostatic: 2–3 L fluid & 10 g Na per day; rise from supine to standing *slowly*, compression stockings; consider midodrine or fludrocortisone; ? atomoxetine (*HTN* 2014;64:1235)

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 approved for single chamber RV pacing (*Circ* 2017;135:1458); His bundle pacing ↓ death/HF/CRT upgrade vs RV pacing alone (*JACC* 2018;71:2319).	

Indications for Permanent Pacing (*Circ* 2008;117:350 & 2012;126:1784)	
AV block	3° or type II 2° AVB a/w sx or w/ either HR <40 or asystole ≥3 sec (≥5 if in AF) while awake; ? asx 3° or type II 2° AVB; bifasc or alter. L & R BBB
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 ? Neurocardiogenic syncope w/ prominent cardioinhib. response ? Syncope with bi- or trifascicular block and not likely 2° to other causes

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 ≥130ms) (*NEJM* 2014;370:1694)
  ? benefit in NYHA I–III, EF ≤50% w/ PPM indication for AVB (*NEJM* 2013;368:1585)

Implantable cardiac defibrillator (ICD) (*JACC* 2013;61:e6; *Circ* 2015;132:1613)

- 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 ∅ pace/ATP.
- Pt selection (*JACC* 2008;51:e1; *Circ* 2012;126:1784)
  2° prev: survivors of VT/VF arrest w/o revers cause; asx sustained VT + struct. heart dis.
  1° prevention: LVEF ≤30% & post-MI *or* LVEF ≤35% & NYHA II–III (wait: ≥40 d if post-MI, ≥90 d for niCMP) *or* LVEF ≤40% & inducible VT/VF; *life expectancy must be >1 y;*
  More recently, for niCMP ICD ↓ SCD but not overall mortality (*NEJM* 2016;375:1221);
  Consider if unexplained syncope + DCM, or if HCM, ARVC, Brugada, sarcoid, LQTS, Chagas, or congenital heart disease if risk for SCD;
  Pts w/ recent MI: wearable vest ? ↓ death (*NEJM* 2018;379:1205)
- 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: older systems may be OK (*NEJM* 2017;377:2555); may need to reprogram prior to MRI

Device infection (*JAMA* 2012;307:1727; *NEJM* 2012;367:842 & 2019;380:1895)

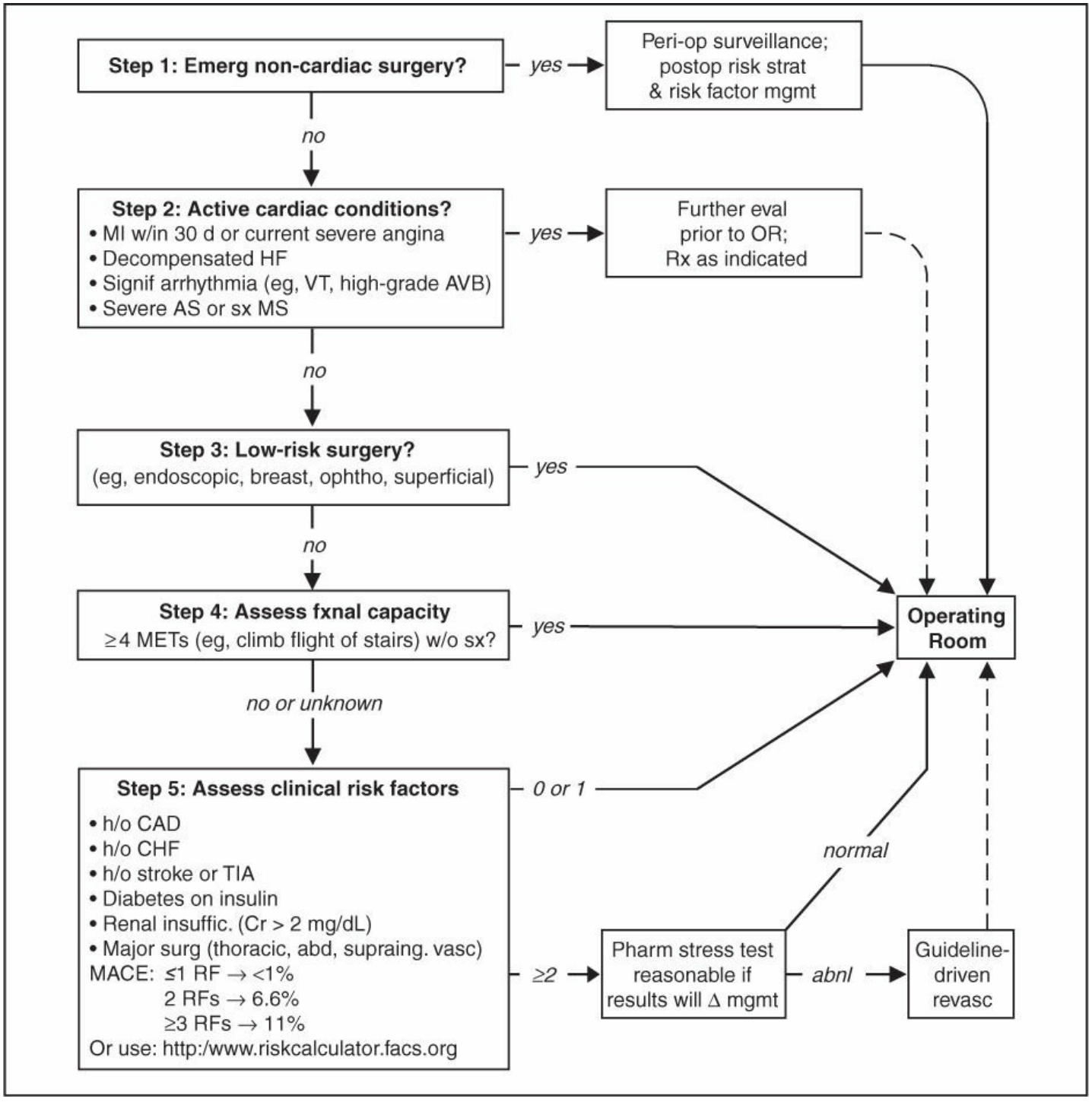
- Presents as *pocket infection* (warmth, erythema, tenderness) and/or *sepsis w/ bacteremia*
- ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%; antibacterial envelope ↓ risk
- TTE/TEE used to help visualize complic. (eg, vegetation), but even ⊖ TEE does not r/o
- Rx: abx; system removal if pocket infxn or GPC bacteremia; ∅ 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 (*NEJM* 2015;373:2258)

Figure 1-7 Approach to preop CV eval for non-CV surgery (modified from *Circ* 2014;130:e278)



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 (*JACC* 2014;64:e77)

- 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* 2015;313:2486)

  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)

- 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 ∅ 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)

Diagnosis (*Circ* 2016;135:e686)

- ↓ 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; *JAMA* 2013;309:453 & 2015;314:1936)

- Risk factor modif. Screen for CAD/AAA. Structured exercise program (*JAMA* 2013;310:57).
- 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 & death but ↑ bleeding (*NEJM* 2017;377:1319)
- 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		Cap.		
Art.	Ven.	fxn Loss	Sen. Loss	Refill	Status	Treatment
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

NOTES

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

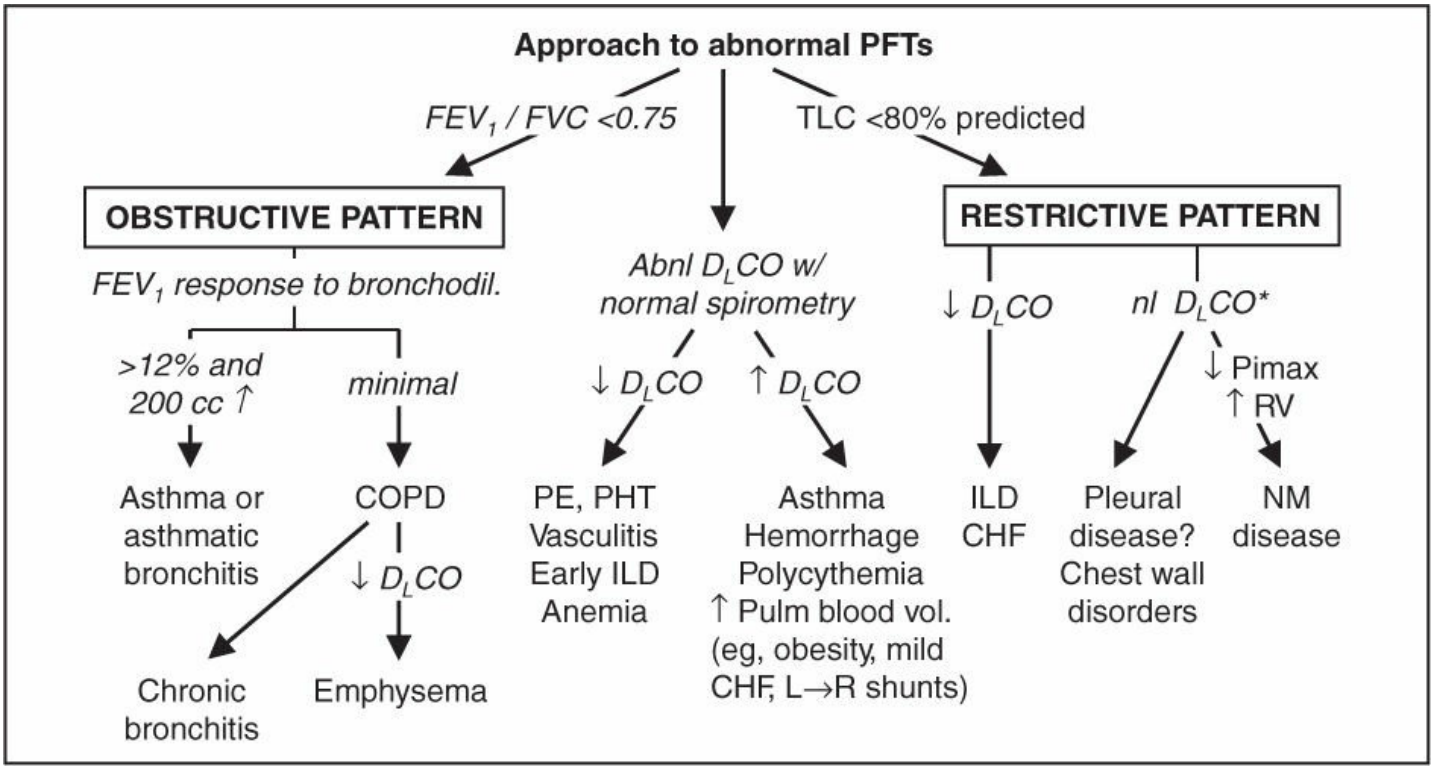
Evaluation

- 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 heart failure, ∴ need to compare to known "dry BNP"

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



FEV_1/FVC LLN typically 0.75. D_LCO can be diminished due to secondary atelectasis.

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 + allergic rxn 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)

- *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* 2017;318:279)

- Inh corticosteroids (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.
- *Long-acting* inh β_2-agonists (LABA; eg, salmeterol) safe & ↓ exacerbations 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 (*AJRCCM* 2002;165:9) and exercise-induced (*Annals* 2000;132:97). May be noninferior to ICS initial Rx and LABA add-on Rx (*NEJM* 2011;364:1695).
- 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)
- 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)

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, ∅ 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 Global Initiative for Asthma [GINA] 2018 update)					
For all patients, rapid-acting β_2-agonists prn					
Controller options	Step 1	Step 2	Step 3	Step 4	Step 5
	Consider	*Select one*	*Select one*	*Do one or more*	*Add one or both*
	Low-dose ICS	**Low-dose ICS** LTRA	**Low-dose ICS + LABA**	↑ **ICS dose (w/ LABA)**	**Refer for biologics**
			Medium-dose ICS	Add LAMA	Oral steroids (lowest dose)
			Low-dose ICS + LTRA	Add LTRA	
			Low-dose ICS + theoph	Add theoph	

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)

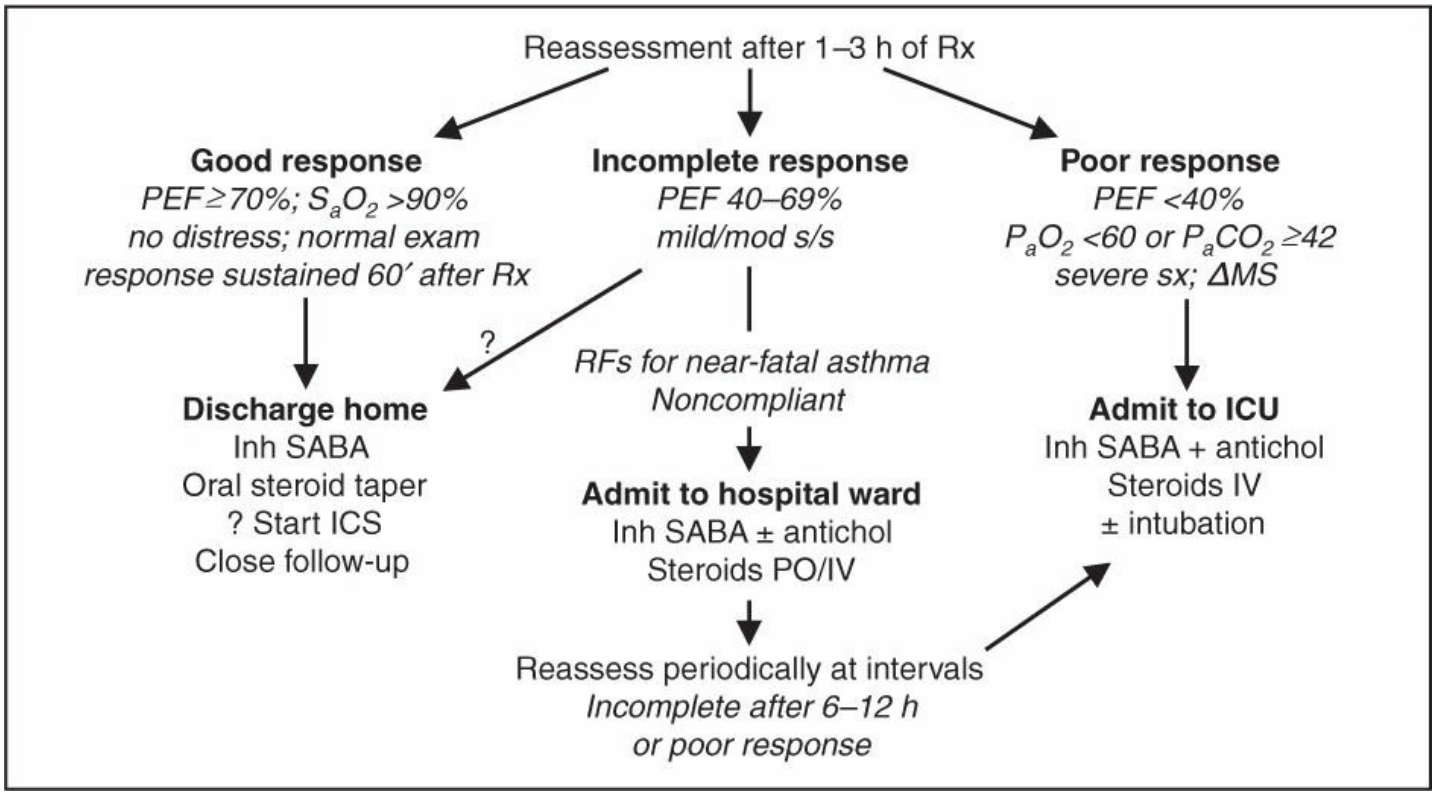
Severity of Asthma Exacerbation			
Feature	**Mild**	**Moderate**	**Severe**
Breathless w/. . .	Walking	Talking	At rest
Talking in . . .	Sentences	Phrases	Words
RR	↑	↑	>30
Accessory muscles	∅	⊕	⊕
Wheeze	Moderate, end-expir	Loud	Usually loud
HR	<100	100–120	>120
Pulsus paradoxus	Normal (<10)	10–25	>25
PEF	>80%	60–80%	<60%
S_aO_2	>95%	91–95%	<90%
P_aO_2	Normal	>60	<60
P_aCO_2	<45	<45	>45

Resp arrest imminent: drowsy, abdominal paradox, wheezes inaudible (b/c ∅ air movement), bradycardia, loss of abdominal paradox (respiratory muscle fatigue). Presence of several parameters (not necessarily all) indicates classification (adapted from GINA 2019 update).

Initial treatment (*NEJM* 2010;363:755)

- Oxygen to keep S_aO_2 ≥90%
- 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*

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



ICU-level care

- High-dose steroids: methylpred 125 mg IV q6h (*NEJM* 1999;340:1941)
- 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
- 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: IM 0.3–0.5 mL of 1:1000 dilution q5–20min; gtt at 0.1 mcg/kg/min if HoTN; avoid IVB
- 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) ± H2RA (ranitidine 50 mg IV)
- Steroids w/o immediate effect but may help prevent relapse: methylpred 125 mg IV q6h
- 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 (*NEJM* 2010;363:513), ecallantide (kallikrein inhibitor; *NEJM* 2010;363:523).

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, 1–3% of COPD cases. Suspect if age <45, lower lungs affected, extrathoracic manifestations (liver disease [not if MZ subtype], FMD, pancreatitis). ✔ serum AAT 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: infxn, 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 scooping 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 (*JAMA* 2019;321:786)

- 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 risk of PNA or in mortality (*Lancet* 2016;387:1817)
- "Triple Therapy" (ICS-LAMA-LABA) ↓ exac, ↓ hosp, ↑ PNA (*Lancet* 2016;388:963 & 2018;391:1076; *NEJM* 2018; 378:1671)
- Roflumilast (PDE-4 inhib) + bronchodil: ↑ FEV_1, ↓ exacerb (*Lancet* 2015;385:857)
- Anti-IL5 (eg, mepolizumab, benralizumab): mixed data on ↓ exacerb in Pts w/ eos (*NEJM* 2017;377:1613 & 2019;DOI:10.1056/NEJMoa1905248)
- 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)
- 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;315175)
- 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)

COPD Staging and Recommended Therapies by GOLD Criteria			
GOLD FEV_1 Stage	**Exacerbation per Year**	**Mild Symptoms**	**Mod/Severe Symptoms**
I: ≥80%	<2	**A** Short-acting inh dilator prn	**B** LAMA
II: 50–79%			
III: 30–49%	≥2	**C** LAMA+LABA	**D** LAMA+LABA+ICS
IV: <30%		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. (Adapted from GOLD Executive Summary [*AJRCCM* 2017;195:557])

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, clarithro, 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 ↑ sputum purulence or CRP >40 (*Chest* 2013;144:1571)
Oxygenation	↑ F_iO_2 to achieve P_aO_2 ≥55–60 *or* S_aO_2 90–93%	Watch for CO_2 retention (due to ↑ V/Q mismatch, loss of hypoxemic resp drive, Haldane effect) *but must maintain oxygenation!*
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
  ∅ 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 metabolic activity of tumors, 97% Se & 78% Sp for malig (esp if >8 mm)
  useful for surgical staging b/c may detect unsuspected mets (*JAMA* 2001;285:914)
  useful in deciding which lesions to bx vs. follow w/ serial CT (*J Thor Oncol* 2006;1:71)
- Transthoracic needle biopsy (TTNB): if tech feasible, 97% will obtain definitive tissue dx (*AJR* 2005;185:1294); if noninformative or malignant → resect
- Video-assisted thoracoscopic surgery (VATS): for percutaneously inaccessible lesions; highly sensitive and allows resection; has replaced thoracotomy
- Transbronchial bx (TBB): most lesions too small to reliably sample w/o endobronchial U/S (*Chest* 2003;123:604); bronch w/ brushings low-yield unless invading bronchus; navigational bronchoscopy w/ 70% yield, ↑ sens w/ larger nodules (*Chest* 2012;142:385)
- PPD, fungal serologies, ANCA

Management (if >8 mm; if ≤8 mm, serial CT q6-12mo) (*Chest* 2013;143:840)

- Low risk (<5%, see ref): serial CT (freq depending on risk); shared decision w/ Pt re: bx
- Intermediate risk (5–60%): PET; if → → follow low-risk protocol, if ⊕ → → high-risk protocol
- High risk (and surgical candidate): TBB, TTNB, or VATS → lobectomy if malignant
- Ground-glass nodules: longer f/u (b/c if malignant can be slow-growing) & PET

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, Goodpasture's, Behçet's), AVM, anticoag (w/ underlying lung dis), 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, 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	Diagnostic Testing
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, SLE	Resp sx may precede joint sx	RF, ANA
IBD	Not relieved by bowel resection	Colonoscopy, biopsy
α_1-AT deficiency	Lower lobe emphysema	α_1-AT level
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 → FLQ
- Chronic mgmt: treat underlying condition, chest PT, inhaled hypertonic saline, bronchodil.; prophylactic azithro shown to ↓ exacerb in non-CF bronchiectasis (*JAMA* 2013:1251)

Non-tuberculous mycobacterium (NTM; ubiquitous hydrophilic bacteria)

- Chronic cough, ↓ wt; Lady Windermere syndrome: R middle lobe bronchiectasis in elderly ♀ who suppress expectoration
- Dx: CT scan (tree-in-bud, nodules, cavities, bronchiect.), sputum ×3 or BAL, AFB stain + Cx
- Treatment: [azithro or clarithro] + rifamycin & ethambutol for ≥12 mo (*Chest* 2004;126:566)

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* 2016;388:2519)

- 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; combination approved for patients homozygous for ΔF508 (most common mutation) (*NEJM* 2011;365:1663; 2015;373:220; 2017;377:2013 & 2024)
- 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) Exposure-related (eg, drugs, XRT, organic & inorganic dusts); (3) Collagen vascular dis. (eg, scleroderma, GPA, RA); (4) Idiopathic PNAs (eg, IPF)

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, muscle weakness, clubbing)

Diagnostic studies (see Appendix & Radiology inserts)

- CXR and high-resolution chest CT
  - Upper lobe predom: hypersensitivty pneumonitis, coal, silica, smoking-related ILD
  - Lower lobe predom: IPF, NSIP, 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, ANCA, CCP, SSA/SSB, Scl 70, CK, aldolase, myositis panel
- If diffuse alveolar hemorrhage (DAH), Hb typically ↓ 1-2 g/dL
- Bronchoalveolar lavage: dx infxn, hemorrhage, eosinophilic syndromes
- Bx (transbronch, CT-guided, VATS depending on location of findings) if unclear etiology

SPECIFIC ETIOLOGIES OF ILD

Sarcoidosis (*Lancet* 2014;383:1155)

- 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, 24-h urine for 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/Iatrogenic
  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); pigeon fancier's lung (proteins from feathers and excreta of birds); humidifier lung (thermophilic bacteria)

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

- Rheumatologic disease

Scleroderma: fibrosis in ~50%; PHT seen in ~10% of CREST Pts
PM-DM: ILD & skin/muscle findings; MCTD: PHT & fibrosis
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 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; symmetric, peripheral, basal, subpleural. Cellular & fibrotic subtypes, latter similar to UIP.	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%
AIP	Diffuse ground-glass opacities, consolidations w/ lobular sparing. Path similar to DAD.	Sx <3 wk 6-mo mort 60%
DIP	Diffuse ground-glass opacities, reticular lines; lower zones. Peripheral Mφ 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 (*Lancet* 2017;389:1941 & *NEJM* 2018;378:1811); NSIP, non-specific 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 (*NEJM* 2014;370:2071 & 2083; *AJRCCM* 2015;192:3)
  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 ± peripheral blood

- Allergic bronchopulmonary aspergillosis (ABPA)
- 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, risk of bleed low w/ U/S & experienced operator (*Chest* 2009;135:1315 & 2013;144:456; *Archives* 2010;170:332)
- 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} $>^2/_3$ 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 surgical referral (*NEJM* 2011;365:518)
- 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 (*NEJM* 2001:779)
  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 (*Chest* 2012;141:e195S, 227S, 278S)	
Patient & Situation	Prophylaxis
Low-risk med; same-day surg & <40 y	Early, aggressive ambulation
Minor surgery in mobile Pt	Mechanical Ppx
High-risk medical (immobile, h/o VTE, thrombophilia or cancer) & most surgery Pts	UFH 5000 U SC bid/tid, or LMWH, or fonda (if HIT ⊕), or mech Ppx (esp. if high bleed risk); ? extended Ppx w/ DOAC (*NEJM* 2016;375:534). DOAC in ambul. cancer Pts (*NEJM* 2019;380:711 & 720).*
High-risk surg. (trauma, stroke, spinal cord injury, h/o VTE/thrombophilia)	[LMWH or UFH SC] + mech Ppx
Orthopedic surgery	LMWH [or fonda or warfarin (INR 2–3)] + mech Ppx; DOACs appear favorable vs LMWH After 5 d of DOAC, ASA≈DOAC (*NEJM* 2018;378:699)

For enox, 30 mg bid for highest risk or 40 mg qd for mod. risk or spinal/epidural anesth. *If Khorana score ≥2.

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%)
- *Phlegmasia cerulea dolens:* massive prox DVT w/ edema, *cyanosis*, pain, compart. synd.
- 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

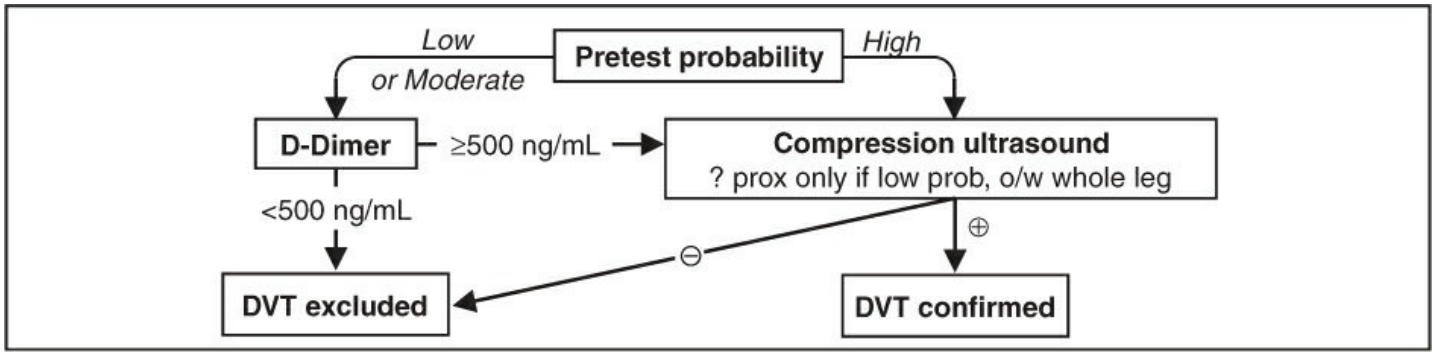
Pretest Probability Assessment (useful if outPt, less so if inPt; *JAMA IM* 2015;175:1112)		
Score ≤0	Score 1 or 2	Score ≥3
Low probability (5%)	Moderate probability (17%)	High probability (53%)

- 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

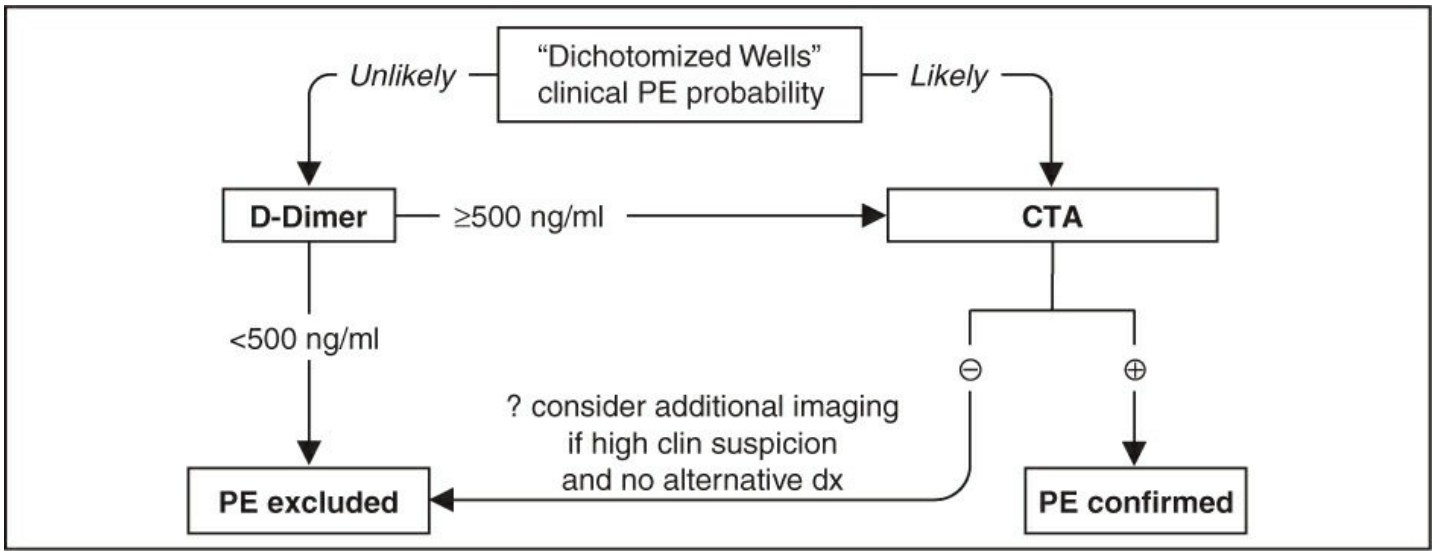
Simplified Wells Pretest Probability Scoring for PE (*Annals* 2011;154:709)	
• Prior PE or DVT • Active cancer • Immobilization (bed rest ≥3 d) or surgery w/in 4 wk • Alternative dx less likely than PE	• Clinical signs of DVT • HR >100 bpm • Hemoptysis
Dichotomized Wells Probability Assessment	
≤1 Variable = "Unlikely" (13% probability)	≥2 Variables = "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. Not helpful for Pt if will not Δ management (eg, plan for long-term anticoagulation regardless), although could be of use to relatives.
- 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

- High risk ("massive"): sustained hypotension (SBP <90), bradycardia, or cardiac arrest
- Intermediate risk ("submassive"): evidence of right heart strain w/o hypotension
  - echocardiogram: RV dysfxn (even if normal troponin) (*Chest* 2013;144:1539)
  - biomarkers: ↑ troponin, ↑ BNP (*Chest* 2015;147:685)
  - CTA: RV/LV dimension ratio >0.9 (*Circ* 2004;110:3276)
  - clinical assessment (persistent tachycardia, low BP or hypoxemia) may prompt consideration of advanced Rx (see below)
- Low risk: no right heart strain or hypotension

Whom to treat (*Lancet* 2016;388;3060; *Chest* 2016;149:315; *JAMA* 2018;320:1583)

- 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

Anticoagulation options (*Chest* 2016;149:315)

- *Initiate parenteral Rx immediately if high or intermed suspicion while dx testing underway*
- 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
  can give as sole anticoag w/ initial loading dose (riva or apixa) or initiate after ≥*5 d of parenteral anticoag* (edox or dabi; 1st dose when d/c IV UFH or w/in 2 h before when next LMWH dose would have been due)
- 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)
  can use as outPt bridge to long-term oral anticoagulation
- If cancer, LMWH ↓ recurrence and mortality c/w UFH & warfarin (*Lancet Oncol* 2008;9:577); ✔ head CT for brain mets if melanoma, renal cell, thyroid, chorioCA; edoxaban may be as effective, but ↑ major bleeding, espec in GI malig (*NEJM* 2018;378:615)
- Fondaparinux: 5–10 mg SC qd (*NEJM* 2003;349:1695); use if HIT ⊕; avoid if renal failure
- 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
- Warfarin (goal INR 2–3): start w/ parenteral anticoag unless instability and ? need for lytic, catheter-based Rx or surg; overlap ≥5 d w/ parenteral anticoag & until INR ≥2 × ≥24 h

Systemic thrombolysis (*Chest* 2012;141:e419S & 2016;149:315)

- Typically TPA 100 mg over 2 h or wt-adjusted TNK bolus; risk of ICH ~1.5%, ↑ 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) & lower PVR long term (*JACC* 1990;15:65)
- Intermediate-risk PE: ↓ hemodyn decompensation, ↑ ICH & other major bleeding, ↓ mortality in short term, but no long-term benefit on mortality, PHT or RV fxn; ? consider if <75 y and/or low bleed risk (*NEJM* 2014;370:1402; *JAMA* 2014;311:2414; *JACC* 2017;69:1536)
- *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

- Catheter-directed (fibrinolytic & thrombus fragmentation/aspiration; *Circ* 2012;126:1917)
  - Consider if PE w/ hemodyn. compromise or high risk & not candidate for systemic lysis or surgical thrombectomy (*Circ* 2011;124:2139). Preferred to systemic lytic by some centers.
  - U/S-assisted improves hemodynamics & RV fxn vs. anticoag alone (*EHJ* 2015;36:597)
  - No benefit in extensive DVT (*NEJM* 2017;377:2240)
- Thrombectomy: if large, proximal PE + hemodynamic compromise + contraindic. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn (*J Thorac CV Surg* 2005;129:1018)
- 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)

Extended antithrombotic 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)
- Warfarin, either regular (*JAMA* 2015;314:31) or low-intensity (*NEJM* 2003;348:1425)
- Aspirin: 32% ↓ recurrent VTE (*NEJM* 2012;366:1959 & 367:1979)

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 ≥25 mmHg at rest (in future ? ≥20 mmHg based on emerging data *[* Lancet Respir Med *2018;6:168]*)

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; ~1/2 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 (*JACC* 2013;62:D40; *Circ* 2014;130:1820)

- 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 ↓ $D_L$co, 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), RF, anti-Scl-70, anticentromere, ESR; LFTs; HIV
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Treatment (*JACC* 2013;62:25S & 2015;65:1976; *EHJ* 2016;37:67)

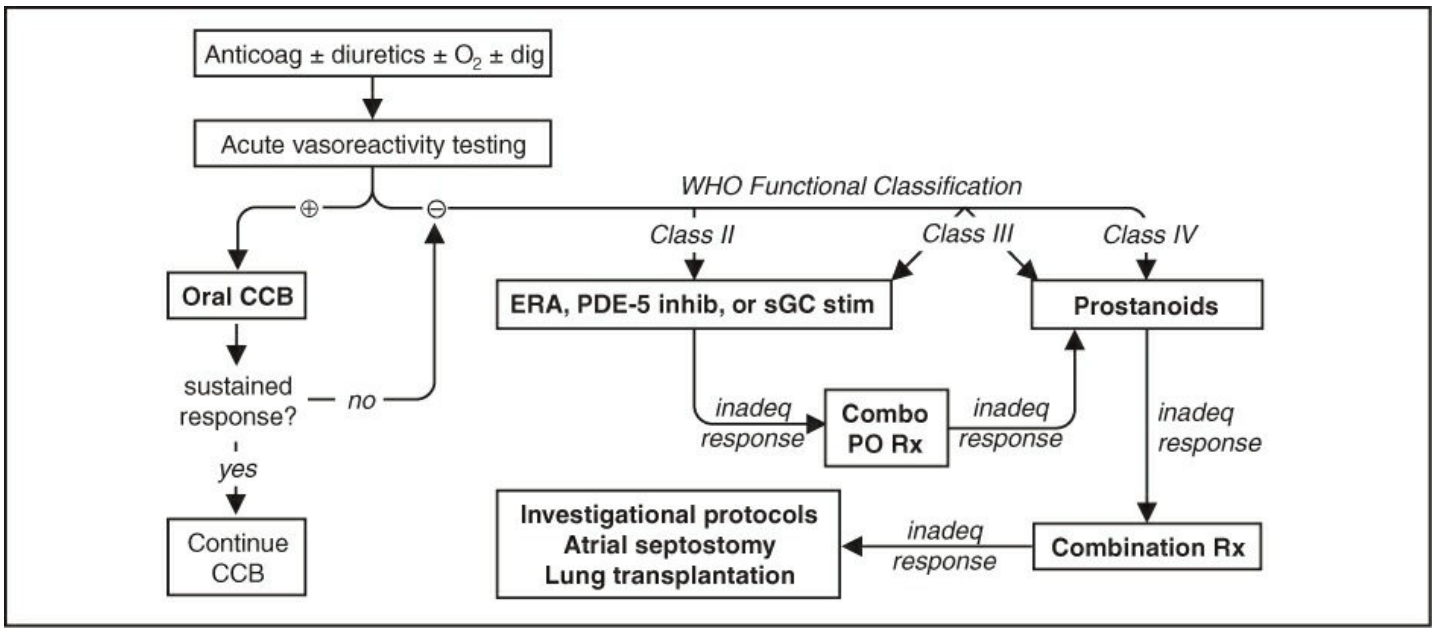
- Principles: 1) prevent & reverse vasoactive substance imbalance and vascular remodeling
  2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq systemic DBP
- Supportive
  Oxygen: maintain S_aO_2 >90–92% (reduces vasoconstriction)
  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent
  Digoxin: control AF, ? counteract neg inotropic effects CCB
  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; little evidence in 2° PHT)
PDE-5 inhibitor sildenafil, tadalafil, vardenafil	↑ cGMP → vasodilation, ↓ smooth muscle proliferation, ↓ sx, ↑ 6MWT, no data on clinical outcomes. Often first-line b/c minimal side-effect profile: HA, vision Δ's, sinus congestion (*NEJM* 2009;361:1864).
Endothelin receptor antagonists (ERAs) bosentan, ambrisentan, macitentan	↓ Smooth muscle remodeling, vasodilation, ↓ fibrosis, ↓ sx, ↑ 6MWT, ↓ worsening PAH or need for prostanoids w/ trend for ↓ PAH mort (w/ macitentan). Side effects: ↑ LFTs, HA, anemia, edema, teratogen (*NEJM* 2002;346:896; *Circ* 2008;117:3010; *NEJM* 2013;369:809).
IV Prostacyclin epoprostenol (Flolan)	Vasodilation, ↓ plt agg, ↓ smooth muscle proliferation; benefits ↑ w/ time (? vascular remodeling). ↑ 6MWT, ↑ QoL, ↓ mortality. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, catheter infxn (*NEJM* 1996;334:296 & 1998;338:273; Annals

	2000;132:425).
Prostacyclin analogues [iloprost (inh) treprostinil (IV, inh, SC)] & receptor agonist selexipag (PO)	Same mechanism as prostacyclin IV but easier to take, ↓ side effects, and w/o risk of catheter infxn, ↓ sx, ↑ 6MWT; trend to ↓ clinical events w/ iloprost but not treprostinil. Inh Rx with improved V/Q matching. Selexipag ↓ disease prog & hosp by ~40% (*NEJM* 2015;373:2522).
Soluble guanylate cyclase (sGC) stim riociguat	NO-independent ↑ cGMP → vasodilation, ↓ 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 (tadalafil + ambrisentan vs. monotherapy): ↓ sx, ↓ NT-BNP, ↑ 6MWT, ↓ hospitalizations (*NEJM* 2015;373:834)
- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence
- CTEPH: Rx as above. Pulm endarterectomy potentially curative (*AJRCCM* 2011;183:1605).
- 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)

Figure 2-5 Treatment of PAH (modified from *JACC* 2013;62:D60 & *EHJ* 2016;37:67)



Management of ICU patient

- Avoid tachyarrhythmias & overly aggressive volume resuscitation
- Caution w/ vasodilators if any L-sided dysfxn. *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)

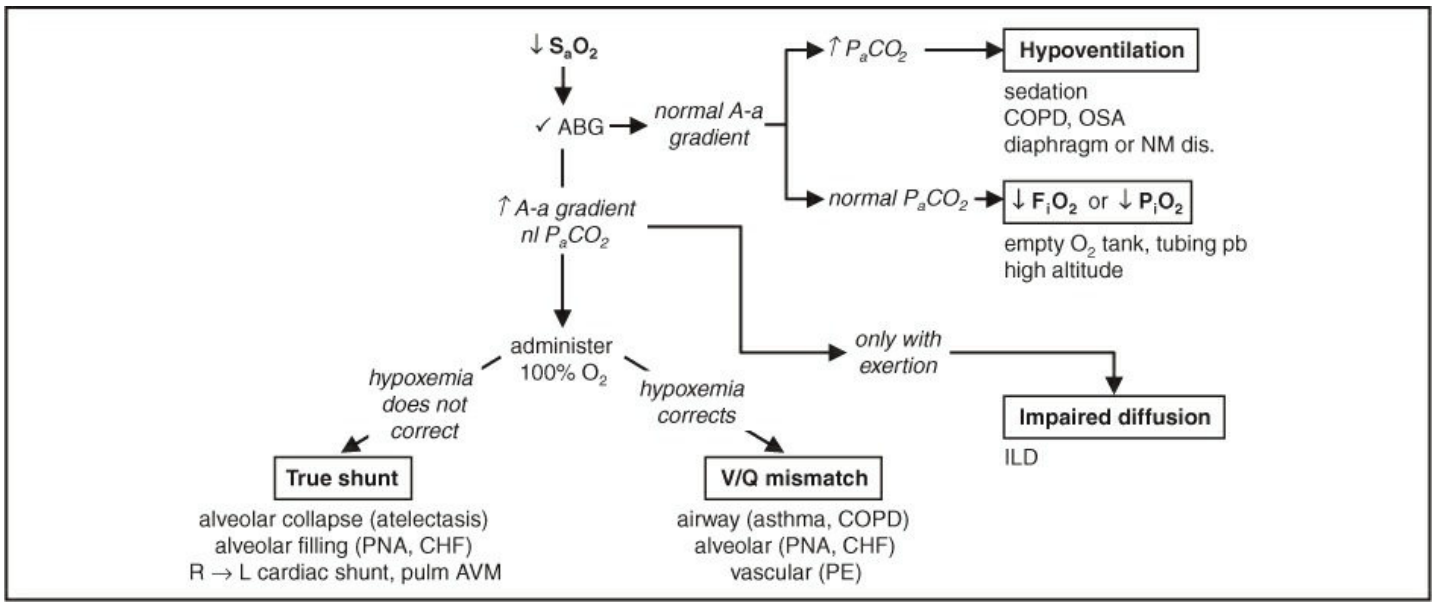
- Lung transplant: 1-y survival 66–75%; 5-y survival 45–55% (*Chest* 2004;126:63S)

RESPIRATORY FAILURE

$$\textbf{Hypoxema} \rightarrow P_AO_2 = F_iO_2 = (760 - 47)\frac{P_aCO_2}{R}$$

- 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: seen when >4 g/dL of reduced Hb in blood 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 ↓	↓	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.

Cyanide inhibits mitochondrial O_2 use → cellular hypoxia but pink skin and ↑ *venous* O_2 sat.

$$\textbf{Hypercapnia} \rightarrow P_aCo_2 = \frac{k \times Vco_2}{RR \times \left(1 - \frac{V_D}{V_T}\right)}$$

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 hyperventilation 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:** sed-atives, 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 ↑ P_aCO_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 O_2 (*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, ΔMS, vomiting, cannot protect airway, extrapulm organ failure, HD instab, sev UGIB, ↑ secretions
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 Pt 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 *Lancet* 2000;355:1931 *AJRCCM* 2006;173:164	Cardiogenic pulmonary edema: may ↓ intub. & mortality (*JAMA* 2005;294:3124; *Lancet* 2006;367:1155) although recent trial (w/ high crossover) did not show any mortality benefit (*NEJM* 2008;359:142) COPD exac w/ ↑ P_aCO_2: ↓ intub. & mort, but if pH <7.3 → intubate 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).
JAMA 2016;315:1345 *NEJM* 2001;344:481	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 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 ↑ 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.
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: inadequate exhalation time → lungs unable to completely empty before the 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
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 ⌀ 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:

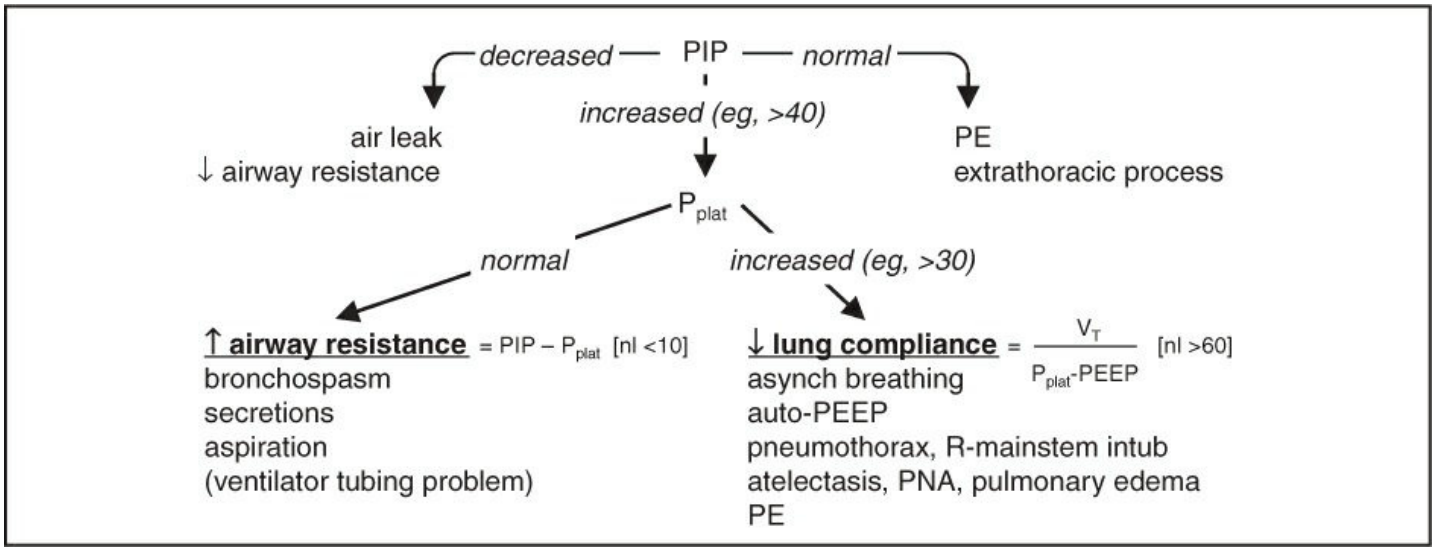
  If ↑ P_aO_2/F_iO_2 *and* P_{plat} stable, suggests recruitable lung (ie, atelectasis). If PEEP 20 & F_iO_2 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see "ARDS").

  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
- 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 1/2 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
- In high-risk Pts, extubation to either NPPV or high-flow O_2 equivalent (*JAMA* 2016;316:1565)
- ? 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 (~1/2 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 clear benefit on vent-free days (*JAMA* 2016;315:1460 & 2017;317:1321); dosen't work as sole agent, but spares use of other (*NEJM* 2019;380:2506)

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%) • Inhalation injury • Aspiration (~15%) • Lung contusion • Near drowning	• Sepsis (~25%) • Pancreatitis • Shock • Trauma/multiple fractures • DIC • Transfusion (TRALI)

Treatment (*NEJM* 2017;377:562; *ARJCCM* 2017;195:1253; *JAMA* 2018;319:698)

- Goal is to maintain gas exchange, sustain life, & avoid ventilator-induced lung injury (VILI)

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* 2011;365:1905 & 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 Δ ≥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)	

Systemic inflammatory response syndrome (SIRS): ≥2 of the following: (1) Temp >38 or <36°C, (2) HR >90, (3) RR >20 or $PaCO_2$ <32, (4) WBC >12k or <4k or >10% bands. No longer used.

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

MANAGEMENT

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)
- Balanced crystalloid (LR, Plasma-Lyte) ↓ rate of major kidney events (composite of death, need for RRT, or persistent renal dysfxn) compared w/ NS (*NEJM* 2018;378:829)
- $NaHCO_3$ 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 65–70 mmHg as good as 80–85 and ↓ AF (*NEJM* 2014;370:1583)
- 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 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 following 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 (pulse ox invalid)	100% normobaric oxygen, hyperbaric O_2 in severe cases
Organophosphate	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

(*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 >65 (rel.), uncontrolled/unRx'd infxn, malig in prior 2 y, severe non-pulm dis., BMI ≥35, active smoking, EtOH/drug depend., med noncompliance, psychosocial

Posttransplant care

- Immunosuppression: center dependent; no single best regimen. Tacro > cyclosporine (↓ incidence of acute rejection) + steroids + MMF/azathioprine
- Monitoring: clinic visits, serial PFTs, chest X-ray, bronchoscopy w/ transbronchial biopsy

Complications

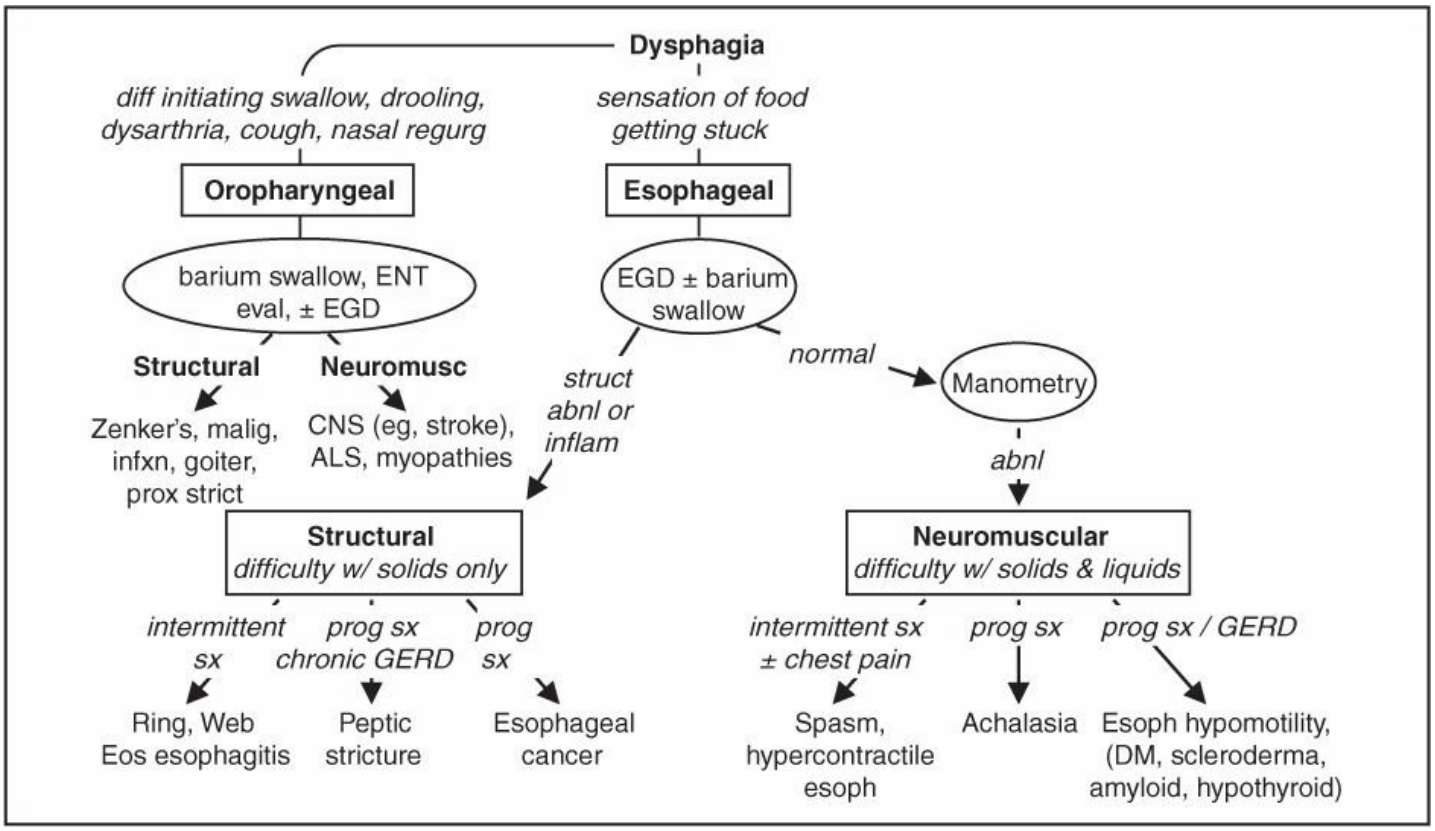
- Primary graft dysfunction (PGD): acute lung injury following txp; assoc w/ early mortality
- Anastomotic: vascular (stenosis, thrombosis) and airway (infection, necrosis, dehiscence, granulation tissue, tracheobronchomalacia, stenosis, fistula)
- Acute rejection: ↓ lung fxn, cough, SOB, fever; Dx w/ 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, eg, Schatzki ring): near GE jxn, a/w food impaction, linked to GERD; Rx w/ PPI, dilation
  - Webs (nonconcentric): usually prox, can be a/w Fe defic. (Plummer-Vinson synd.)
  - Peptic or XRT strictures, foreign body, tumor, vascular compression (dysphagia lusoria)
  - Infxn esophagitis: odynophagia > dysphagia; often immunosupp w/ *Candida*, HSV,

CMV

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

Eosinophilic esophagitis: 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 try elimination Diet (∅ milk, soy, eggs, wheat, nuts, fish); if no Δ, Drugs (swallow inh steroids); if ongoing sx & stricturing, Dilation.

Neuromuscular dysphagia (solids & liquids; *Neurogastero Motil* 2015;27:160 & 2016;22:6)

- 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 v3.0:
  1. Incomplete LES relaxation: *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 ∅ surg cand.
  2. Major motility disorders: *Absent contractility; Distal spasm* (uncord. peristalsis w/ simult. contractions); *Hypercontractile* (high amp contract.; Rx w/PPI, nitrates/CCB/PDEi, TCA)
  3. Minor motility disorders: *Fragmented peristalsis; Hypomotility* (↓ amp of distal esoph contractions; seen in scleroderma, DM, hypothyroid.; Rx w/ underlying disorder & w/ PPI)

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Pathophysiology

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

Clinical manifestations

- Esophageal: heartburn, atypical chest pain, regurgitation, water brash, dysphagia
- Extraesophageal: 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 (1) ∅ response to PPI; or if (2) *alarm features*: dysphagia, vomiting, ↓ wt, anemia
- 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)

- Lifestyle: avoid precipitants, lose weight, avoid large & late meals, elevate head of bed
- Medical: PPI achieve relief in 80–90% of Pts; H2 blockers for intermittent sx
- Refractory: confirm w/ pH testing (on PPI to assess need for ↑ Rx, or off PPI to verify dx).
  - 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: Dx: "functional heartburn". Rx w/ TCA, SSRI or baclofen.

Complications (*Gastro Clin NA* 2015;44:203; *Gastro* 2015;149:567 & 1599)

- 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 (*Lancet* 2017;390:613)

- Ulcers (break in mucosal lining >5 mm) & erosions (<5 mm) in stomach and duodenum
- Principal risk factors: *H. pylori* infection > NSAID/ASA use
- *H. pylori* infection: causes ~60–70% 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)
- Complications: UGIB, perforation & penetration, gastric outlet obstruction

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 low prevalence areas (most of U.S.)
- EGD (definitive dx): if fail empiric Rx or alarm features (see "GERD"); bx GU to r/o malig & *H. pylori;* relook in 6–12 wk if >2 cm, malig features, risk factors for gastric cancer (ie, ⊕ FHx, ⊕ *H. pylori*, atrophic gastritis, dysplasia/ 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 complications (see above)

GI prophylaxis in Pts taking ASA and/or NSAIDs (*JACC* 2016;67:1661)

- PPI if h/o PUD/UGIB and either (a) also on clopidogrel or (b) ≥2 of the following: age >60 y, steroids or dyspepsia; prior to start test & Rx *H. pylori*
- 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 from R colon)
- Hematochezia = bloody or maroon-colored stools (LGIB or rapid UGIB)

Initial management

- 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 systems predict rebleeding & mortality: AIMS65 & 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), NSAID/ASA 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, 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 PT; plts to keep count >50,000
- 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, ⌀ melena, syncope, heart failure, liver disease (*Clin Gastro Hepatol* 2015;13:115)

Diagnostic studies

- UGIB: EGD w/in 24 h. If severe bleed, ↑ Dx/Rx yield by gastric lavage and erythro 250 mg IV 30 min prior to endoscopy to clear stomach contents (*Am J Gastro* 2006;101:1211).

- LGIB: colonoscopy (identifies cause in >70%); if severe, colo w/in 12 h → consider rapid purge w/ PEG solution (6–8 L over 4–6 h). 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, can then → IR procedure 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
PUD (20–67%) (*Am J Gastro* 2014;109:1005; *NEJM* 2016;374:2367; *Br J Clin Pharm* 2017;83:1619) See "PUD"		*Treatment:* PPI: 40 mg PO or IV BID. ? Octreotide if suspect varices. 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 (4–31%)		Precipitants: NSAIDs, ASA, 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
Erosive esopha-gitis (5–18%)		Risk factors: cirrhosis, anticoagulation, critical illness. Rx offending cause + high-dose PPI; repeat EGD later to r/o underling 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. <u>*Pharmacologic*</u> Start octreotide pending EGD if suspect varices: 50 µg IVB → 50 µg/h (84% success). Rx for 2–5 d, but most benefit w/in 24–48 h. Abx: 20% cirrhotics p/w GIB have infxn, & ~50% develop infxn during hospitalization; Ppx w/ IV CTX, cipro, or levoflox × 7 d <u>*Nonpharmacologic*</u> 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.
Portal HTN gastropathy		↑ portal venous pressure → ectatic vessels, hyperemia in prox. gastric body. No endoscopic option; Rx portal HTN (octreotide), βB.
Vascular (2–8%)	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. Endo 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 suspected, diagnose by endoscopy or CT.
Malignancy (2–8%)		Endoscopic hemostasis of mass temporizing measure till cancer Rx
Mallory-Weiss tear (4–12%)		GE jxn lacerations due to vomiting → ↑ intraabd pressure & shearing effect. Can self-resolve w/o endo Rx. Rx w/ antiemetics, PPI.
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.

(*GI Endosc Clin N Am* 2015;25:415)

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 spont. (~75%) but may take hrs–days; ~20% recur. Can perform endo hemostasis w/ epi injections ± electrocautery, hemoclip, banding. Intra-arterial vasopressin or embo. 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 cirrhotics), XRT
Vascular (<10%)	Angioectasia & AVMs (see above). *Hereditary hemorrhagic telangiectasia (Weber-Osler-Rendu):* diffuse AVMs, telangiectasias throughout GI mucosa (also involve lips, oral mucosa, fingertips).
Meckel's diverticulum	Congenital blind intestinal pouch due to incomplete obliteration of vitelline duct. 2% of pop, w/in 2′ of IC valve, 2″ long, ♂:♀ 2:1, often present age 2 y (but can cause 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 (*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 (*NEJM* 2014;370:1532; *JAMA* 2015;313:71; *CDC Yellow Book* 2018)		
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, fish, shellfish; "rice water" stools w/ severe dehydration & electrolyte depletion.
Parasitic	*Giardia*	Streams/outdoor sports, travel, outbreaks. Bloating. Acute (profuse, watery) → chronic (greasy, malodorous).
(± malab for mos after Rx)	*Cryptosporidia*	In soil; water-borne outbreak; usually self-limited, can → chronic infxn if immunosupp. Abd pain (80%), fever (40%).
	Cyclospora	Contaminated produce
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; gross blood & pus in stool; ↑↑ WBC.
	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	See later
	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, checkpt inhibitors), appendicitis, diverticulitis, 1st presentation of primary 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 (⌀ antichol)
- If mod. dehydration: 50–200 mL/kg/d of oral solution or Gatorade, etc. If severe: IV fluids.
- If suspect traveler's diarrhea → FQ, rifaximin, or rifamycin; if suspect protozoal → flagyl or nitazoxanide
- *Empiric* abx for non–*C. diff inflammatory* diarrhea reasonable: FQ × 5–7 d
  Abx rec for *Shigella*, cholera, *Giardia*, amebiasis, *Salmonella* if Pt >50 y or immunosupp or hospitalized, ? *Campylobacter* (if w/in 4 d of sx onset)
- *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 Δd by abx or chemo → release of toxin A/B → colonic mucosal necrosis & inflammation → pseudomembranes
- Most frequently reported nosocomial infxn; community-acquired infxn may account for up to $^1/_3$ of new cases. Associated w/ *any* abx (esp. β-lactams, clinda, quinolones).
- 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 (occ bloody) ± mucus, often w/ 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 complications (toxic megacolon). Consider flex sig if dx uncertain and/or evidence of no improvement on standard Rx.

Initial treatment (*CID* 2018;66:48)

- If possible, d/c abx ASAP; stop antimotility agents & cholestyramine if using (binds vanco)
- Mild-mod: vanco 125 mg PO q6h or fidaxomicin 200 mg BID × 10 d preferred over MNZ
- Severe (any of the following: >12 BM/d, Temp >103°F, WBC >25, HoTN, ICU care required, ileus): vanco 500 mg PO (or PR) q6h + MNZ 500 mg IV q8h
- If worsening (ileus, ↑ WBC, ↑ lactate, shock, toxic megacolon, peritonitis): abd CT & urgent surgical consult re: 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 may persist 3–6 wk postcessation of sx & should not trigger further Rx (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: vanco 125 mg PO q6h × 10–14 d or fidaxomicin 200 mg PO bid × 10 d
- Subsequent recurrences: vanco PO pulse → taper. Consult ID physician. Fecal microbial transplant (*JAMA* 2017;318:1985; *CID* 2018;66:1) or fidaxomicin (200 mg bid × 10 d).
- Prevention: *vanco* 125–250 mg PO BID ↓ risk of recurrence 27% → 4% (*CID* 2016;65:651); consider for Pts needing abx w/ h/o severe or recurrent CDI. *Bezlotoxumab* (mAb that binds toxin B) ↓ risk of recurrence in adults receiving *C. diff* Rx & at high risk of recurrence (*NEJM* 2017; 376:305).

CHRONIC DIARRHEA (>4 WK; *JAMA* 2016;315:2712)

General evaluation

- Clinically can be organized into *watery*, *fatty*, or *inflammatory stools*
- 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, etc.
- 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 studies, ESR; *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 with fasting)

- Caused by ingestion of poorly absorbed cations/anions (Mg, sulfate, phos; found in laxatives) or poorly absorbed sugars (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 (75% nonwhites & 25% whites lactase-deficient): 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; normal osmotic gap, no Δ diarrhea w/ fasting, often nocturnal diarrhea)

- 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 nl on colo but bx shows lymphocytic & plasmacytic infiltration of mucosa ± thickened submucosal collagen. Rx: antidiarrheals, cholestyramine, bismuth, budesonide; consider anti-TNFs if refractory.
- 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).

Fxnal/IBS (watery; 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)
  - 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 defic anemia; osteoporosis; dermatitis herpetiformis; ↑ AST/ALT
  - Dx: IgA anti-tissue transglutaminase Ab (most Se), IgA anti-deaminated gliadin peptide Ab; IgA ɑ-endomysial Ab. Duodenal bx to confirm dx (blunted villi, crypt hyperplasia, inflamm infiltrate) but may not be necessary if serology ⊕ and Pt sx. HLA-DQ2/Q8 testing useful for high ⊖ predictive value if ⊖ serologies already on gluten-free diet.
  - 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 (eg, rifaximin, MNZ, FQ).

- Other: s/p short bowel resection (short bowel syndrome), chronic mesenteric ischemia, eosinophilic gastroenteritis, intestinal lymphoma, tropical sprue, *Giardia* infection

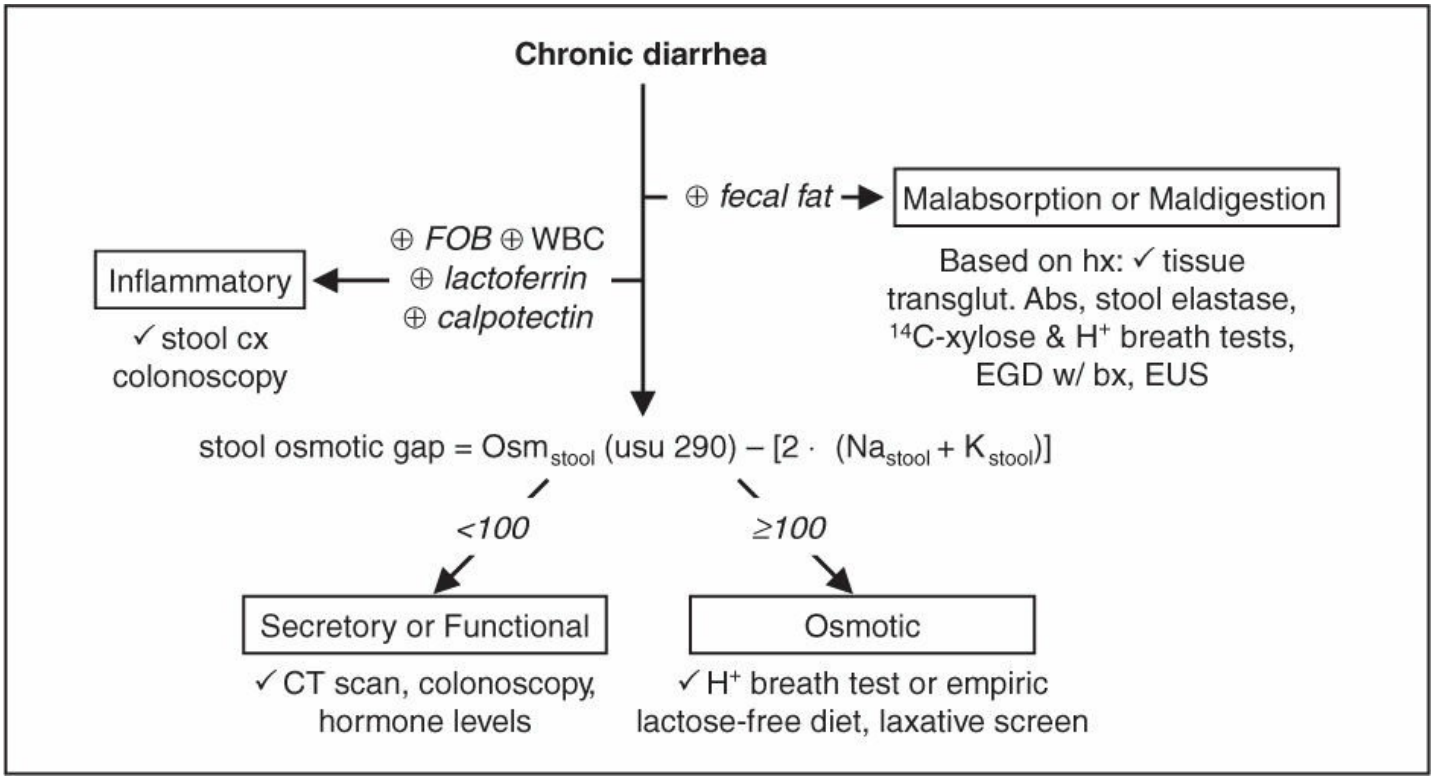
Maldigestion (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- 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, or empiric pancreatic enzyme replacement.
- ↓ bile acids due to ↓ synthesis (cirrhosis), cholestasis (PBC), or s/p ileal resection. Test w/ empiric bile acid replacement therapy.

Inflammatory (⊕ fecal WBC, lactoferrin, or calprotectin; ⊕ 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)
- 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 a/w ≥2 of following: improve 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. behavioral Rx, probiotics, exercise, consider gut-brain modulators (eg, TCA, SSRI), Δ diet (↓ fermentable short-chain carbohydrates)
  - IBS-C: ↑ soluble fiber in diet, laxatives (eg, lubiprostone, linaclotide, PEG), biofeedback
  - IBS-D: loperamide or rifaximin; eluxadoline, μ & κ agonist, δ antag (*NEJM* 2016;374:242)
- Cyclic vomiting syndrome (CVS): acute recurrent vomiting; a/w marijuana use, personal or FHx of migraine. Acute Rx: antiemetics, IVF, sumatriptan, BZDs; prevention: TCAs/AEDs; avoid marijuana.

Gastroparesis (*Gastro Clinics of NA* 2015;44:1; *World J Gastro* 2015;21:6842)

- Delayed gastric emptying w/o 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
- Dx: gastric emptying scintigraphy
- Treatment: prokinetic agents (metoclopramide or erythromycin), antiemetics for sx; feeding tube if refractory; intrapyloric botox & gastric stimulator experimental

Paralytic ileus of the colon (Ogilvie's; *ANZ J Surg* 2015;85:728) & small bowel

- 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 med 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 or 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
- Treatment: conservative measures (NPO, avoid offending meds) usually effective; IV neostigmine (monitor for bradycardia), methylnaltrexone; bowel decompression w/ NGT, rectal tube. Ogilvie's only: colonoscopy; if refractory, colostomy or colectomy.

Constipation (*Annals* 2015;162:ITC1)

- Defined as dissatisfaction w/ defecation or (per Rome IV): ≥2 of following during last 3–6 mo ≥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)
  - Mech obstruction: malignancy, compression, rectocele, strictures
  - Meds: opioids, TCAs, anticholinergics, CCB, NSAIDs, diuretics, Ca^{2+}, Fe
  - 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: ↑ fluid & fiber intake. Emollient laxative (docusate): softens stool.
  - Bulk laxatives (psyllium, methylcellulose, polycarbophil): ↑ colonic residue, ↑ peristalsis
  - Osmotic laxatives (Mg, $NaPO_4$ [avoid in CKD], lactulose, PEG): ↑ H_2O in colon
  - Stimulant laxatives (senna, castor oil, bisacodyl): ↑ motility & secretion
  - Enema/suppository (phosphate, mineral oil, tap water, soapsuds, bisacodyl)
  - Lubiprostone (↑ secretion); methylnaltrexone and alvimopan for opioid-induced
  - Plecanitide (cGMP agonist) for chronic idiopathic constipation (*Gastroenterol* 2016;150:S317)
  - Linaclotide ↑ stool freq, ↓ straining/bloating (*Am J Gastro* 2018;113:105)

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 48–72 hr of ICU admit may ↓ infxn & mort, but repletion of 100% caloric needs may be harmful (*Cochrane* CD0078767). Contraindic. if obstruction, major GIB. Possible complic: ischemic bowel b/c ↑ demand for splanchnic blood; aspiration PNA.
- Parenteral (PN): start after 7 d if unable to tolerate enteral feeds, late (> day 8 of ICU stay) Contraindic: hyperosmolality, severe electrolyte disturbances, severe hyperglycemia; sepsis is *relative* contraindication. Complications: hyperglycemia (due to dextrose), catheter sepsis/thrombus, refeeding syndrome, LFT abnl (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
- Thought to occur in setting of abnormal motility and ↑ intraluminal pressure

Epidemiology

- Risk factors: ↓ fiber, ↑ red meat, obesity, smoking, physical inactivity, EtOH, NSAIDs
- Prevalence higher w/ ↑ age (10% if <40 y; 50–66% if >80 y); "Westernized" societies
- Left side (90%, mostly sigmoid) > R side of colon (except in Asia where 75–85% R-sided)

Clinical manifestations

- Usually asx, but 5–15% develop diverticular hemorrhage (see "GIB") and <5% diverticulitis
- Limited data for ↑ fiber diet or avoiding nuts/seeds (*Ther Adv Gastro* 2016;9:213)

DIVERTICULITIS

Pathophysiology (*Gastro* 2015;149:1944; *Am J Gastro* 2018;112:1868)

- Retention of undigested food and bacteria in diverticulum → fecalith formation → obstruction → compromise of diverticulum's blood supply, infection, perforation
- Uncomplicated: microperforation → localized infection
- Complicated (15%): 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

- Plain abdominal radiographs to r/o free air, ileus or obstruction
- Abdominal CT (I^+O^+): >95% Se & Sp; assess complicated disease (abscess, fistula)
- Colonoscopy *contraindic.* acutely as ↑ risk of perforation; do 6–8 wk after to r/o neoplasm

Treatment (*JAMA* 2017;318:291; *Dig Surg* 2017;34:151; *NEJM* 2018;379:1635)

- Mild: outPt Rx indicated if Pt has few comorbidities and can tolerate POs
  PO abx: (MNZ + FQ) or amox/clav for 7–10 d; liquid diet until clinical improvement
  Possible that abx not needed for uncomplicated diverticulitis (*Br J Surg* 2017;104:52)
- 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
  - Resection superior to laparoscopic lavage (*JAMA* 2015;314:1364), but lavage may be suitable for perforation w/ purulent peritonitis (*Annals* 2016;164:137)
  - 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 (*Cochrane* CD009839; *Am J Gastro* 2016;11:579; *Ann Gastro* 2016;29:24)
- Mesalamine + rifaximin both w/ weak evidence
- Risk of recurrence 10–30% w/in 10 y of 1st episode; more likely 2nd episode complicated

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POLYPS & ADENOMAS

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
- Nonneoplastic polyps: hyperplastic, juvenile, Peutz-Jeghers, inflammatory

Detection
- *Colonoscopy* is gold standard
- Recommended in all Pts starting at age 50 (Amer Cancer Soc. rec age 45) and then typically q10y unless pathology found
- If ⊕ FHx, start age 40, or 10 y before age of dx in youngest family member, repeat q5y

INFLAMMATORY BOWEL DISEASE

Definition

- Ulcerative colitis (UC): inflammation of the colonic *mucosa; contiguous*, starting at rectum
- Crohn's disease (CD): *transmural* inflammation anywhere along GI tract, *skip lesions*

Epidem & pathophys (*Lancet* 2016;387:156 & 2017;390:2769)

- Prevalence ~1-3:1000 in N Am; ↑ incidence in Caucasians, Jews, newly industrialized
- Age of onset 15–30 y; ? bimodal w/ 2nd peak at 50–70 y; 1:1 M:F in N America
- Smokers at ↑ risk for CD, whereas nonsmokers & former smokers at ↑ risk for UC
- Genetic predisposition + environmental risk factors → T cell dysregulation → inflammation

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ULCERATIVE COLITIS (*Lancet* 2018;389:1756)

Clinical manifestations

- Grossly bloody diarrhea, lower abdominal cramps, urgency, tenesmus
- Extracolonic (>25%): erythema nodosum, pyoderma gangrenosum, aphthous ulcers, uveitis, episcleritis, thromboembolic events (esp. during a flare; *Lancet* 2010;375:657), AIHA, seroneg arthritis, chronic hepatitis, cirrhosis, PSC (↑ risk cholangio CA, CRC)
- Multiple scores for assessing dis. severity clinically: Truelove & Witts; SCCAI

Diagnosis

- Colonoscopy: involves rectum (95%) & extends prox., usu 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)

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
- CRC and dysplasia (*see below*)
- 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

CROHN'S DISEASE (*Lancet* 2018;389:1741)

Clinical manifestations (*Nat Rev Gastro Hep* 2016;13:567)

- Abdominal pain, loose/frequent stools (up to 50% ⊕ FOBT), fever, malaise, wt loss
- Mucus-containing, nongrossly bloody diarrhea
- N/V, bloating, obstipation if presence of obstruction; extracolonic manifestations as in UC
- Multiple 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
- 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 symptomatology)
- 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 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* 2016;398:1756; *Mayo Clin Proc* 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) 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) typical approach; consider early biologic if severe disease

Medical Therapy for IBD	
Ulcerative Colitis	
Mild	5-ASA: many formulations (sulfasalazine, mesalamine, olsalazine, balsalazide) depending on disease location. Used for induction & maintenance of remission. Complications: diarrhea, abd pain, pancreatitis.
Mild- moderate	MMX-budesonide: PO budesonide released throughout colon for flare. 1st-pass metab ↓ systemic 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; ↑ remission rate when AZA combined w/ IFX (*Gastro* 2014;146:392). Complic: 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.
Severe or refractory disease (*Lancet* 2014; 384:309 & 2017;389:1218; *NEJM* 2016; 374:1754 & 2017; 76:1723; *JAMA* 2019; 321:156)	IV steroids: eg, 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: reactiv. TB (✔ PPD prior to Rx) or viral hepatitis; small ↑ risk NHL; lupus-like rxn, psoriasis, MS, CHF. *For TNF refractory, alternative biologic for induction & maintenance:* vedolizumab (α4β7 integrin inhibitor); tofacitinib (JAK inh) *Investigational:* fecal microbiota transplant (mixed data – efficacy may depend on mode of delivery & prep); etrolizumab (α4β7 inhib); ozanimod (sphinosine-1-phosphate receptor agonist)
Crohn's Disease	
Mild	Consider 5-ASA for colonic Crohn's disease Abx: FQ/MNZ or amo x/clav for pyogenic complic (fistulas, perineal dis.)
Mild-mod	Budesonide: PO, but pH ± time-dep release → ileum & ascending colon
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)	Anti-TNF: infliximab, adalimumab or certolizumab (pegylated) If flare on infliximab, ✔ trough & presence of anti-inflixi Ab. Low & ⊖ Ab → ↑ dose/freq. If ⊕ Ab → Δ to other biologic (*Am J Gastro* 2011;106:685). Vedolizumab (anti-α4β7 integrin); ustekinumab (anti-IL 12/23) *Investigational:* tofacitinib and filgotinib (JAK-inh; *Lancet* 2017;389:266); adipose- derived stem cells (*Lancet* 2016; 388:1281)

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 disease; endoscopic dilation or 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 colonic

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 is emerging technique. 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

- Total arterial or venous occlusion: sudden abd pain out of proportion to abdominal tenderness on exam, progressing to frank infarction w/ peritoneal signs if untreated
- 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, anti-coagulation 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 warfarin 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

- Definition and causes: ↓ 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 std; gastric tonometry exercise testing
- Treatment: surgical revascularization (1st line); could also consider angioplasty ± stenting

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

Pathogenesis

- Pancreatic duct and acinar injury via direct or indirect toxicity → impaired secretion and premature activation of digestive enzymes → autodigestion and acute inflammation

Etiologies (*NEJM* 2016;375:1972)

- 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 (qv)
- Familial: suspect if early onset (age <20 y); cause acute and chronic pancreatitis (qv)
- 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, post-op), ∴ ✔ amylase/lipase in unexplained shock
- 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: typically not useful to visualize pancreas (obscured by bowel gas), but *should be ordered for all Pts to r/o biliary etiology* (ie, gallstones, BD dilatation)
  Abd CT: not rec for initial eval unless dx unclear (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; also used to assess for stones & ductal disruption
  Endoscopic U/S (EUS): useful for occult biliary disease (microlithiasis)

Severity (*Gut* 2013;62:102)

- 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 48–72h (fluid collect., necrosis) to predict mortality; can lag behind clinical

Treatment (*NEJM* 2016;375:1972; *Am J Gastro* 2017;112:797)

- Fluid resuscitation: *aggressive in 1st 24 hrs, even if mild.* 20 ml/kg IVB → 3 ml/kg/hr. Goal to ↓ BUN & Hct over 12–24 h. ✔ UOP. LR may be 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, organ failure, surgical interventions, and mortality.
- 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, most resolve w/in 1–2 wk w/o Rx
  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 (5% of all cases, 30% of severe): high mortality. Rx w/ carbapenem or MNZ+FQ. If stable, defer drainage to >4 wk to allow liquefication and WOPN (qv). If sx or unstable, perc drainage & minimally invasive surg debridement or endoscopic necrosectomy superior to open necrosectomy (*NEJM* 2010;362:1491).
  WOPN (walled off panc. nec.): fibrous wall surrounds necrosis over ≥4 wk; endoscopic or perc. drainage (preferred over open necrosectomy) if infected or symptomatic

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CHRONIC PANCREATITIS

Pathogenesis & etiology (*Gastro* 2013;144:1292; *BMJ* 2018;361:k2126)
- 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: Toxins (60–80% due to EtOH; smoking), Idiopathic, Genetic (PRSS1, SPINK1, CFTR, CTRC, CASR), Autoimmune, Recurrent panc., Obstruction

Clinical manifestations
- Epigastric pain, N/V; over time can be painless; signs of exocrine insuff (steatorrhea, wt loss) or endocrine insuff (DM: polydipsia, polyuria)

Diagnostic studies (*Pancreas* 2014;43:1143)
- 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 test not widely available.

Treatment (*Gastro* 2011;141:536; *Lancet* 2016;387:1957)
- Pancreatic enzyme replacement (may ↓ pain by reducing CCK). Rx routine vitamin D & Ca.
- Pain control: smoking & EtOH cessation, analgesics, pregabalin, endoscopy (stone removal or stenting strictures), celiac nerve plexus block, surgery

Complications
- Pseudocysts, pseudoaneurysms, pancreatic ascites or pleural eff., 13× ↑ risk of panc Ca

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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 cholangitis, 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
- Corticosteroids 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; skeletal musc. injury, MI (AST > ALT)
- Alkaline phosphatase (Aϕ): enzyme bound in hepatic canalicular membrane ↑ levels seen w/ biliary obstrxn or intrahepatic cholestasis 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.
  ↑ direct hyperbili seen with cholestasis, enzymatic disorders (eg, Dubin-Johnson, Rotor's)
  ↑ indirect hyperbili seen with hemolysis, enzymatic disorders (eg, Crigler-Najjar, Gilbert's)
  jaundice seen when bili >2.5 mg/dL (esp. in sclera or under tongue); if hyperbili conjugated then ↑ urine bilirubin

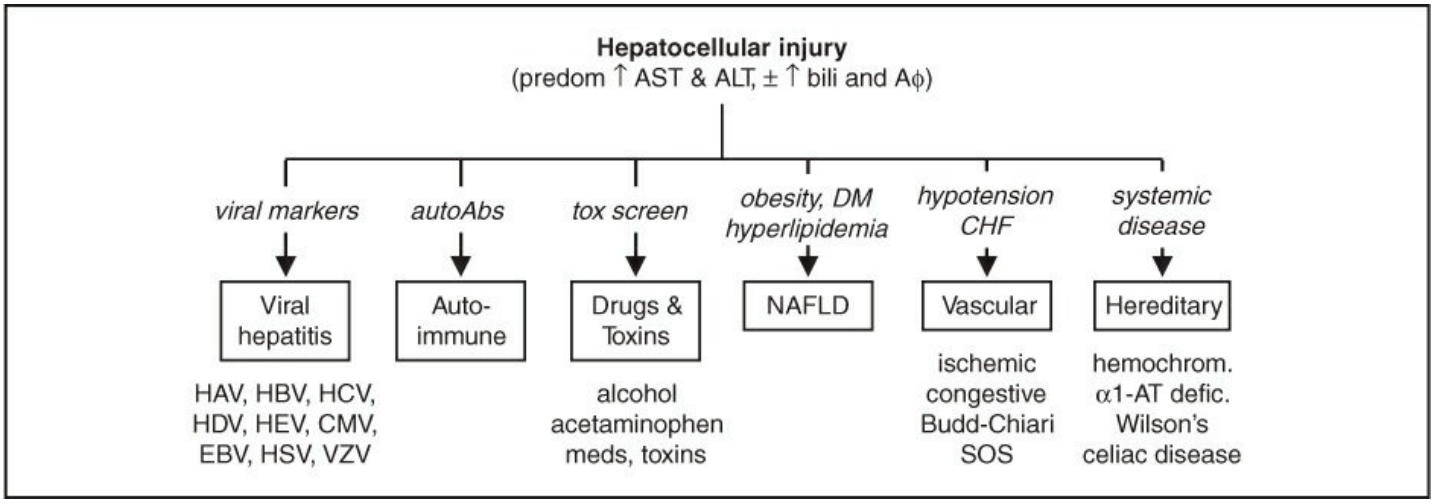
Tests of hepatic function

- Albumin: marker for liver protein synthesis, ↓ slowly in liver failure ($t_{1/2}$ ~15–18 d)
- Prothrombin time (PT): depends on synthesis of coag factors by liver (except FVIII); b/c t½ 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, NASH	Often ALT > AST		±↑	±↑ (direct)
Alcoholic hepatitis	AST:ALT ≥ 2:1		±↑	±↑ (direct)
Ischemic injury	↑↑↑	↑↑↑	↑↑	↑↑ (direct)
Wilson's disease	↑	↑	Aϕ:Tbili < 4	
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

Figure 3-3 Approach to abnormal liver tests with hepatocellular pattern



- Workup for *acute* enzyme elevation (often symptomatic)
  Severe ALT & AST elevation (>1000):
    toxins (usu. acetaminophen) → ✔ tox screen, EtOH, acet. levels. Other toxins: INH, disulfiram, pyrazinamide, OTC/herbal, fenofibrate, niacin, amiodarone, MDMA.
    ischemia (eg, sepsis, hypotension, Budd Chiari) → ✔ liver U/S w/ Doppler. Etiologies usually lead to ↑ LDH, ∴ usually ratio ALT:LDH <1.5 (vs. >1.5 w/ toxins, viruses).
    viruses (Hep A-E; HSV, CMV, VZV) → ✔ viral serologies
    other (AIH, acute Wilson Disease, acute biliary obstrxn) → see ALF & cirrhosis sections
  Acute mild-moderate ALT & AST elevation: as above, think meds/toxins (*see list at end of section*), viruses, ischemia/vascular issues in hospitalized Pts, obstruction (if mixed picture), systemic disease (*see "Workup for chronic enzyme elevation,"* below)
- Workup for *chronic* enzyme elevation (often asymptomatic)
  Screen for common causes: hep serologies, EtOH, liver U/S (? NAFLD, cirrhosis), meds
  If suspect underlying systemic disease: iron studies (HFE); ANA, ASMA, Ig levels (AIH); ceruloplasmin, urinary copper (Wilson); α1-AT (can cause liver dis even w/o lung involvement); celiac screening; thyroid studies; see "Cirrhosis"
  If ⊖ evaluation → lifestyle modification (wt loss, DM control) & repeat testing 3–6 mo
  If evidence of chronic liver disease or persistent lab abnl, consider liver bx

Figure 3-4 Approach to abnormal liver tests with cholestatic pattern

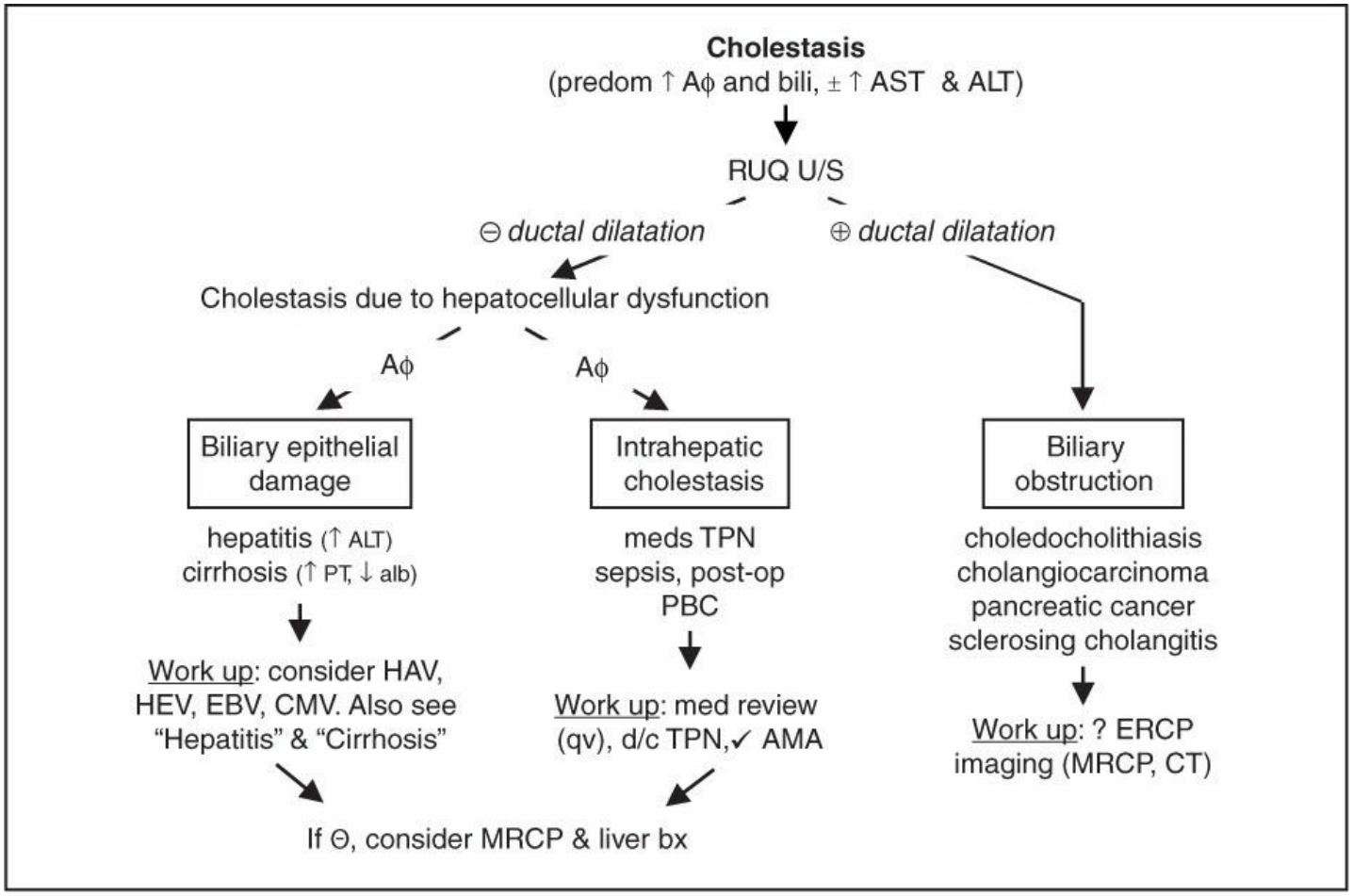
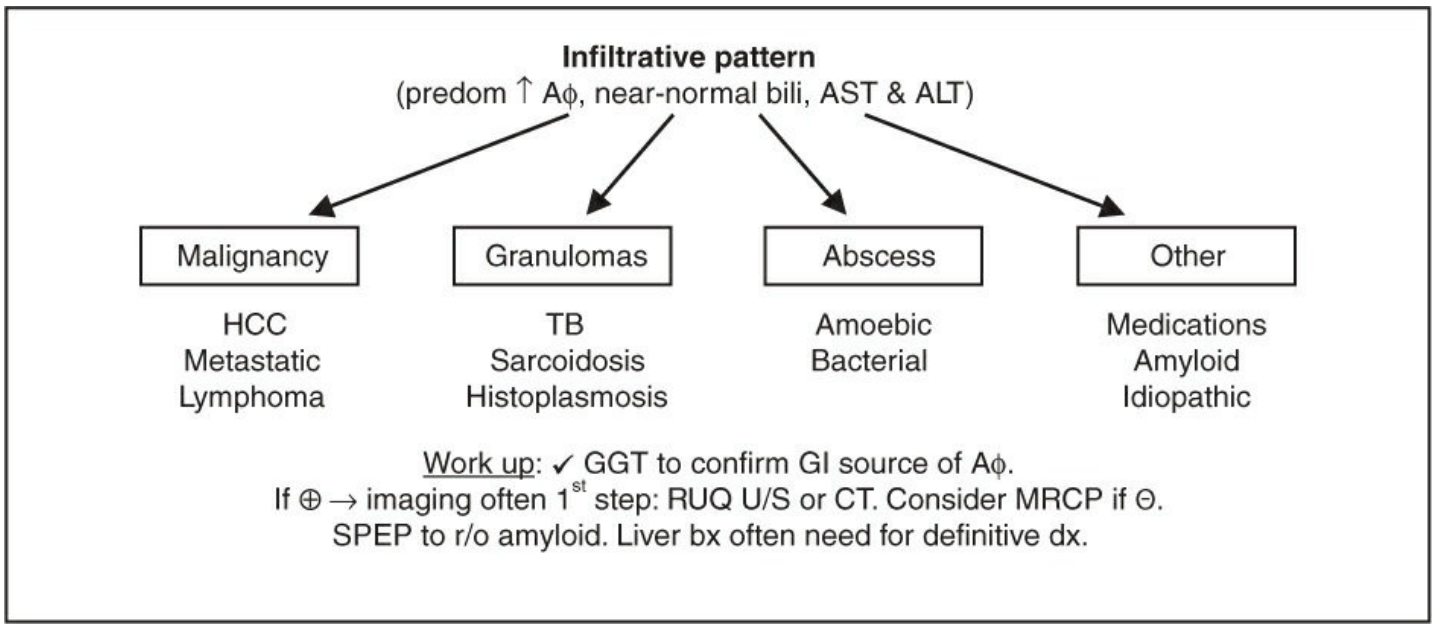


Figure 3-5 Approach to abnormal liver tests with infiltrative pattern



Common medications that cause abnormal liver tests *(http://livertox.nlm.nih.gov)*

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 chlorpromazine estrogens macrolides methimazole	6-MP OCP penicillins protease inhibitors sulfonamides 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
- 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
- Postexposure ppx: age 1–40 y → vaccine; age <1 y or >40 y, immunosupp, liver dis. → Ig

Hepatitis B (dsDNA; ~45% of acute viral hepatitis in U.S.; *JAMA* 2018;319:1802)

- Transmission: blood (IVDU, transfusion), sexual, perinatal
- 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 cirrhotic, ⊕ 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 (see *Annals* 2017;167:794 for screening guidelines)
  - 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	±	±	⊕
Recovery	⊖	⊕	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

- Rx for acute HBV: supportive; hospitalize for Δ MS or ↑ INR (liver transplant center); consider antiviral therapy if severe

Phases of Chronic HBV Infection					
Phase	**ALT (ULN*)**	**HBV DNA (IU/mL)**	**HBeAg**	**Liver Histology (inflam/fibrosis)**	**Rate of cirrhosis**
HBeAg ⊕ HBV infxn (Immune-tolerant)	Nl	≥10^6	⊕	Minimal	<0.5%/y
HBeAg ⊕ hepatitis (Immune-active)	≥2×	≥20k	⊕	Moderate to severe	2–5.5%/y
HBeAg ⊖ HBV infxn (Inactive)	Nl	≤2k	⊖	Min necroinflam.; variable fibrosis	0.05%/y
HBeAg ⊖ hepatitis (Immune reactivation; precore mutant)	≥2×	≥2k	⊖	Moderate to severe	8–10%/y

*ALT ULN <30 U/L for ♂, <19 U/L for ♂. Adapted from *Hepatology* 2016;63:261.

5th phase: chronic HBsAg ⊖ HBV infxn: HBeAg ⊖, anti-HBs ± ALT nl, "occult" HBV

- Rx of chronic HBV: Rx in immune active or immune reactivation phases or cirrhotics w/ elevated HBV DNA or decomp. Consider liver bx if ALT 1–2× ULN or in immune tolerant phase if age >40 y; Rx if mod-to-severe inflammation or fibrosis on bx.
- 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% (*Dig Dis Sci* 2015;60:1457; *Gastro Hep* 2016;1:185). Tenofovir preferred if h/o lamivudine resistance.
- 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) cirrhotic: 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 HBsAb ⊕ 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 rare cause) > 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 cirrhotics/y
- Extrahepatic syndromes: mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, leukocytoclastic vasculitis, thyroiditis, MPGN, IPF, NHL and monoclonal gammopathies
- Serologic, virologic, & genetic tests
  - 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) (*Hep* 2018;68:827; *Lancet* 2019;393:1453)
  - 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 Oral Direct-Acting Antiviral (DAA) Regimens	
Regimen	Indication
sofosbuvir & ledipasvir	Genotypes 1 and 4
grazoprevir & elbasvir	Genotypes 1 and 4
sofosbuvir & daclatasvir	Alternative for genotypes 1–4
sofosbuvir & velpatasvir	Genotypes 1–6
sofosbuvir, velpatasvir, & voxilaprevir	DAA-experienced genotypes 1–6
glecaprevir & pibrentasvir	Genotypes 1–6, DAA-experienced genotype 1
Individual components: *RNA polymerase inhibitor* ("…buvir"); *NS5a inhibitor* ("…asvir"); *NS3/4A protease inhibitor* ("…previr")	

Based on the American Association for the Study of Liver Diseases/Infectious Diseases Society of America 2018 Guidance. www.hcvguidelines.org. *Clin Infect Dis* 2018;67:1477

- Monitoring on Rx: CBC, INR, LFTs, GFR, HCV VL prior to starting Rx. PIs contraindicated if decomp. liver dx (ascites, encephalopathy) or CTP score ≥7. D/c Rx

if jaundice, N/V, weakness, 10x ↑ in ALT, or significant ↑ in bili, Aϕ, INR after 4 wk.
- Goal is *sustained virologic response* (SVR) = ∅ viremia 12 wk 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 mo

Hepatitis D (RNA)
- 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 txplt) 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)

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, exp. to swine. ↑ rates of cases in Europe.
- Natural hx: acute hepatitis w/ ↑ mort. (10–20%) if pregnant; rare chronic in transplant Pts
- Dx: IgM anti-HEV (through CDC), HEV RNA
- 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
- Type 2: anti-liver/kidney microsome 1 (anti-LKM1); anti-liver cytosol type 1 (ALC-1);
- Overlap syndrome: AIH + PBC (suspect if ⊕ antimitochondrial Ab or ⊕ histology → "autoimmune cholangitis") or PSC (suspect if ↑ Aφ, IBD, pruritus, or ⊕ radiology/histology)
- 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; 40% present w/ severe AIH (3% ALF) w/ ALT >10 × ULN; 34–45% asx
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs' ⊕ hemolytic anemia
- Dx: scoring system combining serologies, ↑ IgG, ∅ viral hepatitis, & liver bx (interface hepatitis & lymphoplasmacytic infiltrate) has high Sp & mod Se (*Dig Dis* 2015;33[S2]:53)
- Rx: (1) ALT 10× ULN; (2) ALT 5× ULN & IgG 2× ULN; or (3) bridging/multiacinar necrosis
- 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
- HCC screening and liver transplant referral for ESLD

OTHER CAUSES OF HEPATITIS OR HEPATOTOXICITY

Alcoholic 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
  - Steroids (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, and certain anticonvulsants and anti-TB drugs, resulting in a "therapeutic misadventure" with even low doses (2–6 g) of acetaminophen
- Liver dysfunction may not be apparent for 2–6 d
- 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, ALF

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) (*NEJM* 2017;377:2063)

- Definition: fatty infiltration of liver *and* absence of EtOH or other cause of steatosis
  NAFL = steatosis, ∅ inflam; NASH = steatosis + inflam ± fibrosis on bx
- NAFLD: 10–30% 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 modality (*J Hepatol* 2017;66:1022). NAFLD fibrosis score predicts NASH w/ advanced fibrosis with PPV >80%
- Rx: wt loss (ideally ≥10% to reverse fibrosis, *Gastro* 2015;149:367), exercise, DM control, liraglutide (*Lancet* 2016;387:679) or pioglitazone (even w/o DM), statins (*Metabolism* 2017;71:17); vit E ↓ steatosis but not fibrosis in Pts w/o DM (*Hepatol* 2018;67:328)
- HCC a complication of NAFLD, usually but not always in setting of NASH cirrhosis

ACUTE LIVER FAILURE (ALF)

Definition

- Acute insult to liver + coagulopathy + encephalopathy; most w/o known preexisting liver dis.
- *Hyperacute* if encephalopathy <7 d from jaundice onset; *acute* if 7–21 d, *subacute* if >21 d
- 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)
  - Drugs: acetaminophen (most common cause; >40% of all cases in U.S., typically unintentional overdose); anti-TB drugs (INH, rifampin, pyrazinamide); AEDs (phenytoin, valproate, carbamazepine); NSAIDs (idiosyncratic, not dose related); abx (eg, fluoroquinolones, macrolides); MDMA (ecstasy)
  - Toxins: *Amanita phalloides* (mushroom sp. in West Coast), certain herbal preparations
- Viral (12% of cases in the U.S.): 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 obstructive syndrome
- Other: Wilson disease, pregnancy-related ALF (acute fatty liver, preeclampsia, HELLP), initial presentation of autoimmune hepatitis; idiopathic

Clinical manifestations

- Initial presentation usually nonspecific: n/v, malaise; then jaundice & multiorgan failure
- Neurologic: encephalopathy: grade 1 = attn deficit, tremor; grade 2 = *asterixis*, lethargy, confusion, ataxia; grade 3 = somnolence, rigidity, clonus, hyporeflexia; grade 4 = coma
  cerebral edema: astrocyte swelling likely related to ↑ ammonia levels
- Cardiovascular: hypotension with low SVR, shock
- Pulmonary: respiratory alkalosis, impaired peripheral O_2 uptake, pulm edema, ARDS
- GI: bleeding (due to bleeding diathesis), pancreatitis (? due to ischemia, drugs, infxn)
- Renal: ATN, hepatorenal syndrome, hyponatremia, hypokalemia, hypophosphatemia
- Hematology: thrombocytopenia, ↑ PT/PTT, ↓ fibrinogen, bleeding diathesis (↓ synthesis of coag factors balanced by ↓ protein C/S; bleeding mostly due to low platelet count), DIC
- Infection (~90% of Pts): espec. with *Staph*, *Strep*, GNRs and fungi (↓ immune fxn, invasive procedures); SBP in 32% of Pts; *fever and ↑ WBC may be absent*
- 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)
- 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 for 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 if active bleeding or before invasive procedure; PPI ppx
- Infection: low threshold for abx (broad spectrum, eg, vancomycin & 3rd-gen ceph.) if suspect infection; anti-fungal coverage in high-risk Pts
- 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)
- Liver Tx if poor prog. but could survive surg. Extracorp liver support (molec. adsorbent recirc. system, MARS) & high-volume plasma exchange being studied (*J Hepatol* 2016;64:69).

Prognosis (*Ann Intern Med* 2016;164:724; *World J Gastro* 2016;22:1523)
- Non-acetaminophen ALF mortality ~70%, acetaminophen-induced ALF mortality ~25–30%
- Predictors of poor outcome (King's College Hospital, UK):
  Acetaminophen-induced: pH <7.25, INR >6.5 or PT>100, Cr >3.4, or grade 3/4 enceph.
  Non-acetamin.-induced: INR >6.5 or PT>100; *or* ≥3 of the following: unfavorable etiology (seronegative hepatitis or drug reaction); age <10 or >40 y; INR >3.5 or PT >50; Tbili >17.5; duration of jaundice >7 d prior to onset of encephalopathy
- ~20–25% of Pts undergo liver transplantation w/ 5-y survival rate of 75%
- BMI >30, Cr >2, age >50 y, pressors/vent support a/w poorer acute transplant outcome

CIRRHOSIS

Definition (*Dig Dis* 2016;34:374; *NEJM* 2016;375:767; *J Hep* 2016;64:717)

- Definition: fibrosis and regenerative nodules resulting from hepatocellular injury
- Decompensated = jaundice, variceal bleed, encephalopathy, ascites; worse prognosis

Etiologies

- Alcohol (~60–70%) and other toxins (eg, arsenic)
- Viral hepatitis (~10%): chronic HBV, HCV, HDV infection
- Autoimmune hepatitis: ♀, ↑ IgG, ⊕ ANA, antismooth muscle Ab, anti-LKM-1, anti-LC1
- Metabolic diseases (~5%): hemochromatosis, Wilson disease, α_1-AT deficiency
- Biliary tract diseases (~5%): 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
- Nonalcoholic fatty liver dis. (NAFLD, 10–15%) cause of most "cryptogenic cirrhosis"
- Medications: amiodarone, methotrexate, vitamin A, valproate 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 (↑ estradiol), Dupuytren's contractures, white nail lines (Muehrcke's lines) & proximal nail beds (Terry's nails), ↑ parotid & lacrimal glands, gynecomastia, testicular atrophy, asterixis, encephalopathy, fetor hepaticus, clubbing, hypertrophic osteoarthropathy
- Signs of portal hypertension: splenomegaly, ascites, dilated superficial abdominal veins (caput medusae), epigastric Cruveilhier-Baumgarten venous hum

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.), neutropenia (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 (HBV/HCV), FIB-4 index (NAFLD, HCV), NAFLD fibrosis score

Workup (*Lancet* 2014;383:1749; *Am J Gastro* 2017;112:18)

- 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, anti–smooth muscle Ab), 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

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 (Model for End-Stage Liver Disease; *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; *Liver Int* 2016;36:S1:109; *Dig Dis* 2017;35:402)

- Due to portal HTN (defined as hepatic venous pressure gradient [HVPG] >5 mmHg)
- Develops in 60% w/in 10 y; ~50% mortality at 5 y
- 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 (eg, 100 & 40 mg daily); urine Na/K >1 implies effective natriuresis if Pt compliant w/ low-Na diet
  Avoid NSAIDs in cirrhosis because interfere w/ diuretic action and are nephrotoxic
  Albumin (40 g 2×/wk × 2 wk, then weekly × 16 wk) ↓ mortality 38% (*Lancet* 2018;391:2417)
- Refractory ascites: seen in 5–10% of Pts; 2-y survival 25%
  Diuretic-resistant on 2-g Na diet, minimal weight loss on maximal diuretic doses, 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). Especially consider if SBP <90 or MAP ≤82 mmHg, serum Na <120 mEq/L, AKI, HRS, SBP, sepsis, severe alcoholic hepatitis, 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 (*Chest* 2019;155:307)
  Spontaneous *empyema* can occur (even w/o SBP) → dx thoracentesis; Rx abx

Spontaneous bacterial peritonitis (SBP; see "Ascites"; *Eur J Gastro Hep* 2016;28:e10)

- Develops in ~20%; 20% mortality; risk factors: ascitic TP <1 g/dL, hx of SBP, current GIB
- Can p/w encephalopathy, abd pain, fever, *but often* (*25%*) *asx;* perform paracentesis in all hospitalized cirrhotics w/ ascites
- Micro: GNRs (*E. coli, Klebs*) > GPCs (*S. pneumo, enterococcus*) (see "Ascites")
- Rx: 3rd-gen. ceph *or* amox/clav × 5 d. If uncomplicated (no enceph. or AKI) can use FQ but avoid in ↑ FQ resist. area. ↑ rate MDR organisms, incl. ESBL & carbapenemase. IV albumin 1.5 g/kg at time of dx & 1 g/kg on day 3 → ↑ survival (*NEJM* 1999;341:403); consider using only if Cr >1 mg/dL, BUN >30 mg/dL or Tbili >4 mg/dL (*Gut* 2007 56:597). If not improving, 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 q1–2wk 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 (*Hepatology* 2017;65:310); using both βB and EVL for primary 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., ∅ Δ mort.) (*Hepatology* 2016;63:581)

Hepatic encephalopathy (HE) (*NEJM* 2016;375:1660)

- 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: NH_3 levels have poor Se for dx & monitoring Rx; remains a *clinical dx*
- Rx*:* identify/correct precipitants; lactulose (acidification of colon: $NH_3 \rightarrow NH_4^+$) w/ goal 2–4 stools/d (PEG may be more effective; *JAMA IM* 2014;174:1727); alternatively, rifaximin 550 mg bid (↓ gut bacteria → ↓ NH_3 prod; ? benefit to adding rifaximin to lactulose; *Am J Gastro* 2013;108:1458); adding albumin may speed resolution & ↓ mort. (*J Gastro Hep* 2017;32:1234)
- 2° prevention: lactulose or rifaximin 550 mg bid (*Aliment Pharmacol Ther* 2015;41:39)

Hepatorenal syndrome (HRS) (*Am J Kidney Dis* 2016;67:318; *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) ∅ improvement in Cr after d/c diuretic & volume expansion (1 g/kg/d of albumin × 2 d); (4) ∅ shock (prerenal azotemia/ATN); (5) ∅ nephrotoxic meds; (6) ∅ intrinsic kidney disease
  AKI-HRS: development in <2 wk; usually occurs in severe liver failure, often following precipitating event (see later); median survival 2 wk
  CKD-HRS: more indolent, median survival 6 mo; liver failure present < than in AKI-HRS
- 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. Serelaxin under study (*PLoS Med* 2017;14:e1002248). May need dialysis or TIPS as bridge to liver transplant.

Hepatocellular carcinoma (HCC; qv in Heme-Onc) (*Gastro* 2016;149:1226 & 150:835)

- ↑'d risk w/ cirrhosis of any type but esp. w/ viral (risk of HCC ~3–8%/y), HFE, PBC, ?α1-AT. ↑'d by concomitant EtOH (*J Hepatol* 2016;65:543).
- Clinical: asx vs. hepatic decompensation (eg, ascites, HE), PVT w/ tumor thrombus
- Dx: screen cirrhotics q6mo w/ U/S ± AFP, though many ctrs choose dual-phase CT/MRI
- Rx: see "HCC" in Heme-Onc

Other complications

- Hepatopulmonary syndrome (HPS) (*Dig Dis Sci* 2015;60:1914)
  Abnl gas exchange (A-a gradient ≥15 or P_aO_2 <80) caused by intrapulmonary vascular dilatations leading to intrapulmonary shunting
  S/S: platypnea-orthodeoxia, clubbing, cyanosis
  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; ↑ troponin, BNP (*World J Gastro* 2017;21:11503)
- Infxns: unless already immune, vaccinate for HAV, HBV, PCV13 & PPSV23; flu yearly. Cellulitis in ~20% of Pts hospitalized w/ cirrhosis, often in abd wall or LE a/w skin 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 in DIC.
- Nutrition: monitor and supplement fat-soluble vitamins, zinc
- 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

- Undertake evaluation when MELD ≥15. Exception points added if HCC as above, 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 (EtOH w/in 6 mo), 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 HCV; autoimmune liver disease, such as AIH/PBC/PSC may recur in 10–30% (or more) of allografts

OTHER ETIOLOGIES OF CIRRHOSIS

Hemochromatosis & iron overload syndromes (*Lancet* 2016;388:706)

- 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; primarily affects liver, but also other tissues (brain, eye)
- Epidemiology: 1 in ~30,000, but true allele frequency may be higher due to underdiagnosis; age of presentation generally ranges 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%), rarely penicillamine challenge w/ ↑ urine Cu excretion, liver bx w/ hepatic Cu content. 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 $$). Zinc: ↓ intestinal Cu transport & can help delay disease; best used in conjunction w/ chelation (must give 4–5 h apart from chelators). Elim. Cu-rich foods. Transplant for ALF or for chronic dis. unresponsive to Rx.

α_1-antitrypsin deficiency (α_1-AT) (*J Hepatol* 2016;65:413)
- 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 includes: emphysema, necrotizing panniculitis, ANCA vasculitis
- Dx: serum α_1-AT level (acute phase reactant), level <50% of nl typically diagnostic;
  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(6):1357). Liver bx shows characteristic PAS ⊕ cytoplasmic inclusion bodies.
- Treatment: standard Rx for cirrhosis/chronic liver dis., including liver transplantation

Primary biliary cholangitis (PBC) (*Lancet* 2015;386:1565)
- Autoimmune destruction of *intrahepatic* bile ducts (previously "primary biliary cirrhosis")
- Epi: ♀ 40–60 y; a/w Sjögren's, Raynaud's, scleroderma, celiac & thyroid disease; may be triggered by certain infxns or toxins; a/w X monosomy, variants in IL12α & IL12R genes
- Sx (late): fatigue/sleep disturbance, pruritus, steatorrhea, xanthelasma, jaundice, cirrhosis
- Ddx: PSC, AIH, hepatic sarcoidosis, meds, idiopathic adult ductopenia, biliary stricture/Ca
- Dx: ↑ Aϕ, ↑ bili, ↑ IgM, ↑ chol, ⊕ antimitochondrial Ab (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 (13–15 mg/kg/d) regardless of stage (30% of Pts untreated!)
  ~25% complete response, ↑ survival & ↓ histologic change & complications (eg, varices). Biochemical response predicts clinical outcomes (*Clin Gastro Hep* 2018;16:1342).
  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)
  Obeticholic acid (5 → 10 mg qd, except CPS B/C: 5 mg/wk → 10 mg twice weekly) ↓ Aφ, but no fat-soluble vitamins; screen/Rx osteoporosis fibrosis (*NEJM* 2016;375:631)
  Pruritus: cholestyramine (give 2–4 h after UDCA); if refractory sx: naltrexone, rifampin
  Fat-soluble vitamins; screen/Rx osteoporosis (risk independent of vit D deficiency)
  If ESLD: liver tx; ~20% recur but no impact on long-term survival

Primary sclerosing cholangitis (PSC) (*NEJM* 2016;375:1161; *Lancet* 2018;391:2547)

- 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).
- Clinical: fatigue, pruritus, jaundice, fevers, RUQ pain, concomitant IBD, ESLD
- Ddx: extrahepatic obstruction, PBC, may also have overlap w/ AIH and similar presentation to IgG4 autoimmune cholangitis (steroid responsive) (*J Gastro* 2016;51:295)
- Dx: MRCP ± ERCP → *multifocal beaded bile duct strictures*, but may miss dx if confined to small intrahepatic ducts (~2% "small duct PSC":? different disease). Aφ predicts survival. Liver bx may show "onion-skin" fibrosis around bile ducts but not necessary for dx.
- Treatment: supportive care, fat-soluble vitamins; no meds have improved survival
  Ursodeoxycholic acid may ↓ colon Ca risk in Pts w/ UC & improve LFTs in Pts w/o UC
  Dominant stricture: endoscopic dilation, short-term stenting or surgical resection
  Cholangiocarcinoma (20%): ? biannual surveillance w/ MRCP/RUQ U/S and CA19-9
  Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence

HEPATIC VASCULAR DISEASE

Portal vein thrombosis (PVT) (*Clin Liver Dis* 2017;10:152)

- Definition: thrombosis, constriction or invasion of portal vein; may lead to portal HTN
- Etiologies: cirrhosis, neoplasm (pancreas, HCC), abdominal infxn, hypercoag states (qv), pancreatitis, collagen vascular diseases, Behçet's, IBD, surgery, trauma, OCPs, preg
- Clinical manifestations
  - acute: can p/w abd or lumbar pain, 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 × 6 mo, or indefinitely if irreversible cause. If cirrhotic, anticoag ↑ recanalziation w/o ↑ bleeding (*Gastro* 2017;153:480); screen for high-risk varices prior to Rx (*Nat Rev Gastro Hep* 2014;11:435). DOACs under investigation.
  - Chronic: Anticoag if noncirrhotic or hypercoag state. If cirrhotic, consider 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)

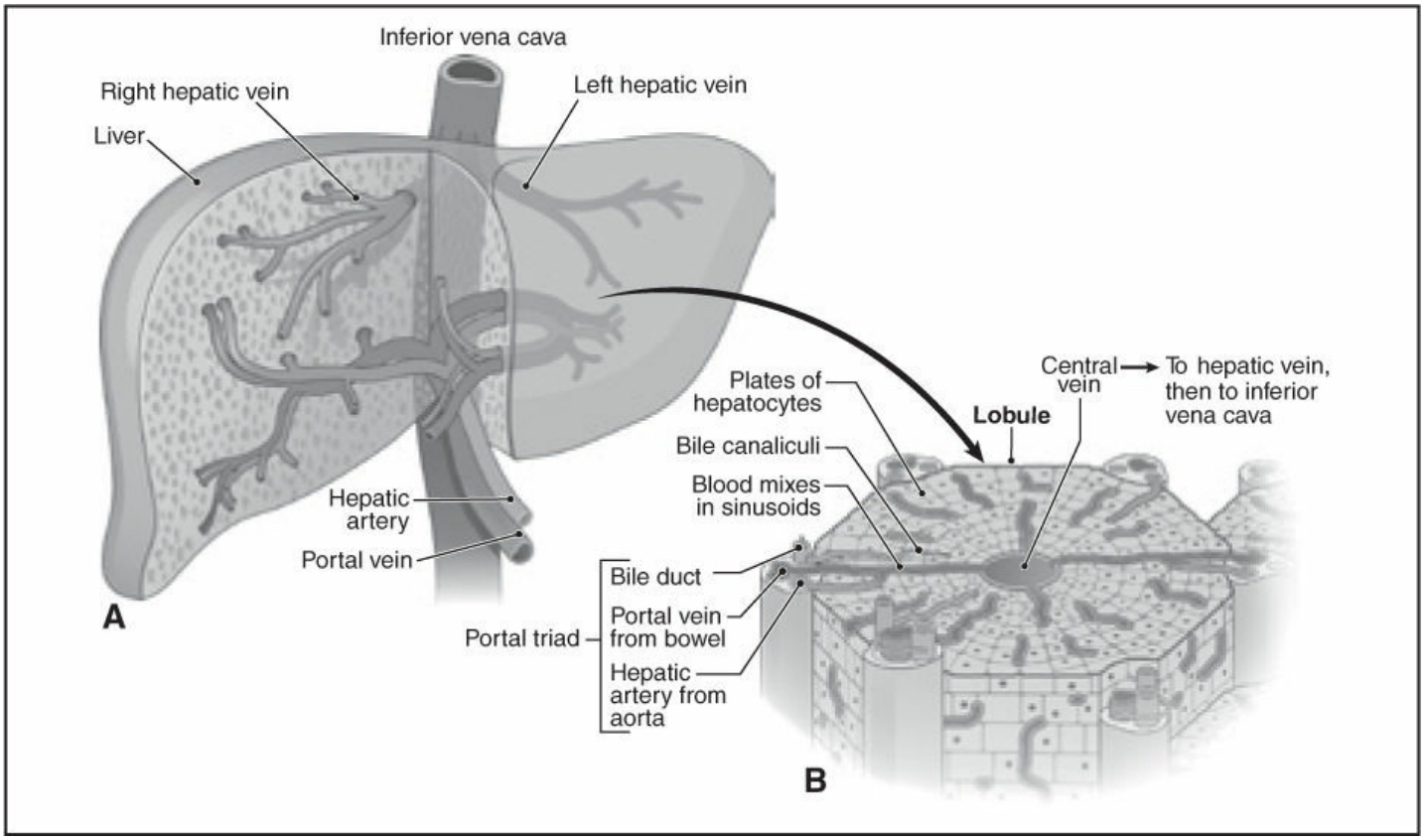
- Hepatic outflow obstruction 2/2 occlusion of hepatic vein(s) or IVC → sinusoidal congestion and portal HTN. Can be 1° (eg, thrombosis) or 2° (eg, extravascular compression).
- Etiol.: ~50% due to myeloprolif. d/o a/w *JAK2* mutations (esp. *P. vera*), other hypercoag state (qv), tumor invasion (HCC, renal, adrenal), IVC webs, trauma, 25% idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals, acute liver failure
- Dx: ± ↑ aminotransferases & Aϕ; Doppler U/S of hepatic veins (85% Se & Sp); CT (I^+) or MRI/MRV → vein occlusion or ↑ caudate lobe (separate venous drainage); "spider-web" pattern on hepatic venography; liver bx showing congestion (r/o right-sided CHF)
- Treatment: Rx underlying condition, anticoag (LMWH → warfarin); consider thrombolysis acutely; if short stenosis, stent may be possible; consider TIPS (↑ occlusion risk c/w side-to-side portocaval shunt); liver transplant if ALF or failed shunt (*J Gastro Surg* 2012;16:286)

Sinusoidal obstruction syndrome (SOS) (*Bone Marrow Transplant* 2015;50:781)

- Occlusion of hepatic venules & sinusoids (formerly veno-occlusive disease) 2/2 toxic insult
- Etiologies: HSCT, chemo (esp. cyclophosphamide), XRT, Jamaican bush tea
- Clinical manifestations: hepatomegaly, RUQ pain, ascites, weight gain, ↑ bilirubin
- Dx: U/S w/ reversal of portal flow, but often not helpful; dx made clinically (↑ bili, wt gain/ascites and RUQ pain) or, if necessary, by liver bx or HVPG (>10 mmHg)
- Rx (20% mort.): supportive, fluid mgmt (diuretics); ? defibrotide (adenosine agonist ↑ TPA)
- Ppx: defibrotide; ursodeoxycholic acid for high-risk HSCT pop; ? use of low-dose heparin

Figure 3-6 Normal hepatic vasculature

Modified from The Nature of Disease Pathology for the Health Professions, 2007. Hepatology 2009;49:1729.



ASCITES

Pathophysiology

- In portal hypertension → systemic vasodilatation (? due to release of NO) → ↓ effective arterial volume → renal Na 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; MRI/CT (also help with Ddx)
- Paracentesis (*Hep* 2013;57:1651): perform in all Pts w/ new ascites, consider in all hosp. cirrhotics w/ ascites. Low complic. rate (~1% hematoma formation). Prophylactic FFP or plts does *not* ↓ bleeding complic. Most useful tests: cell count, alb, total protein, culture.
- Serum-ascites albumin gradient (SAAG): serum alb (g/dL) – ascites alb (in g/dL)

Etiologies	
Portal HTN Related (SAAG ≥1.1)	Non–portal HTN Related (SAAG <1.1)
Presinusoidal obstruction portal or splenic vein thrombosis, schistosomiasis, sarcoidosis *Sinusoidal* obstruction: cirrhosis (81%), acute hepatitis, malignancy (HCC or mets) *Postsinusoidal* obstruction Right-sided CHF (ex: constriction, TR), Budd-Chiari syndrome, SOS	Malig: peritoneal carcinomatosis; chylous ascites from malignant lymphoma; Meigs' syndrome (ovarian tumor) Infection: TB, chlamydia/gonorrhea (ie, Fitz-Hugh-Curtis syndrome) Inflam: pancreatitis, ruptured pancreatic/biliary/lymph duct; bowel obstrxn Hypoalbuminemic states: nephrotic syndrome, protein-losing enteropathy

SAAG >1.1 diagnoses portal HTN with ~97% accuracy
If portal HTN + another cause (seen in ~5% of cases) SAAG still ≥1.1

- 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 (see below).
- 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.

Treatment (see "Cirrhosis" for details)

- If 2° to portal HTN: ↓ Na intake + diuretics; if refractory → LVP or TIPS
- If non–portal HTN related: depends on underlying cause (TB, malignancy, etc.)

Bacterial peritonitis (*Gut* 2012;61:297)

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. Cx w/ 1 org: *E. coli* (37%), *Klebs* (17%), *S. pneumo* (12%), misc. GPC (14%), misc. GNR (10%) 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.	Culture-⊖ neutrocytic ascites (CNNA): cell counts suggest infxn but cx ⊖. No recent abx, w/o other explan. for counts. Rare when sens cx methods.
<250/µL	Nonneutrocytic bacterascites (NNBA): ⊕ cx w/o ↑ PMNs. Natural course may resolve w/o Rx or may progress to SBP. Cx w/ 1 org.: Misc. GPC (30%), *E. coli* (27%), *Klebs* (11%), misc. GNR (14%)	(Normal)
Peritoneal dialysis-associated: cloudy fluid, abd pain, fever, nausea. ≥100 WBCs/µL, poly predom. Cx ⊕ (typ. 1 org.): Misc. GPC (50%), misc. 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 10–20% of Western populations
- 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, Cftx); ileal dis., genetic
- 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; thus found pred in bile ducts; seen w/ duod. diverticula, biliary strictures, parasites

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 large majority
- RUQ U/S: Se & Sp >95% for stones >5 mm; can show complications (cholecystitis); should be performed only after fasting ≥8 h to ensure distended, bile-filled gallbladder
- Endoscopic US (EUS) Se 94–98% in Pts w/ biliary pain but nl abd US (*J Hepatol* 2016;65:146)

Treatment (*Am Fam Physician* 2014;89:795; *J Hepatol* 2016;65:146)

- Cholecystectomy (CCY), usually laparoscopic, if symptomatic
- CCY in *asx* Pts if: GB calcification (↑ risk of cancer), GB polyps >10 mm, Native American, stones >3 cm; consider in morbidly obese undergoing bariatric surgery, cardiac Tx candidates, hemolytic anemia
- Ursodeoxycholic acid (rare) for cholesterol stones w/ uncomplicated biliary pain or if poor

surgical candidate; also reduces risk of gallstone formation with rapid wt loss
- Pain: NSAIDs drug of choice, efficacy ≈ opiates & ↓ complic.

Complications
- Cholecystitis: 20% of sx biliary pain → cholecystitis w/in 2 y
- Choledocholithiasis → cholangitis or gallstone pancreatitis
- Mirizzi syndrome: common hepatic duct obstruction by cystic duct stone → jaundice, biliary obstruction
- Cholecystenteric fistula: stone erodes through gallbladder into bowel
- Gallstone ileus: SBO (usually at term ileum) due to stone in intestine that passed thru fistula
- Gallbladder carcinoma: ~1% in U.S.

CHOLECYSTITIS (*J Hepatol* 2016;65:146; *World J Gastro Surg* 2017;9:118)

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)
- Post CCY: bile duct leak, BD injury or retained stones, cystic duct remnant, sphincter of Oddi dysfxn

CHOLEDOCHOLITHIASIS

Definition
- Gallstone lodged in common bile duct (CBD)

Epidemiology
- Occurs in 15% of Pts w/ gallbladder stones; can form de novo in CBD

Clinical manifestations
- Asymptomatic
- RUQ/epigastric pain 2° obstrxn of bile flow → ↑ CBD pressure, jaundice, pruritus, nausea

Diagnostic studies (*Gastro Endo* 2010;71:1; *J Hepatol* 2016;65:146)
- 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) when ERCP unavailable or unsuccessful; EUS/MRCP to exclude BD stones when suspicion intermediate (eg, no stone, but: dilated ducts on US, bili 1.8–4 mg/dL, gallstone panc., age >55, or abnl non-bili LFT)

Treatment
- ERCP & papillotomy w/ stone extraction (± lithotripsy)
- CCY typically w/in 6 wk unless contraindication (>15% Pts will develop indication for CCY if left unRx'd)

Complications
- Cholangitis, cholecystitis, pancreatitis, stricture

CHOLANGITIS

Definition & etiologies
- BD obstruction → infection proximal to the obstruction
- Etiologies: BD stone (~85%)
  Malignant (biliary, pancreatic) or benign stricture
  Infection w/ fluke (*Clonorchis sinensis*, *Opisthorchis viverrini*)

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
- 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 × ΔHCO_3

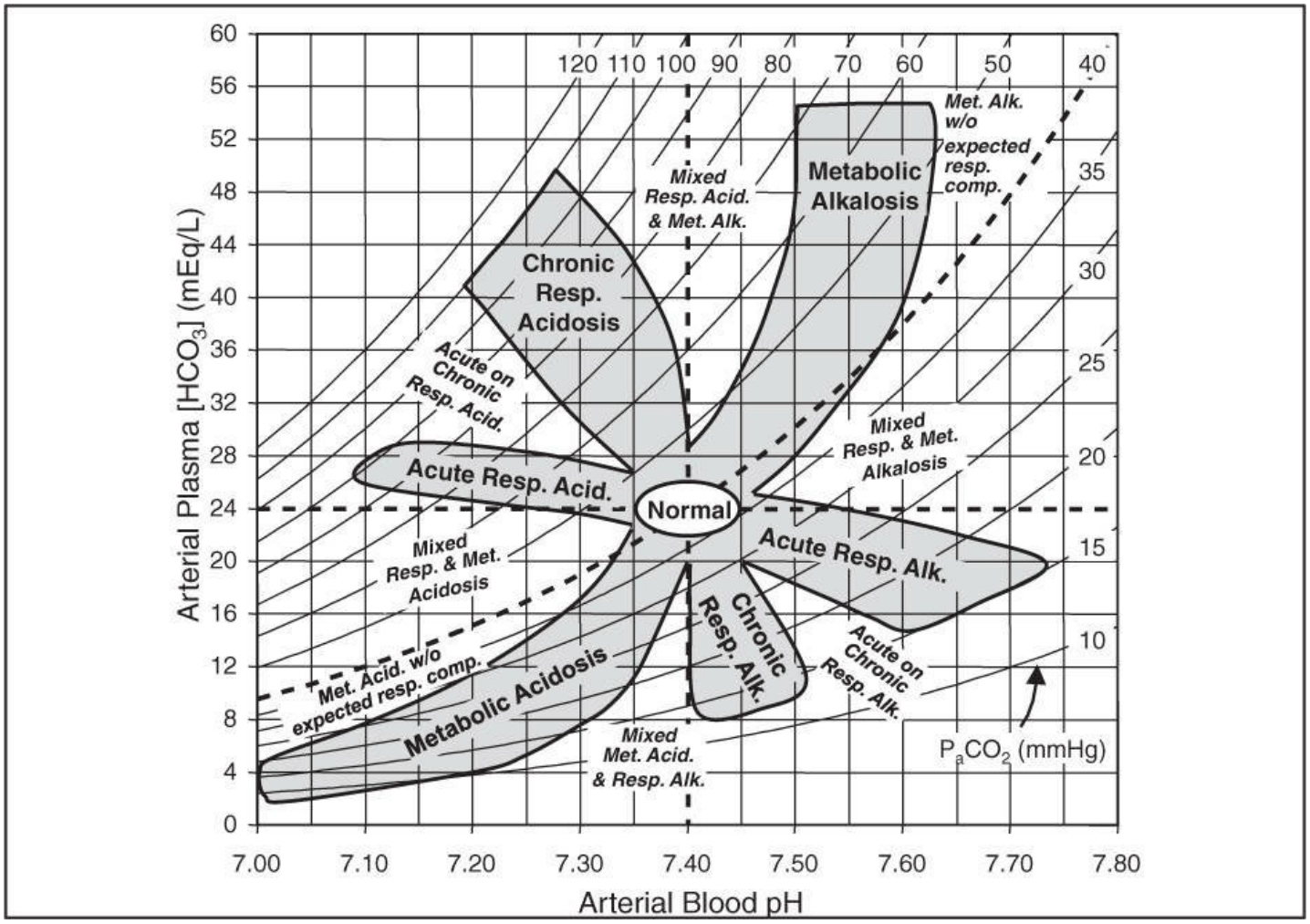
	or $P_aCO_2 = (1.5 \times HCO_3) + 8 \pm 2$ (Winters' formula) (also, $P_aCO_2 \approx$ last 2 digits of pH)
Metabolic alkalosis	$\uparrow P_aCO_2 = 0.7 \times \Delta HCO_3$ or $P_aCO_2 = 0.7\ (HCO_3\text{-}24) + 40 \pm 2$ or $HCO_3 + 15$
Acute respiratory acidosis	$\uparrow HCO_3 = 0.1 \times \Delta P_aCO_2$ (also, $\downarrow$ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory acidosis	$\uparrow HCO_3 = 0.35 \times \Delta P_aCO_2$ (also, $\downarrow$ pH = $0.003 \times \Delta P_aCO_2$)
Acute respiratory alkalosis	$\downarrow HCO_3 = 0.2 \times \Delta P_aCO_2$ (also, $\uparrow$ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory alkalosis	$\downarrow HCO_3 = 0.4 \times \Delta P_aCO_2$

- 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*...
  - $\uparrow P_aCO_2 + \uparrow HCO_3$ → resp. acid. + met. alk.
  - $\downarrow P_aCO_2 + \downarrow HCO_3$ → 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), $\Delta HCO_3 = (24 – HCO_3)$
  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 lacatate clearance

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	Diabetes mellitus, alcoholism, starvation (*NEJM* 2014;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.)
Ingestions	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

- ✔ 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 have 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)
  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.
		Propylene glycol	AKI, liver injury
		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, proximal RTA, 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 polyuria, Na depletion (U_{Na} <20), U_{pH} >6.5 & HAGMA (causes ⊕ UAG b/c excretion of organic anions). 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) (*Int J Clin Pract* 2011;65:350)

- 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

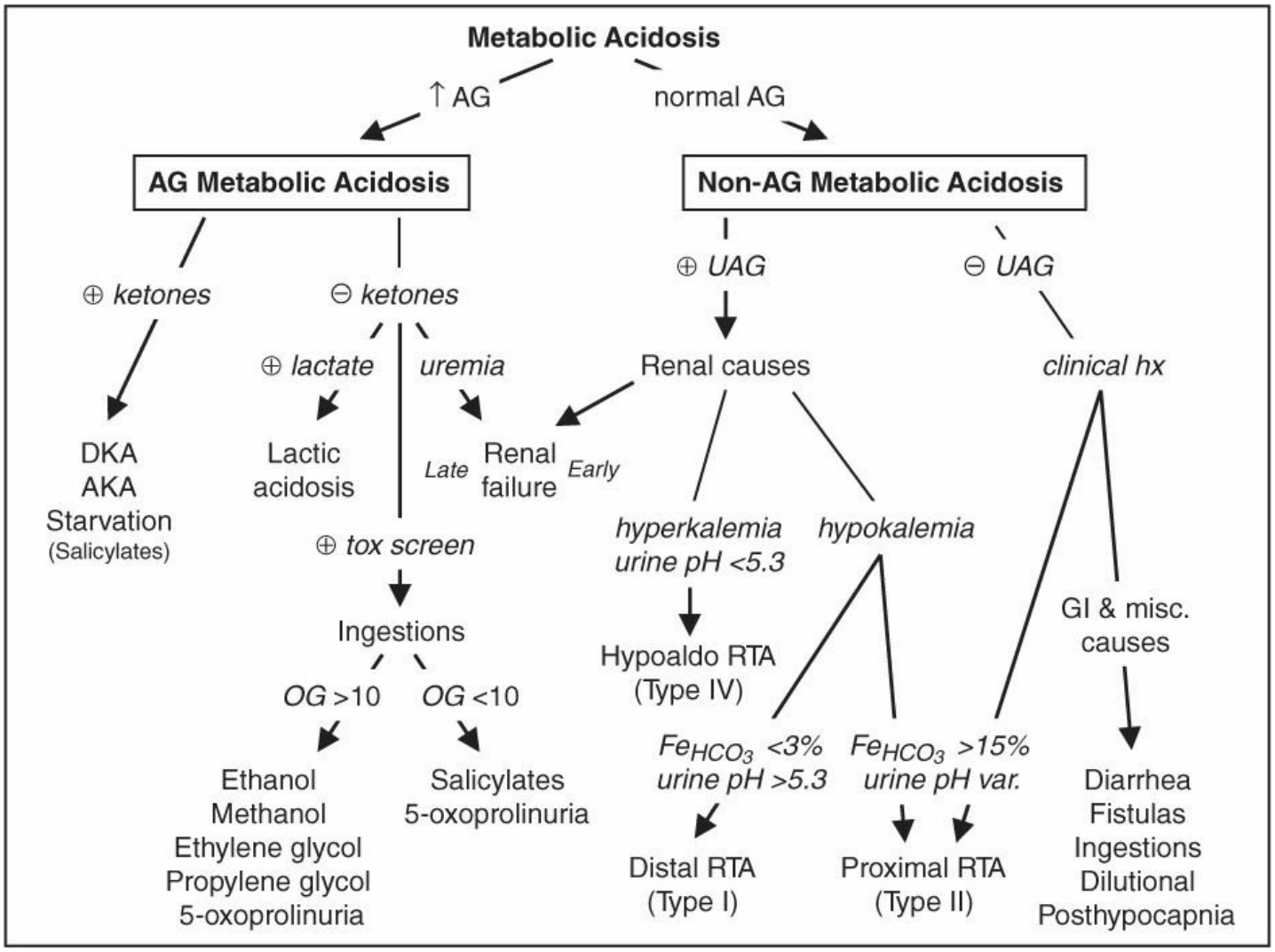
Renal Tubular Acidosis								
Location	**Type**	**Acidosis**	**UAG**	**HCO_3^-**	**UpH**	**FE_{HCO_3} [b]**	**K**	**Complications**
Proximal	II	Moderate	±	12-20	<5.3[a]	>15%	↓	Osteomalacia
Distal	I	Severe	⊕	<10	>5.3	<3%	↓[c]	Kidney stones
Hypoaldo	IV	Mild	⊕	>17	<5.3	<3%	↑	Hyperkalemia

[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 (*Lancet* 2018;392:21)
- $NaHCO_3$: 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 [desired-current $HCO_3]_{serum}$ × 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 (*Clin Physio Acid-Base* 2001; *CJASN* 2008;3:1861)

- 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)

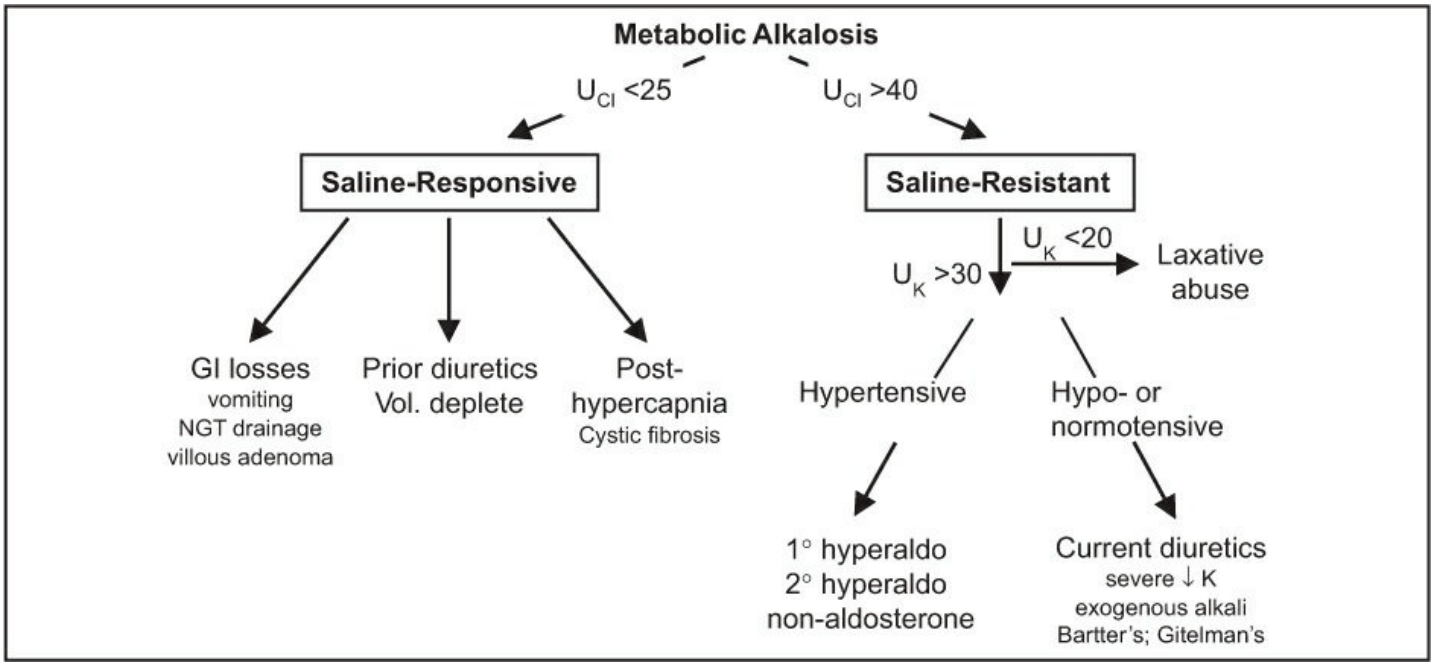
Etiologies of Metabolic Alkalosis	
Saline responsive UCl < 25	GI loss of H^+: emesis, NGT suction, villous adenoma, chloridorrhea Renal loss: loop/thiazide, ↓ Cl intake, milk-alkali, Pendred syndrome Posthypercapnia, sweat losses in cystic fibrosis
Saline resistant UCl >40	*Hypertensive* (mineralocorticoid 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
- If NGT drainage that cannot be stopped: PPI or H_2-blocker (*Clin Nephro* 2006;66:391)
- 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"; PaCO2 = VCO2/VE(1-VD/VT); VE= RR x VT)

- ↑ 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

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)

- Free water clearance (C_{H^2O}) = solute (intake) excretion/U_{osm} normal dietary solute load ~750 mOsm/d, minimum U_{osm} = 50 mOsm/L → excrete ~15 L
- 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 $[Na]_{serum}$
  ↑ *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 females 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

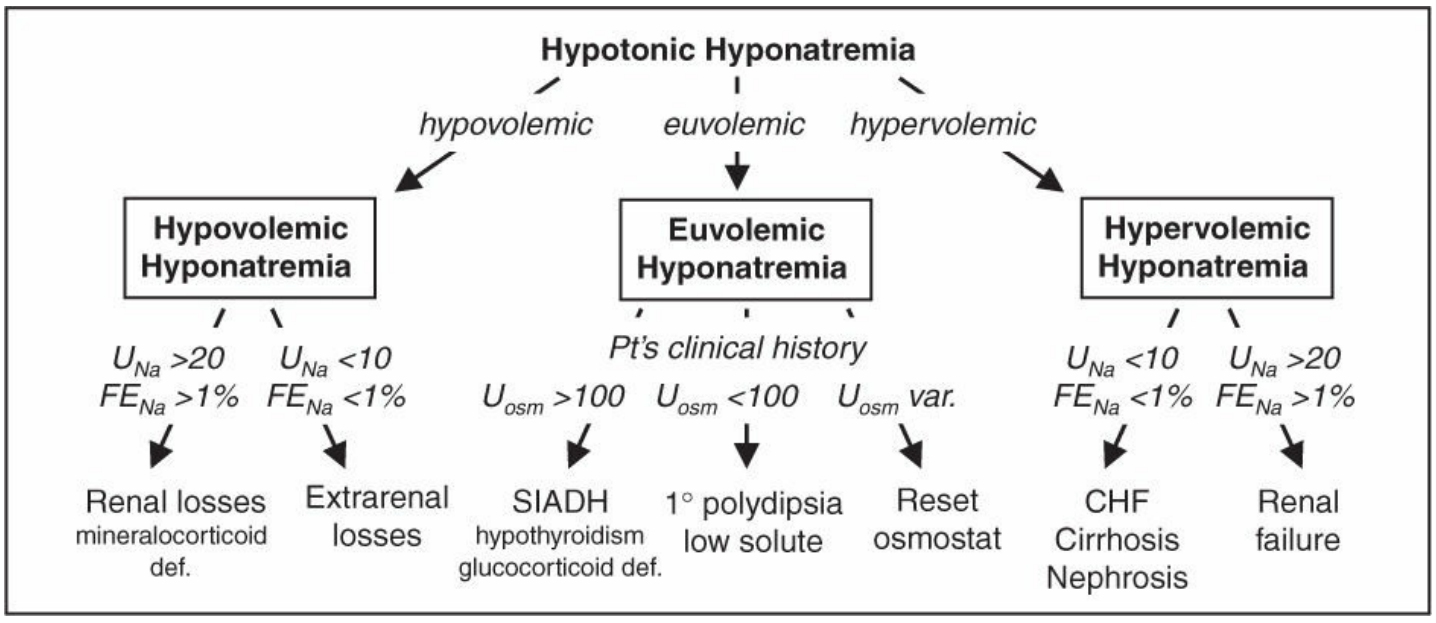
- For hypotonic hyponatremia, ✔ volume status (JVP, skin turgor, dry axilla, mucous membranes, edema, ascites), effusions, vital signs, orthostatics, BUN/Cr, $FE_{UricAcid}$, U_{Na}
- Measure U_{osm}, although useful for dx in limited circumstances, b/c almost always >300

  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 µg 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 (http://www.medcalc.com/sodium.html)

$$\text{initial } \Delta[Na]_{serum} \text{ per L infusate} = \frac{[Na]_{infusate} - [Na]_{serum}}{TBW + 1}$$

TBW = wt (kg) × 0.6(♂) or 0.5 (♀); if elderly use 0.5 (♂) or 0.45 (♀)

If $[Na]_s$ = 110 mEq/L in 70-kg Male:			
IVF Type	**$[Na]_{content}$**	**1 L IVF ↑ $[Na]_s$**	**Rate to ↑ $[Na]_s$ by 0.5 mEq/L/h**
5% NaCl	856 mEq/L	17.3 mEq/L	~25 mL/h
3% NaCl	513 mEq/L	9.4 mEq/L	~50 mL/h
0.9% NaCl	154 mEq/L	1 mEq/L	~500 mL/h
LR	130 mEq/L	0.5 mEq/L	~1000 mL/h

However, above assumes infusate retained *without output of Na/H*$_2$O; adjust for UOP.

If Pt euvolemic (eg, SIADH), infused Na will be excreted: for 1 L NS (154 mEq Na or 308 mOsm solute in 1 L H_2O); in SIADH with U_{osm} = 616 → 308 mOsm solute excreted in 0.5 L H_2O → net gain 0.5 L H_2O → ↓ $[Na]_{serum}$. ∴ NS *worsens* Na if U_{osm} > $infusate_{osm}$.

- 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* 2015;65:435): fluid restrict + treat underlying cause
  hypertonic saline (± loop diuretic) if sx or Na fails to ↑ w/ fluid restriction 1 L hypertonic saline (3% NaCl) will raise $[Na]_{serum}$ by ~10 mEq (see above) ~50 mL/h will ↑ [Na] by ~0.5 mEq/L/h; 100–200 mL/h will ↑ [Na] by ~1–2 mEq/L/h formula only provides estimate; ∴ recheck serum Na frequently (at least q2h)
  NaCl tabs if chronic and no CHF. Consider urea 0.25-0.5g/kg/d (*Nephrol Dial Trans* 2014;29:ii1)
  aquaresis: vaptans (vasopressin receptor antag) for refractory SIADH (*NEJM* 2015;372:23)
  demeclocycline: causes nephrogenic DI, ↓ U_{osm} (rarely used)
- 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

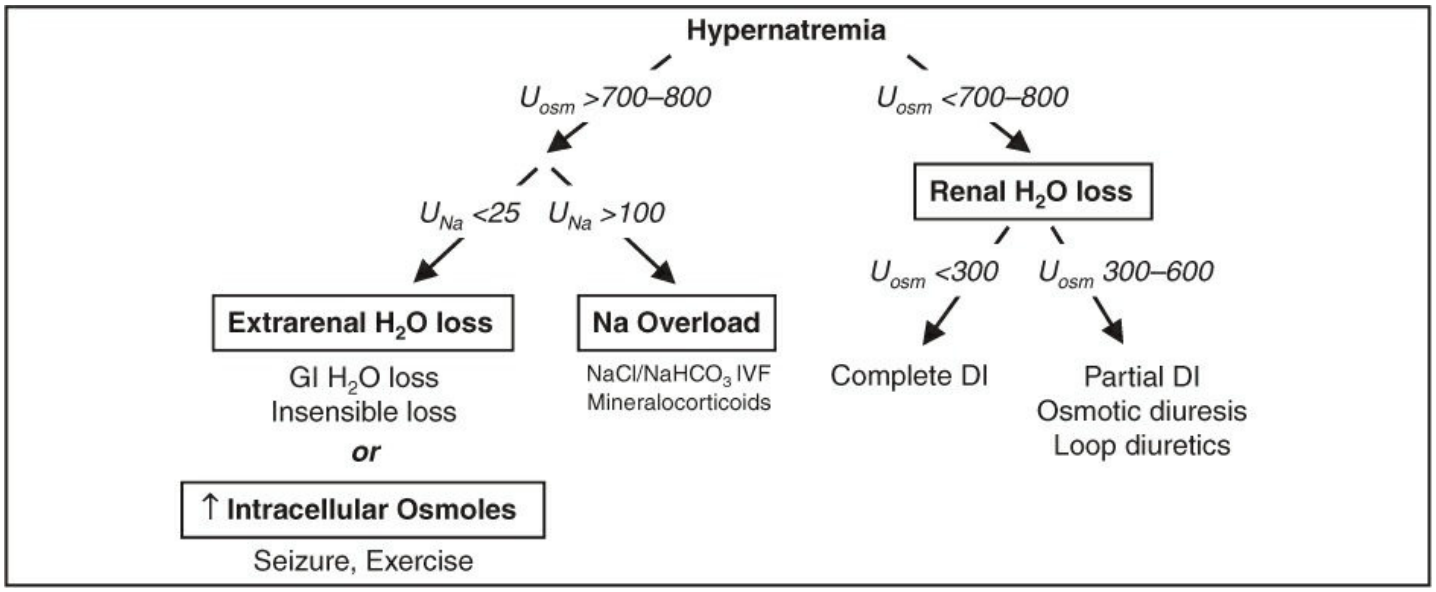
Pathophysiology (*Crit Care* 2013;17:206; *NEJM* 2015;372:55)

- 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 (*J Clin Endocrinol Metab* 2012;97:3426)
  - 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; *Ped Nephrol* 2012;27:2183)
    - 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

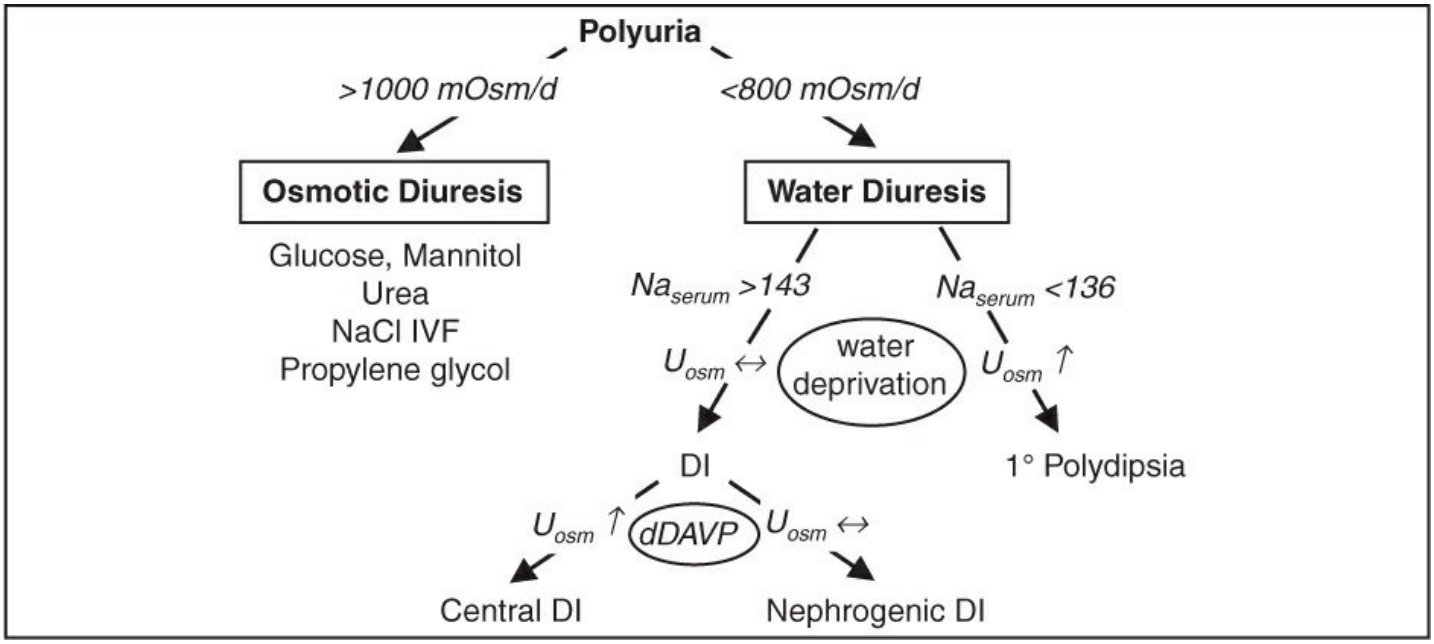
- Etiologies
  Hyperglycemia (>180 exceeds PCT reabsorption), mannitol, propylene glycol
  Na: NaCl IVF, recovering AKI (eg, post obstruction)
  Urea: ↑ protein feeds, hypercatabolism (burns, steroids), GI bleed, resolving azotemia

Water diuresis

- Etiologies: diabetes insipidus (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 (start in a.m., ✔ Na_{serum}, P_{osm}, U_{osm}, UOP q1–2h)
  Deprive until P_{osm} >295, then ✔ U_{osm}. If U_{osm} <300, then administer vasopressin (5 U SC) or dDAVP (10 mg intranasal), then check U_{osm} in 1–2 h: U_{osm} ↑ by >50% = central DI U_{osm} unchanged = nephrogenic DI
  ✔ADH level before and after water deprivation to evaluate proper response
  Hypertonic saline-stimulated plasma copeptin >4.9 $p_{moL/L}$ 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 [proximal RTA (type II) and some distal RTAs (type I)]
  - 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 & PCN, gent., amphotericin, 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)

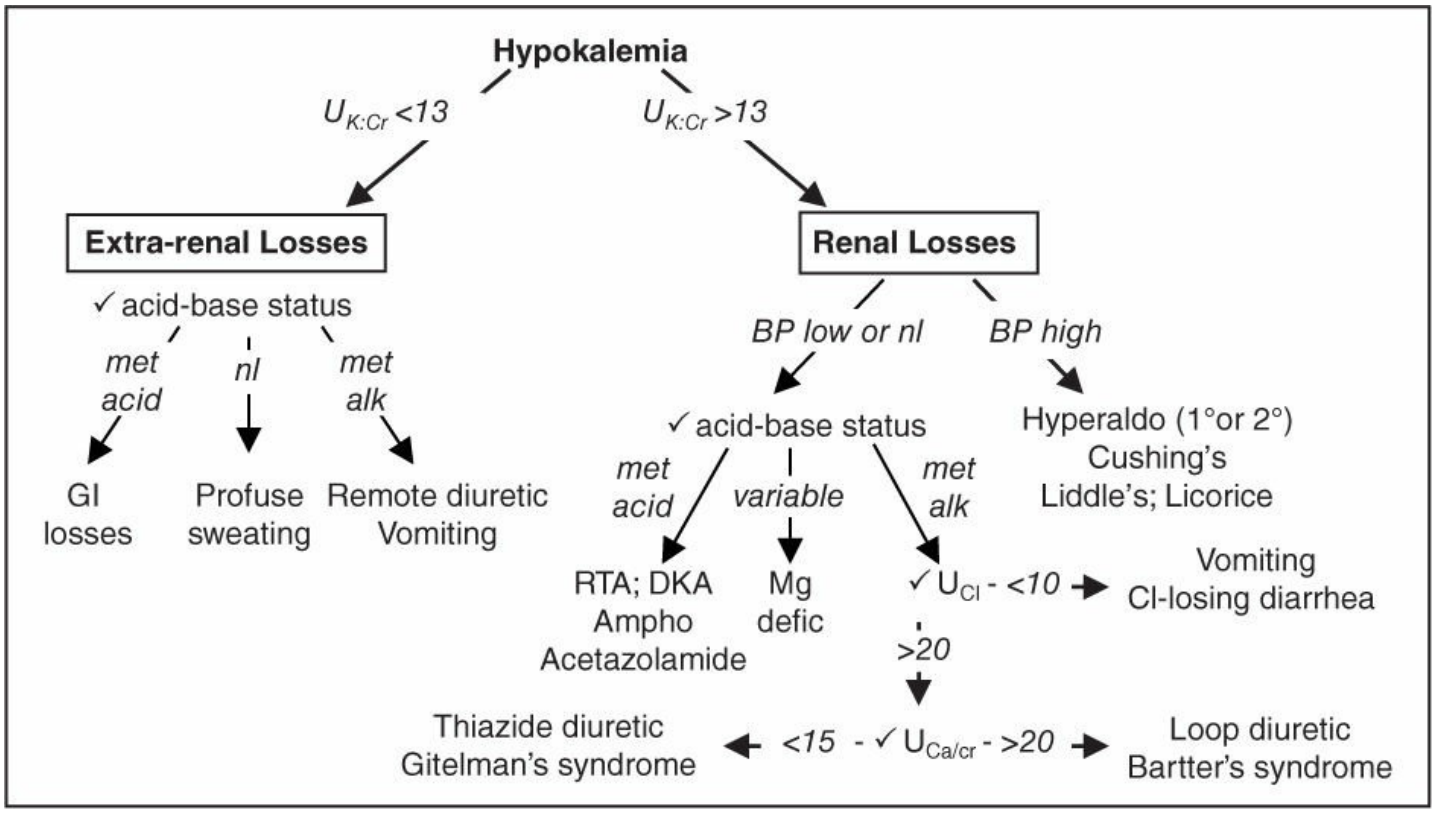
Clinical manifestations

- 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 (*Nat Rev Nephrol* 2011;7:75)

- 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 (*Archives* 2004;164:1561)
- 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 1L 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 (oral Mg-oxide poorly tolerated b/c 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
- Assess GFR, if normal, then ✔U_K, U_{Na} (<25 mEq/d ↓ distal Na delivery). ✔ $U_{K:Cr}$ (<13 favors ↓ renal K excretion).

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
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 1L D5W	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] 15–60g 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)

- *Rate of onset* important to note when establishing a treatment plan
- Stabilize (initial): 10% CaCl (central) or gluconate (IV). ↑ memb. potential → ↓ excitability
- Redistribute: insulin + dextrose (continuous if NPO), HCO_3 (*KI* 1991;41:369), β_2-agonists
- Eliminate: SPS (Kayexalate, *NEJM* 2015;372:211), patiromer (expensive), 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

RENAL FAILURE

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 (*Lancet* 2012;380:756)		
Etiologies		UA, Sediment, Indices
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 in ~75% ± 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 syndrome, IgG4, SLE	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,	± RBCs

	DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	⊕ urine eos in chol emboli
	Glomerulonephritis (see "Glomerular Disease")	Dysmorphic RBCs, RBC casts
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). May be benefit to balanced crystalloids (LR) in ICU (*NEJM* 2018;378:829).
- 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)
  - Acid-base disturbance: refractory acidemia
  - Electrolyte disorder: hyperK; hyperCa, hyperPO_4, tumor lysis syndrome
  - Intoxications (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)
  - Overload: refractory hypervolemia → hypoxemia (eg, CHF)
  - Uremia: pericarditis, encephalopathy, bleeding
- No mortality benefit to early initiation of RRT (*NEJM* 2016;375:122 & *Jama* 2018;379:1431)

DISEASE-SPECIFIC MANAGEMENT

Acute interstitial nephritis (AIN) (*CJASN* 2017;12:2046)

- 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

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: data mixed, but may be helpful if high risk (*Int Med* 2014;53:2265; *Lancet* 2017;389:1312). No benefit to $NaHCO_3$ over NaCl (*NEJM* 2018;378:603).
  - Outpatients: 3 mL/kg/h × 1h prior, 1–1.5 mL/kg/h × 6h 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.
  - No benefit to NAC (*NEJM* 2018;378:603) or preemptive RRT (*Am J Med* 2012;125:66)
- 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.

Diabetic nephropathy (*NEJM* 2016;375:2096)

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* 2004;350:151; 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.

Thrombotic microangiopathies (TMAs): *see "Hematology"*

CHRONIC KIDNEY DISEASE (CKD)

Definition and etiologies (*Lancet* 2012;379:165; *JAMA* 2015;313:837)

- 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 (www.kidney.org/professionals/KDOQI/gfr_calculator.cfm)
  CKD-EPI preferred over MDRD because less likely to underestimate at normal GFRs
  cystatin-C–based formulae perform better than Cr-based (*NEJM* 2012;367:20)
- Etiologies: DM (45%), HTN/RAS (27%), glomerular (10%), interstitial (5%), PKD (2%) (*NEJM* 2008;359:1477; *AJKD* 2019;73:A7), congenital, drugs, myeloma (*JAMA* 2009;302:1179), repeated insults (eg, Mesoamerican nephropathy *AJKD* 2018;72:469)
- Progression to ESRD: kidney failure risk equation (*JAMA* 2016;315:164)

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 (KDIGO 2013)

- 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; SGLT2i slow CKD progression (*NEJM* 2017;377:1765 & 2019;380:2295)
- BP control: goal <130/80, a/w ↓ mortality (*NEJM* 2015;373:2103; *JASN* 2017;28:2812). ACEI or ARB (NEJM 2004;351:1952), not both (*NEJM* 2013;369:1892). 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 2wk)

iron supplementation to keep transferrin sat >20% (often given IV in HD Pts)
- Uremic bleeding: desmopressin (dDAVP) 0.3 μg/kg IV or 3 μg/kg intranasally
- 2° hyperPTH: ↑ PO_4, ↓ Ca, ↓ calcitriol, ↑ FGF-23 → ↑ 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)
Consider sevelamer first, Ca acetate & lanthanum other options. Non-Ca–based binders 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, Na thiosulfate (*CJASN* 2013;8:1162), manage hyperPTH, no vit D & Ca, NOACs > warfarin, pain control, palliative care
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 1*973;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, CVVH, 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

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 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
- Crescentic GN (pathologic description) ≈ RPGN (clinical description)

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 (c-ANCA)	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO (p-ANCA)	70%
Eosinophilic gran with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO (p-ANCA)	50%

[a]Predominant type; p- or c-ANCA can be in all (*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)
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)

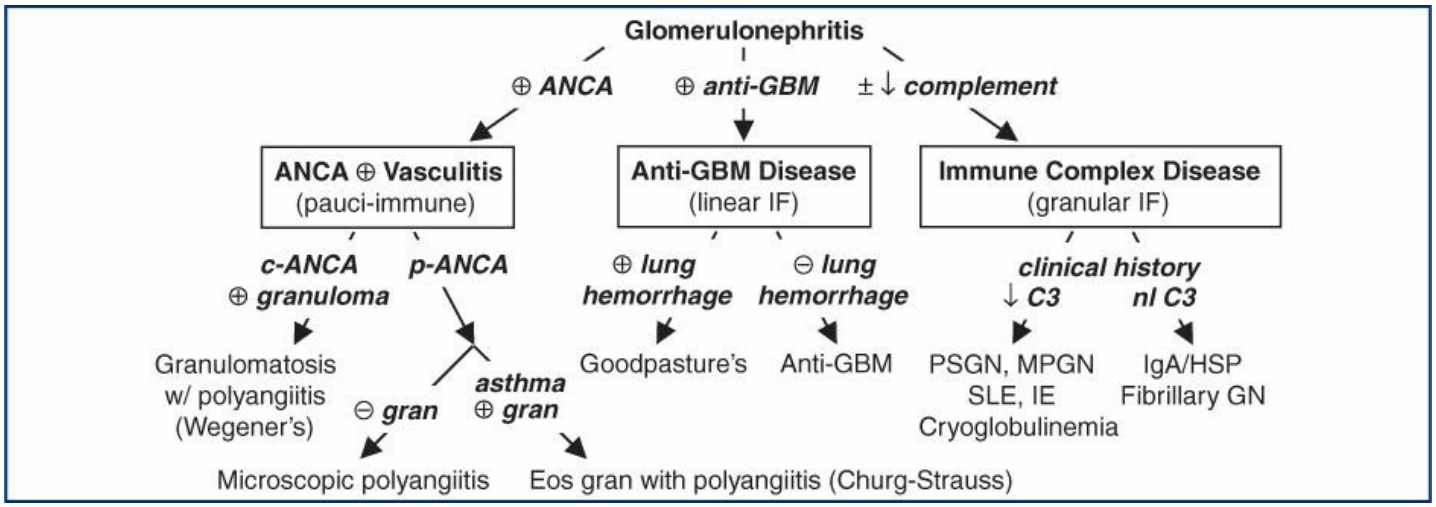
Oncology-related glomerulopathy (*CJASN* 2016;11:1681)

- Associations between malig (solid tumors & heme) and/or their Rx (HSCT & chemotherapeutics) 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 (*CJASN* 2017;12:1680)

- If acute GN/RPGN suspected, give 500–1000 mg methylpred. IV qd × 3d *ASAP* while awaiting bx results. Consider plasmapheresis & further Rx based on underlying disease.
- 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 severe AKI or pulm hemorrhage (*JASN* 2007;18:2180; *NEJM* 2010;363:221; *AJKD* 2011;57:566).
- See "Vasculitis" for further disease-specific treatment details

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 (*NEJM* 2013;368:25; *CJASN* 2017;12:677)

- 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 (*JASN* 1999;10:1772); steroids if persistent proteinuria (> 1g/d; *NEJM* 2015;373: 2225); ± cytotoxic Rx for crescentic GN or HTN & ↑ Cr (*JASN* 2012;23:1108); ? 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): 1° (cytokine mediated); *adaptive* (hyperfiltration, sickle cell, obesity, anabolic steroids, OSA, ↑ protein, vesico-ureteral reflux); *genetic* (*ApoL1* mutation in AA (*JASN* 2015;26:1443); *viral* (HIV most strongly associated); *meds/toxins* (IFN, bisphosphonates, NSAIDs, heroin)
- Membranous nephropathy (30%; *Lancet* 2015;385:1983; *CJASN* 2017;12:938): 1° (Ab to PLA2R [70%] or THSD7A [5%]; *NEJM* 2014;371:2277); *infection* (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 ± cytotoxic therapy (*KI* 2012;2:139; *CJASN* 2014;9:1386)
- 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. Sn 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	Disruption of filtration	Glomerulonephritis

(can be >3.5 g/d)	barrier → lose albumin	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
Nephrolithiasis Neoplasm: transitional cell, prostate Infxn: cystitis, urethritis, prostatitis Foley trauma BPH Schistosoma haematobium	Nephrolithiasis or crystalluria Neoplasm Trauma/exercise (? extrarenal component) Vascular: renal infarcts, renal vein thromb., sickle cell, ruptured hemangioma 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 (*JAMA* 2017;177:800)

- Urine dipstick: ⊕ if ≥3 RBCs; ⊕ dipstick and ⊖ sediment → myo- or hemoglobinuria
- Urine sediment: dysmorphic RBCs or RBC casts → GN → consider renal bx
- Dx: *CT urography*: r/o nephrolithiasis & neoplasia (Se 96%, Sp 98%); *urine cytology* (Se 70%, Sp 95%); *cystoscopy*: r/o bladder neoplasia, esp if Pt ≥35 y
- Rx: if obstruction: bladder irrigation and 3-way Foley on CBI

NEPHROLITHIASIS

Types of stones and risk factors (*Nat Rev* 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 (*Urology* 2014;84:533)

- 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 (*CJASN* 2016;11:1305)

- 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)*

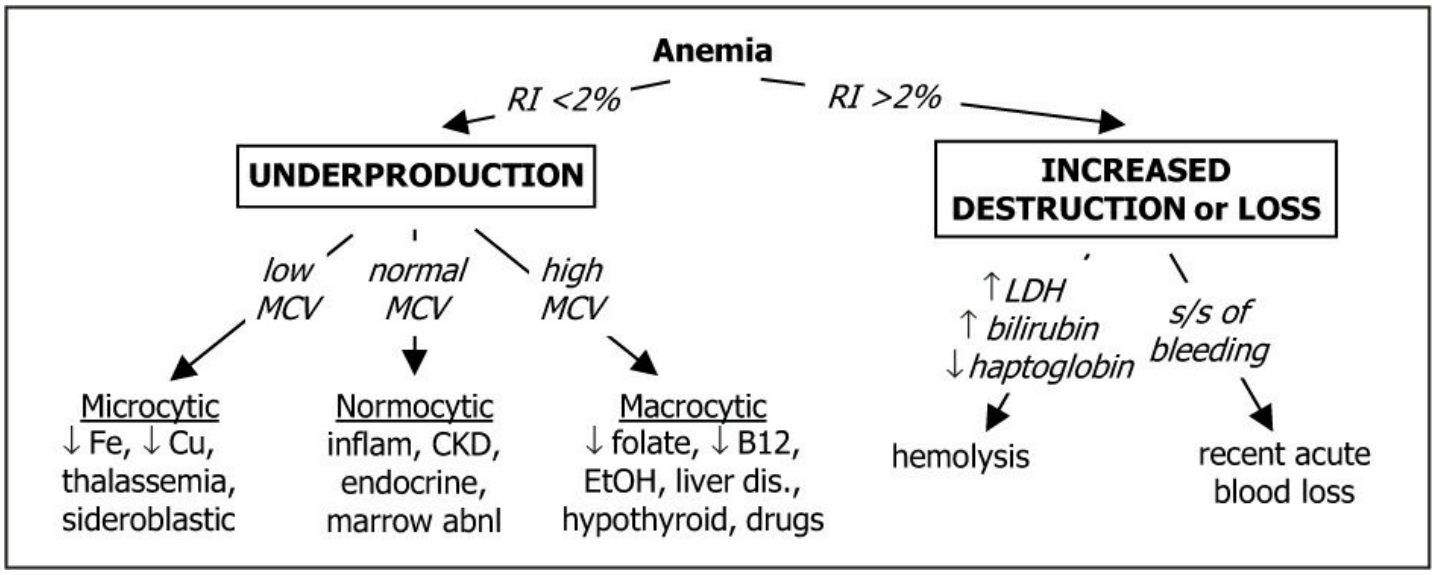
Clinical manifestations

- 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

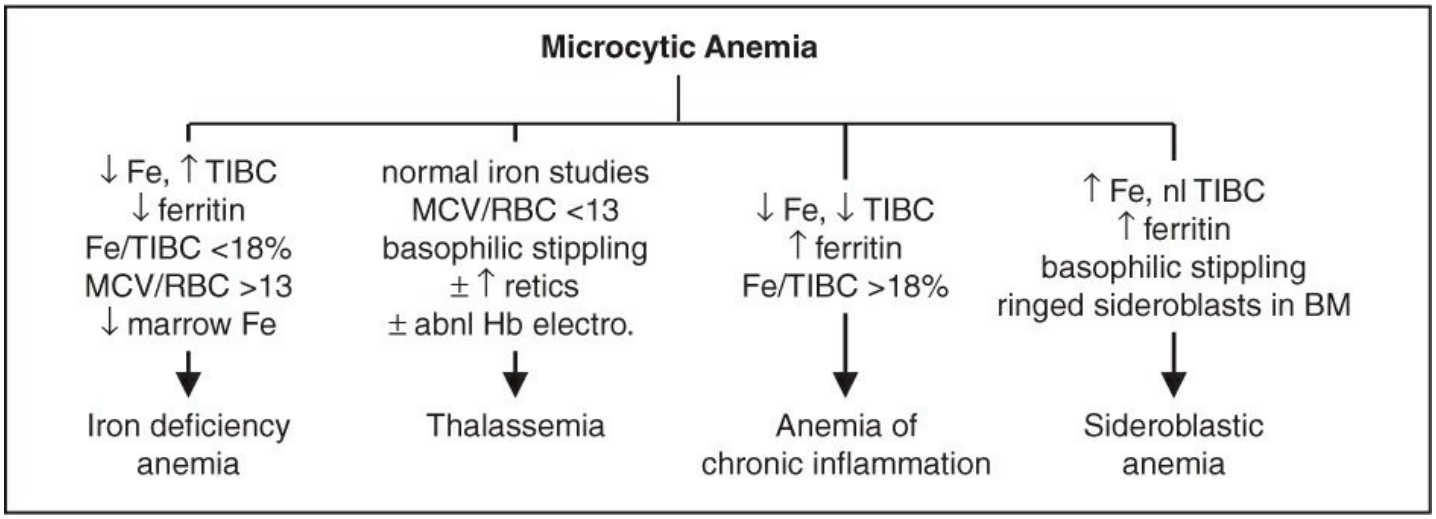
- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including pica), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- Reticulocyte index (RI) = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor
  maturation factors for a given Hct: 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 (*NEJM* 2015;372:1832; *Lancet* 2016;387:907)

- ↓ 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, antigliadin, anti-endomysial Abs). Cytogenetics & molecular testing as indicated.
- Treatment: oral Fe tid (~6 wks to correct anemia; ~6 mo to replete Fe stores; nb, oral Fe does not give ⊕ Hemoccult). In excessive/persistent GI losses or dialysis, cancer, CHF, or prior to Epo Rx, *IV iron* (Fe-sucrose, -gluconate, -dextran) should be considered.

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 → α-thal-2 trait = silent carrier; 2 α → α-thal-1 trait or α-thal minor = mild anemia
  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; consider allo-HSCT in children w/ severe β-thal; gene therapy in development (*NEJM* 2018;378:1479)

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

NORMOCYTIC ANEMIAS

Pancytopenia (see below)

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 chronic kidney disease: ↓ Epo; treat w/ Epo (see "Chronic Kidney Disease")

- Endocrine deficiencies: hypometabolism and ↓ O_2 demand with thyroid, pituitary, adrenal, 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 and 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); immuno-suppression/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 and lateral columns of the spinal cord and cortex → numbness, paresthesias, ↓ vibratory and positional sense, ataxia, dementia
- Dx: ↓ B_{12}; ↑ homocysteine and methylmalonic acid; anti-IF Ab; Schilling test; ↑ 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 mo
  - folate can reverse *hematologic* abnormalities of B_{12} deficiency but not *neurologic* changes (and can lead to "steal" of 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
- Reticulocytosis
- Other causes: hypothyroidism; MDS; meds that impair DNA synthesis (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
- Marrow replacement (myelophthisis): myelofibrosis, metastatic solid tumors, granulomas
- Systemic diseases: hypersplenism, sepsis, alcohol, toxins

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/ cytogenetics showing hypocellularity
- Etiologies: idiopathic ($^1/_2$ – $^2/_3$ of cases)
  - Stem cell destruction: radiation, chemotherapy, chemicals (eg, benzene)
  - Idiosyncratic 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

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 (and alloimmunization) pretransplant

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* 2017;376:1540)

Supportive care: transfusions, abx, possible utility of G-CSF & Epo (if Epo <500)

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 aggreg., & 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

  eculizumab (Ab inactivates terminal complement C5s): ↓ hemolysis, improves QoL & stabilizes Hb levels (*NEJM* 2004;350:552 & 2006;355:1233; *Lancet* 2009;373:759); effective in pregnancy (*NEJM* 2015;373:1032); must have meningococcal vaccination

Myelophthisic anemia (see also "Primary Myelofibrosis")

- Infiltration of bone marrow by cancer, 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)

Location	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

- ↑ reticulocyte count (RI >2%), ↑ LDH, ↓ haptoglobin (83% Se, 96% Sp), ↑ indirect bili
- Autoimmune hemolysis: Coombs' test = direct antiglobulin test (DAT) → ⊕ if agglutination occurs when antisera against Ig or C3 are applied to patient RBCs
- Intravascular: ↑↑ LDH, ↓↓ haptoglobin; hemoglobinemia, hemoglobinuria, hemosiderinuria
- Extravascular: splenomegaly
- 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, aseptic 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; ? L-glutamine to prevent pain crises (*NEJM* 2018;379:226)
- Vaccines: pneumo, meningo, H flu, HBV
- Voxelotor (Hbs polymerization inhib) ↑ hemolysis to ↑ Hb (*NEJM* 2019;epub)
- Pain & vaso-occlusive crises: analgesia (consider PCA), IVF, transfusion if sx & Hgb < baseline; crizanlizumab (anti-P-selectin; *NEJM* 2017;376:429)
- Acute chest: O_2, abx, IVF, exchange transfusion
- TIA/stroke: often exchange transfusion (goal Hgb 10) ± thrombolytics
- Gene therapy in development (*NEJM* 2017;376:848)

Hereditary spherocytosis (HS) (*Lancet* 2008;372:1411)

- Defect in a cytoskeletal protein of RBC membrane → membrane loss mutations in ankyrin, α- and β-spectrin, band 3, and pallidin have been identified
- 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)

Drug-induced hemolytic anemia

- Acquired, Ab-mediated, RBC destruction precipitated by a med. 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 ± thrombocytopenia ± abnormalities a/w specific disorders (eg, ↑ PT in DIC, ↑ Cr in HUS, ↑ LFTs in HELLP)
- Rx underlying dx; urgent plasma exchange w/ TTP (replace low ADAMTS13)

Hypersplenism

- Stasis/trapping in spleen → Mφ attack & remodeling of RBC → 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)

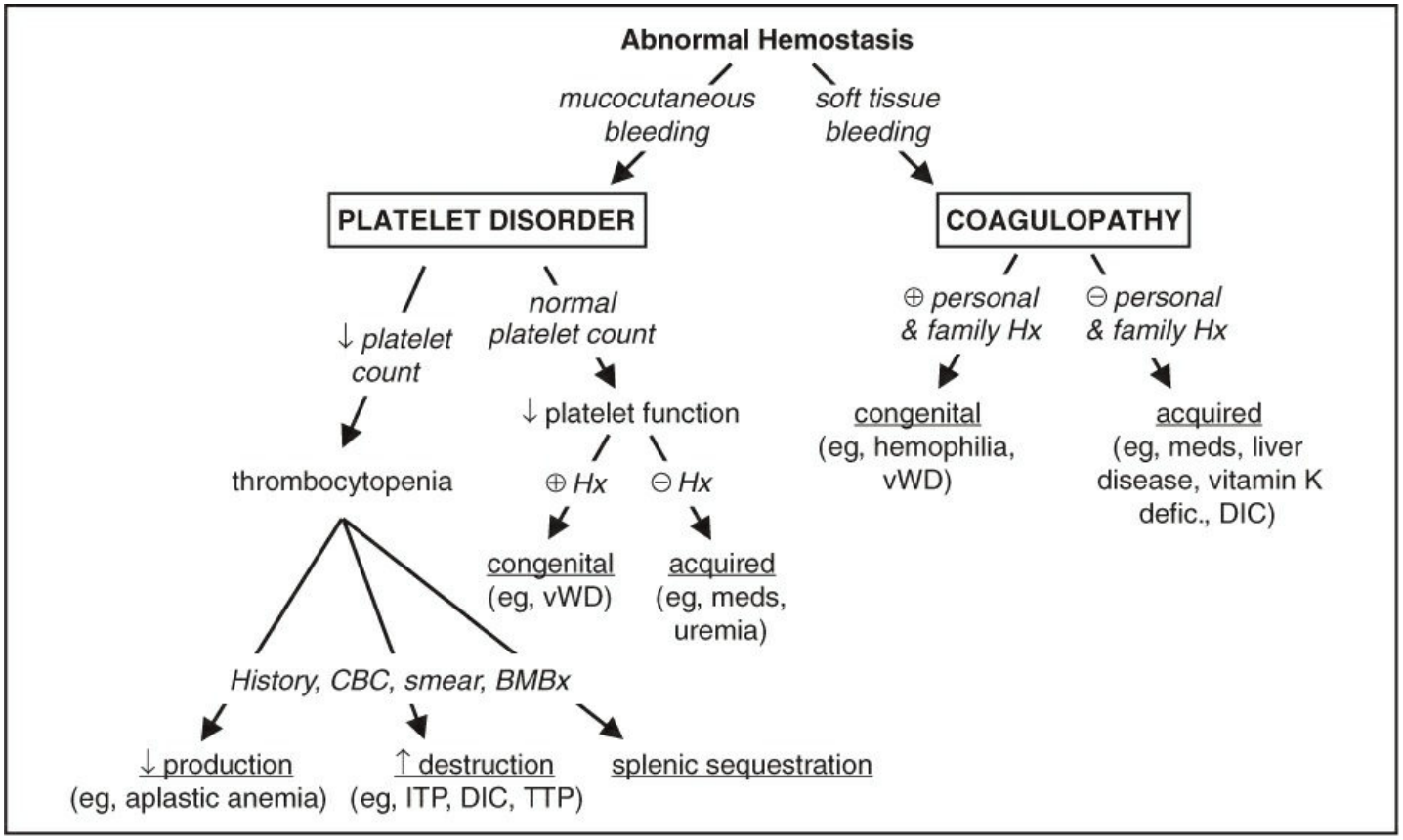
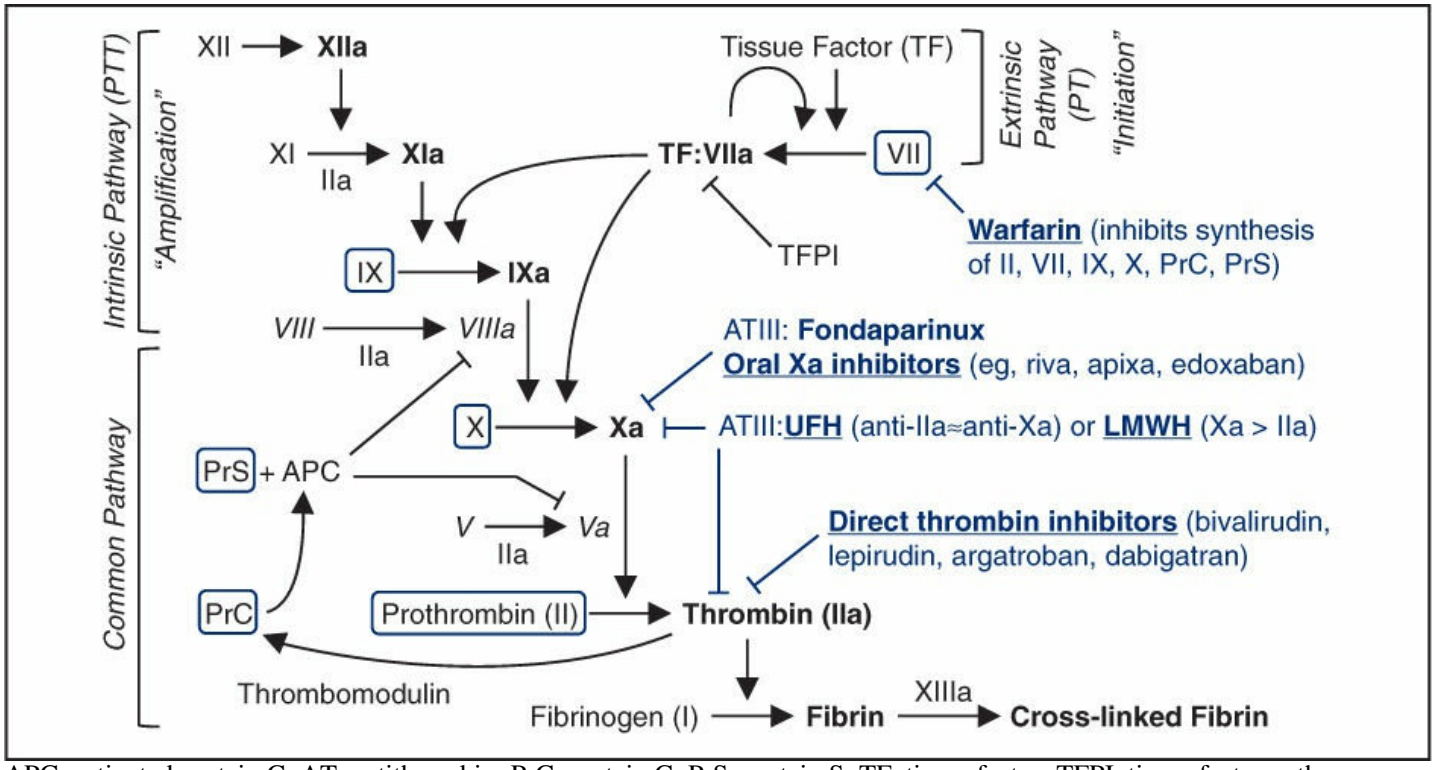


Figure 5-4 Coagulation cascade (*NEJM* 2008;359:938)



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
  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
20,000–50,000	Risk with minor trauma or surgery
<20,000	Risk of *spontaneous* bleeding (less so with ITP)
<10,000	Risk of severe, life-threatening bleeding

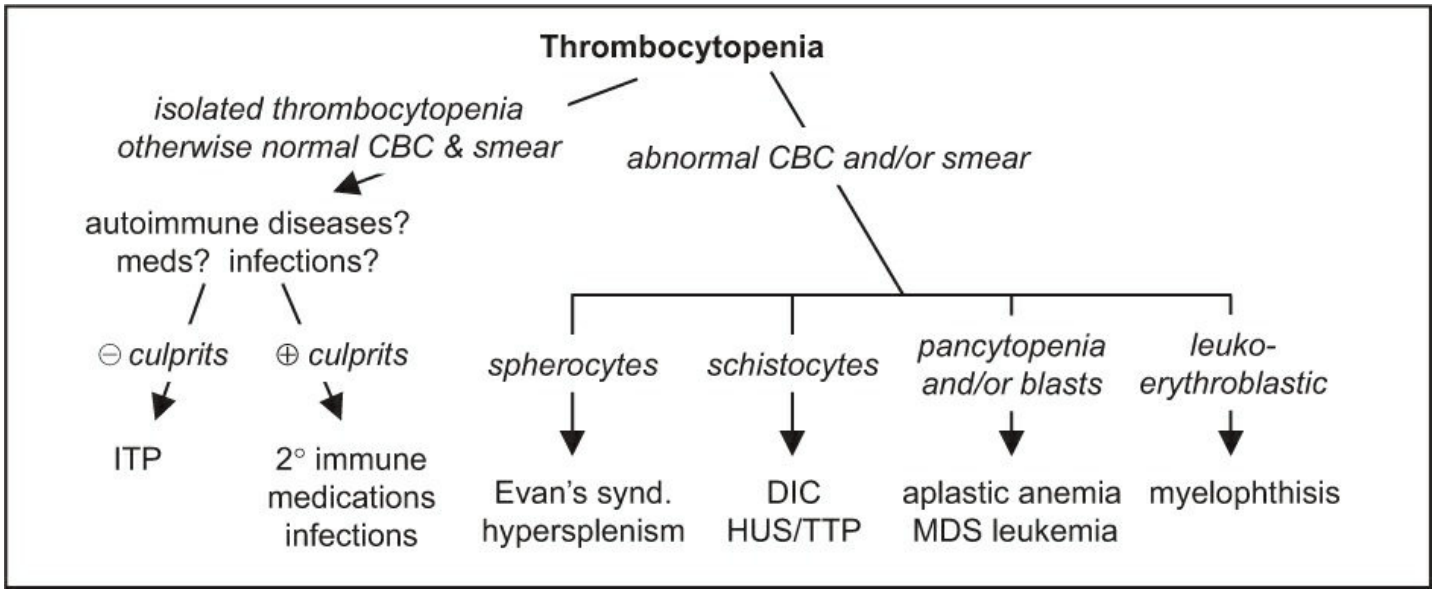
Etiologies

- ↓ production
  - Hypocellular bone marrow: aplastic anemia (qv), rarely MDS, drugs (eg, thiazides, antibiotics, chemotherapy), alcohol, cirrhosis
  - 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)
    - Primary (idiopathic): immune thrombocytopenic purpura (ITP, see below)
    - Secondary: infxn (HIV, HCV, HSV), collagen vascular diseases (SLE), APS, lymphoproliferative (CLL, lymphoma), drugs (*many*, including heparin, abciximab, quinidine, sulfonamides, vancomycin), alloimmune (posttransfusion)
  - 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
- 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, 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
- *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)
  Clinical manifestations: insidious onset of mucocutaneous bleeding; ♀:♂ = 3:1
- 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 or eltrombopag	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
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1g/d IV × 3 d	See above
	IVIg	See above
	Platelet transfusion	Given w/ IVIg or anti-Rh(D)

(*Blood* 2017;129:2829 & 130:3624; *Lancet Haem* 2016;3:e489; *Eur J Haem* 2018;100:304; *Immunother* 2018;10:9)

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 not useful.*
- Treat underlying etiology

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% Rare hemorrhagic complications
Management	Can continue heparin and observe	Discontinue heparin Alternative anticoagulation

- 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 aggregation (serotonin-release) assay (>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) (*Chest* 2012;141:e495S; *Blood* 2012;119:2209; *NEJM* 2013;368:737)
  - 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 (✔ chromogenic Xa to titrate)
  - ⊕ 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)
- Thrombotic thrombocytopenic purpura (TTP)
  - Pathophys: ↓↓ ADAMTS13 protease activity (hereditary or autoAb) → persistence of large vWF multimers on endothelial surface → adhesion & aggregation of plts → thrombosis
  - Clinical: pentad (all 5 in only ~5%) = ↓ plts + MAHA (100%) ± Δ MS (65%) ± renal failure (50%, late feature) ± fever (25%)
- 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)
- Drug-induced TMA (*Blood* 2017;129:2857)
  - Immune-mediated (Ab reacts w/ plts & endothelial cells): eg, quinine, gemcitabine?
  - Direct toxicity mediated: eg, gemcitabine, mitomycin, tacrolimus, CsA, bevacizumab
  - Clinically similar to TTP
- 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

- Rx: urgent plasma exchange ± glucocorticoids if TTP; FFP if delay to plasma exchange? rituximab or caplacizumab (anti-vWF Ab) (*NEJM* 2019;380:335) for TTP eculizumab for atypical HUS (*J Nephrol* 2017;30:127) *plt transfusions contraindicated* → ↑ microvascular thromb (*NEJM* 2006;354:1927)

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	Ticlopidine, clopidogrel, GP IIb/IIIa 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 (usually auto dom) bleeding disorder; ~85% (type 1) have partial quantitative defic of vWF, ~15% (type 2) have qualitative defic in vWF
- Acquired vWD: a/w many disorders (malig, MPN w/ ↑ plt count; autoimmune; hypothyroidism; 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) → ↑ endothelial cell release of vWF; efficacy depends on type (avoid in type 2), ∴ ✔ response before use w/ subseq. bleeding or procedures; vWF replacement: cryoprecipitate, factor VIII concentrates rich in vWF, 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, ⊕ due to 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 (*NEJM* 2016;374:2054) or IX; desmopressin (mild dis.); aminocaproic 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 (most commonly anti–factor VIII)

- Etiologies: hemophilia; postpartum; lymphoproliferative & autoimmune disorders; cancers
- Diagnosis: ↑ PTT (does *not* normalize w/mixing study); Bethesda assay quantitates titer
- Treatment: if high titer → recomb. factor VIIa, porcine factor concentrates, activated prothrombin complex; for others → high-purity human factor, plasmapheresis, immunosupp. w/ steroids, CYC and/or RTX (*Curr Opin Hematol* 2008;15:451)

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)

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%
Bivalirudin	25′, K	↑ PTT	Dialysis
Argatroban	45′, L	↑ PTT	? Dialysis
Warfarin	36°, L	↑ PT	*No bleeding:* consider 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 + **FFP** 2–4 U IV q6–8h; 4F-PCC (KCentra) faster, less volume, ↓ transfusion
Fibrinolytic	20′, LK	↓ fbgn	**Cryoprecipitate**, **FFP**, ± aminocaproic acid
Dabigatran	~12°, K	↑ PTT*	Idarucizumab: mAb binds drug (*NEJM* 2017;377:431)
Rivaroxaban Apixaban Edoxaban	8–12°, K > L	↑ PT* anti-Xa*	Andexanet alfa (factor Xa decoy receptor) (*NEJM* 2019;380:1326); consider 4F-PCC if andexanet not available (*Circ* 2017;135:e604; *JACC* 2017;70:3042)

*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%	4.3×	Activated protein C (APC) resist.
Prothrombin mutation	2%	2.8×	G20210A → ↑ prothrombin level
Hyperhomocysteinemia	5–10%	2.5×	Inherited or acquired
Protein C deficiency	0.02–0.05%	11×	Warfarin-induced skin necrosis risk
Protein S deficiency	0.01–1%	32×	
Antithrombin III def.	0.04%	17.5×	May be heparin resistant

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 are affected by 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: ⊕ moderate–high titer anticardiolipin (ACL), ⊕ lupus anticoagulant (LA), or ⊕ β_2-glycoprotein-I (β_2-GP-I) Ab, on ≥2 occasions, at least 12 wk apart
- Clinical: 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 in which 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 (*Arth Rheum* 2007;57:1487)

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 (ANC <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	Vit B_{12} defic., copper defic.
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)

Lymphocytosis (>4000–5000/μL)	
Infection	Usually viral; "atypical lymphocytes" with mononucleosis syndromes Other: pertussis, toxoplasmosis
Hypersensitivity	Drug-induced, serum sickness
Stress	Cardiac emergencies, trauma, status epilepticus, postsplenectomy
Autoimmune	Rheumatoid arthritis (large granular lymphocytes), malignant thymoma
Neoplasm	Leukemia (eg, CLL, hairy cell, LGL), lymphoma (eg, mantle cell, folic.)

Monocytosis (>500/μL)	
Infection	Usually TB, SBE, *Listeria*, *Brucella*, *Rickettsia*, fungi, parasites
Inflammation	IBD, sarcoidosis, collagen vascular diseases
Neoplasm	Hodgkin lymphoma, leukemias, MPD, carcinomas

Eosinophilia (>500/μL)	
Infection	Usually parasitic (helminths)
Allergic	Drugs; asthma, hay fever, eczema; ABPA
Collagen vasc dis.	RA, Churg-Strauss syndrome, eosinophilic fasciitis, PAN
Endocrine	Adrenal insufficiency
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)

Basophilia (>150/μL)	
Neoplasm	MPN, Hodgkin lymphoma
Alteration in BM or reticuloendothelial compartment	Hemolytic anemia, splenectomy
Inflammation or allergy	IBD, chronic airway inflammation

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 and parasitic	Histoplasmosis, coccidioidomycosis, paracoccidioidomycosis Toxoplasmosis
Immunologic	Collagen vascular disease, drug hypersensitivity (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	Age (>40 y), size (>2 cm), location (supraclavicular is always abnormal), duration (>1 mo) Consistency (hard *vs.* rubbery *vs.* soft) & tenderness are not reliable

TRANSFUSION THERAPY

Blood Products and Indications (*Lancet* 2013;381:1845)	
Packed red blood cells (PRBCs) (*JAMA* 2016; 316:2025)	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); maybe >9 if cancer & septic shock (*Crit Care* 2017;45:766). Controversy re: coronary ischemia, although Hb 7–8 likely adequate (*AHJ* 2018;200:96), including peri-cardiac surg (*NEJM* 2018;379:1224).
Platelets (plts) (*Annals* 2014;162:205)	For plts <10k (*NEJM* 2010;362:600) *or* <20k w/ infxn *or* ↑ bleeding risk *or* <50k w/ active bleeding or preprocedure. 6 U pooled donor plts ≈ 1 single donor plt apheresis unit (↓ alloimmunization) → ↑ plt ~30–60k. *Contraindic:* TTP/HUS, HELLP, HIT. *Refractory* if ↑ <5k 30–60′ post-plts. Suggests consumption such as ITP, DIC, or alloimmunization → trial ABO-matched plts. 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 deficiency of multiple coagulation factors (eg, DIC, TTP/HUS, liver disease, warfarin excess, dilution) or INR >2 preprocedure (*Transfusion* 2006;46:1279).
Cryoprecipitate	Enriched for fibrinogen, vWF, VIII, and XIII. For bleeding in vWD, factor XIII deficiency or fibrinogen <100 mg/dL.
Irradiated	Prevents donor T-cell proliferation. Use if 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.
Intravenous 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 large molec wt subst. (eg, cryoglobulinemia, Goodpasture's, Guillain-Barré, hyperviscosity syndrome, TTP) or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis, sickle cell) from plasma.
Massive transfusion	Large-vol. PRBC → ↓ Ca, ↑ K, ↓ plt, ↑ coags; initial ratio of 1 PRBC: 1 plt:1 FFP repletion generally accepted but controversial, follow labs (*JAMA* 2015;313:471; *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	1:1000	Hepatitis C	1:1,600,000
Acute hemolytic	<1:250,000	HIV	1:1,800,000
Fatal hemolytic	<1:100,000	Bacteria (PRBCs)	1:500,000
TRALI	1:5000	Bacteria (platelets)	1:12,000

Transfusion reactions

- For all reactions (except minor allergic): stop transfusion; send remaining blood product and fresh blood sample 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
  Due to undetected allo-Abs against minor antigens → anamnestic response.
  Rx: usually no specific therapy required; dx is 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: bronchospasm, laryngeal edema, hypotension
  Reaction to transfused proteins; anaphylaxis seen in IgA-deficient Pts w/ anti-IgA Abs.
  Rx: urticaria → diphenhydramine; anaphylaxis → epinephrine ± glucocorticoids
- 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): noncardiogenic pulmonary edema Due to donor allo-Abs that bind recipient WBCs, which then aggregate in pulmonary vasculature and release mediators causing ↑ capillary permeability. Rx: see “ARDS.”

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 *FGFR1* or w/ *PCM1-JAK2*	May be responsive to TKI therapy (eg, imatinib) for *PDGFR* rearrangement
Mastocytosis	Systemic disease, assoc w/ *KIT* mutations
Myeloid neoplasms w/ germ line predisposition	MDS, MDS/MPN, acute leukemias in background of predisposing germline mutations

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 infx (eg, HIV); chemo; 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 *SF3B1* 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	EB-1: 5–9% BM/2–4% PB blasts, no Auer rods

	RAEB-2	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. RS, ring sideroblast; BM, bone marrow; PB, peripheral blood. * <5% RS if *SF3B1* 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)
  - Low/intermediate risk → Epo (if Epo level <500); lenalidomide (esp. for 5q syndrome; *Blood* 2011;118:3765); DNA hypomethylating agents (azacitidine or decitabine)
  - Intermediate/high risk (>4.5 on IPSS-4) → allogeneic HSCT if medically fit, otherwise DNA hypomethylating agents (decitabine or azacitidine; *Lancet Oncol* 2009;10:223)
  - Hypoplastic MDS (rare) → consider immunosuppression (CsA, ATG, pred), HSCT
- Prognosis: *TP53*, *RAS*, *JAK2* mutations (*NEJM* 2017; 376:536) & IPSS-R correlate w/ 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
- Different from MDS in that the cells are not dysplastic (ie, normally developed)
- 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, not otherwise specified; myeloproliferative neoplasms unclassifiable
- 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-ABL* fusion in all cases of CML; *SETBP1* in aCML
  - *CALR* exon 9 mutation (most MPNs w/o *JAK2* or *MPL* mutation, including ~25% of ET, ~35% of myelofibrosis Pts; *NEJM* 2013;369:2379 & 2391)
  - *MPL*, *TET2, & ASXL1* mutation w/ lower frequency
  - *CSF3R* mutation present in ~60% of CNL; *KIT* 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

- Relative ↑ RBC (↓ plasma): dehydration; "stress" erythrocytosis (Gaisböck's syndrome)
- *Absolute* ↑ RBC: 1° (PV, other MPD) or 2° due to hypoxia; carboxyhemoglobinemia; inappropriate erythropoietin (renal, hepatic, cerebellar tumors); Cushing's syndrome

Clinical manifestations (common between PV and ET)

- Symptoms → often termed "vasomotor symptoms"
  - Hyperviscosity (erythrocytosis): headache, dizziness, tinnitus, blurred vision
  - Thrombosis (hyperviscosity, thrombocytosis): transient visual disturbances (amaurosis, ocular migraine); Budd-Chiari syndrome; erythromelalgia = intense burning, pain and erythema of extremities due to microvascular ischemia; ↑ risk of DVT, MI, stroke. Risk of thrombosis highly correlated with ↑ WBC in PV and ET (see below).
  - 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
- Expression profiling beyond *JAK2* may define different phenotypes (*NEJM* 2014;371:808)

Diagnostic evaluation
- Men: Hb >16.5 g/dL or HCT >49%, women: Hb >16 g/dL or HCT >48%, or ↑ red cell mass
- 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
- ✔ Epo to rule out secondary causes of erythrocytosis; if Epo ↓, PV more likely
  If Epo ↑, then ✔ SaO_2 or PaO_2, carboxyhemoglobin, BM exam
- ± ↑ WBC, platelets, basophils; ↑ uric acid, leukocyte alkaline phosphatase, vit B_{12}
- Peripheral smear → no morphologic abnormalities

Treatment
- 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 symptomatic thrombocytosis (plt >1.5 × 10^6/μL), 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)

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%)

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, acute bleeding, iron deficiency, postsplenectomy, neoplasms (eg, Hodgkin lymphoma)
- Of patients with plt >10^6/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, pruritus; mild splenomegaly; migraine, TIA; early fetal loss

Diagnostic evaluation
- Peripheral smear: large hypogranular platelets
- BM bx: megakaryocytic hyperplasia; absence of Philadelphia chromosome; rarely minor reticulin fibrosis; normal iron stores; if atypical megakaryoctyes, consider pre-PMF
- Mutations: *JAK2* V617F in 60-65%; *CALR* in 20-25%; *MPL* in 5%; triple negative 10-

15%

- Patients should not meet WHO criteria for diagnosis of CML, PV, PMF, or MDS

Treatment of ET			
Risk	**Features**	**ASA 81 mg qd**	**Cytoreduction**
Low	Age <60 *and* no h/o thrombosis *and* plt $<1.5\times10^6$/μL *and* no CV risk factors	Consider for vasomotor symptoms	No
Int.	Neither low nor high	±	Consider if plt $>1.5\times10^6$/μL
High	Age ≥60 *or* h/o thrombosis *or* plt $>1.5\times10^6$/μL	⊕ (consider holding if plt $>1\times10^6$/μL and lab evid. of acquired vWD)	**Hydroxyurea.** Goal plt $<0.4\times10^6$/μL or sx free. IFNα if young or pregnant.

Prognosis

- Low-risk Pts have overall survival ≈ control population
- Risk of transformation into acute leukemia <2%; risk of progression to MF similar

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PRIMARY MYELOFIBROSIS (PMF)

Definition

- Clonal myeloproliferation with reactive marrow fibrosis & extramedullary hematopoiesis
- Prefibrotic stage (pre-PMF): megakaryocyte prolif, grade 1 reticulin fibrosis, ↑ BM cellularity. Important to distinguish from ET: ↑ thrombosis, ↑ progression, ↓ survival (*Blood* 2012;120:569)

Etiologies of myelofibrosis

- Myeloproliferative neoplasm = primary myelofibrosis; post-PV/ET myelofibrosis
- Other hematologic (CML, AML, ALL, MDS) and solid cancers (breast, prostate)
- Autoimmune (SLE and other collagen vascular disorders)
- Toxins (benzene); radiation; granulomas (TB, fungal, sarcoid); deposition dis. (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 (*JAMA* 2010;303:2513; *Blood* 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; also does not meet criteria for PV or MDS

Treatment (*Blood* 2011;117:3494)

- In absence of adverse prognostic factors (eg, anemia or sx) → no treatment
- Allogeneic HSCT only potential cure → consider in young Pts with poor prognosis
- Supportive care: transfusions; ESA if Epo <500 but risk worsening splenomegaly; consider androgens vs immunomodulatory agents (eg, lenalidomide) + prednisone; ? splenectomy if refractory to transfusions, failed chemoRx, painful splenomegaly
- Hydroxyurea for significant leukocytosis or thrombocytosis
- Ruxolitinib (JAK1/JAK2 inhibitor) ↓ sx, ↓ splenomegaly, ↑ survival (*NEJM* 2012;366:787 & 799)
- JAK2 inh: pacritinib, momelotinib, & fedratinib are in phase 3 trials (*JAMA Oncology* 2018;4:652)
- 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 syndrome, ataxia telangiectasia, Li-Fraumeni, germline mutations in *RUNX1*, *CEBPa*, & *GATA2*

Clinical manifestations

- Cytopenias → fatigue (anemia), infection (neutropenia), bleeding (thrombocytopenia)
- More common in AML
  - Leukostasis (more often when blast count >50,000/μL): dyspnea, hypoxemia, headache, blurred vision, confusion,TIA/CVA, interstitial infiltrates
  - DIC (esp. with APL); leukemic infiltration of skin, gingiva (esp. with monocytic subtypes); chloroma: extramedullary tumor of leukemic cells, virtually any location
- More common in ALL
  - bony/lumbar pain, LAN, hepatosplenomegaly (also in monocytic AML), SVC syndrome
  - CNS involvement (up to 10%): cranial neuropathies, N/V, headache
  - anterior mediastinal mass (esp. in T-cell); tumor lysis syndrome (qv)

Diagnostic evaluation (*Blood* 2009;114:937)

- Peripheral smear: anemia, thrombocytopenia, variable WBC + circulating blasts (seen in >95%; ⊕ Auer Rods in AML), peripheral flow cytometry for blast origin (ALL vs. AML)
- Bone marrow: >20% blasts; mostly hypercellular; test for cytogenetics and flow cytometry
- Presence of certain cytogenetic anomalies, eg, t(15;17), t(8;21), inv(16) or t(16;16), are sufficient for dx of AML *regardless of the blast count*
- ✔ for tumor lysis syndrome (rapid cell turnover): ↑ UA, ↑ LDH, ↑ K, ↑ PO_4, ↓ Ca
- Coagulation studies to r/o DIC: PT, PTT, fibrinogen, D-dimer, haptoglobin, bilirubin

- LP (w/ co-admin of intrathecal chemotherapy to avoid seeding CSF w/ circulating blasts) for Pts w/ ALL (CNS is sanctuary site) and for Pts w/ AML w/ CNS sx
- TTE if prior cardiac history or before use of anthracyclines
- HLA typing of Pt, siblings > parents/children for potential allogeneic HSCT candidates

ACUTE MYELOGENOUS LEUKEMIA (AML; *LANCET* 2018;392:593)

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
- Prognosis: *age*, prior *antecedent MPN/MDS* and *genetics* (cytogenetics + molecular mutation status) are key independent risk factors

ENL 2017 Genetic Risk Classification (*Blood* 2017;129:424)	
Risk Category	Genetic Abnormality
Favorable	APL: t(15;17); t(8;21): RUNX1-RUNX1T1; inv(16): CBFB-MYH1; mutated *NPM1 w/o FLT3-ITD or w/ FLT3-ITD^{low}*; biallelic mutation in *CEBPA*
Intermediate	FLT3-ITD^{low}; mutated NPM1 & 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 & NPM1
Adverse	-5 or del(5q); -7; -17/abn(17p); complex or monosomal karyotype; t(6;9): DEK-NUP214 ; t(9;22) BCR-ABL1; inv(3): GATA2-MECOM; wildtype NPM1 & FLT-ITD^{high}; mutated TP53, RUNX1, ASXL1

Upfront treatment

- Induction chemo "7+3": 7 d cont. infusion cytarabine (Ara-C) + 3 d bolus anthracycline
- Ability to tolerate 7+3 regimen key determinant in subsequent Rx received (see below)
- Newer regimens if *fit* (generally age <75 y)
  - FLT3-ITD/TKD mutation: 7+3+midostaurin (early generation FLT3 inhib; *NEJM* 2017;377:454)
  - Cord-binding factor ⊕ → t(8;21) or inv(16): 7+3 ± gemtuzumab ozogamicin (mAb+cytotoxin)
  - 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
- Newer regimens if *unfit* (generally age ≥75 y or comorbidities; *Leukemia* 2013;27:997)
  - venetoclax (Bcl2 inhibitor) + *either* hypomethylating agents (azacytidine or decitabine) *or* low-dose cytarabine (*Blood* 2019;133:7)

Consolidation therapy

- If enters *complete remission* (CR) = ANC >1000, plts >100, off RBC Rx, <5% BM blasts
- CR does *not* equal cure

- Favorable risk: high-dose cytarabine (HiDAC); Intermediate/Poor risk: Allo-HSCT

Refractory/relapsed disease

- *Repeating mutation analysis* key b/c clonal evolution common and may affect Rx
- FLT3-ITD/TKD mutation: gilteritinib or quizartinib (both potent FLT3 inhibitors)
- *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)

Prognosis

- CR achieved in 70–80% of Pts <60 y and in 40–50% for Pts >60 y
- Overall survival variable, depends on prognostic factors: ranges from <10% of older Pts w/ poor-risk tumor genetics to >65% for 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 as soon as 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 (ATRA) syndrome: ~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)

Classification

- Lymphoblastic neoplasms may present as acute leukemia (ALL) with >20% BM blasts or as lymphoblastic lymphoma (LBL) w/ mass lesion w/ <20% BM blast
- Morphology: no granules (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL
- 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 Adolescents & young adults (<40 y): pedi-like regimen typically w/ PEG-asparaginase Adults (40–75 y): multiagent chemo incl. anthracycline, vincristine, steroids, CYC Older (>75 y): reduced-intensity chemo

- CNS prophylaxis: intrathecal MTX/cytarabine ± cranial irradiation *or* systemic MTX
- Postremission 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 (CD19 CAR-T cell, *NEJM* 2018;378:449), TKI+chemo/steroids (Ph ⊕ t(9;22) only)

  T cell: nelarabine

  Both B & T cell: chemo including high-dose cytarabine regimens; clofarabine

CHRONIC MYELOGENOUS LEUKEMIA (CML)

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-ABL fusion → ↑ Abl kinase activity

  BCR-ABL 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

- Chronic phase (CP): <10% blasts (peripheral or bone marrow)
- Accelerated phase (AP): 10–19% blasts, ≥20% basos, plts <100k, clonal evolution (karyotype changes) not seen at dx, megakaryocyte proliferation & fibrosis
- Blastic phase (BP): ≥20% blasts (2/3 w/ myeloid, 1/3 w/ lymphoid), may see extramedullary leukemia
- 85% present in the chronic phase, classic triphasic clinical course rarely seen in TKI era
- 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;* anemia, thrombocytosis, basophilia

- Bone marrow with karyotype: hypercellular, ↑ myeloid to erythroid ratio

Treatment (*Lancet* 2015;385:1447; *Hematol Oncol Clin North Am* 2017;31:577)

- Tyrosine kinase inhibitors (TKI) inhibit abl kinase activity
  - First line: imatinib, 1st TKI against BCR-ABL, remains gold standard (*NEJM* 2017;376:917). 2nd gen TKI: nilotinib, dasatinib, bosutinib; ↑ potency abl inhibitors, but ↑ toxicity.
  - Resistance: due to ↑ in BCR-ABL transcript level on TKI, often result of *BCR-ABL* mutation or amplification. Nilotinib, dasatinib, bosutinib & ponatinib approved for resistant disease, w/ only ponatinib effective on T315I resistance mutation (*NEJM* 2012;367:2075).
  - Side effects: nausea, 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-abl transcript) for >2 y. Up to 50% of Pts remain off TKI at 2 y (ie, no molec. recurrence). Likelihood of success proportional to duration of CMR and risk score at presentation.
- Consider upfront allogeneic HSCT for AP and BP.
- CML in pregnancy: hydroxyurea & all TKIs contraindicated. If Rx needed IFN an option.

Milestones of Therapy	
Definition	Optimal Time
BCR-ABL ratio <10% IS = 1-log reduction by quantitative PCR	3 mo
BCR-ABL ratio <1% IS or <35% Ph chr in metaphase cells	6 mo
Absence of the Ph chromosome in metaphase cells	12 mo
BCR-ABL ratio <0.1% IS = 3-log reduction by quantitative PCR	12 mo
BCR-ABL ratio determined using RT-PCR & compares expression of BCR-ABL fusion in Pt to averaged expression in unRx'd Pts. Reported on International Scale (IS), which standardizes reporting across labs.	

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 with 4 log ↓ in bcr-abl transcript have normal life expectancy.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

see "Small Lymphocytic Lymphoma"

LYMPHOMA

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 (nontender)
  - HL: Reed-Sternberg (RS) cells; 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; BM bx or PET (except in HL clinical stage IA/IIA w/ favorable features or CLL by flow); 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, b/c can lead to HBV reactivation); consider HIV, HTLV, & EBV serologies and connective tissue diseases autoAbs
- Imaging: PET-CT scans b/c CT alone does not reliably detect spleen/liver involvement (espec. in HL, DLBCL). PET response to Rx can be prognostic & possibly guide Rx (*NEJM* 2015;372:1598 & 2016;374:2419). 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 disease = greatest transverse diam. of mediastinal mass/max diam. of chest wall >1/3 on CXR or >10 cm if in abd; E = involves single contiguous extranodal site; H = hepatic; S = splenic	

HODGKIN LYMPHOMA (HL) (*Am J Hematol* 2018;93:704)

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 (5%): nodular lymphocyte predominant (NLP); involves peripheral LN
  - 80% present in stages I–II and Rx can be RT alone or combination chemo + RT w/ 4-yr progression-free survival 88% and overall survival 96% (*JCO* 2008;26:434)
  - Consider rituximab because most NLP RS cells are CD20+
  - Stages III–IV treated with combination chemo (see below)

Treatment (*Lancet* 2012;380:836)

- Stages I–II: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± RT if favorable disease
- 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); or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); 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 (eg, pembrolizumab or nivolumab) (*NEJM* 2015;372:311)
- Late 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
    - *lung*, efficacy of screening chest CT remains a topic of research
    - *acute 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)		
Negative Prognostic Indicators	Total # of Indicators	5-y PFS
Albumin <4 g/dL; Hb <10.5 g/dL	0	88%
Male; Age >45 y	1	84%
Stage IV	2	80%
WBC ≥15k/μL	3	74%
Lymphocytes <600/μL or <8% of differential	4	67%
	≥5	62%

NON-HODGKIN LYMPHOMA (NHL)

Epidemiology and risk factors

- ~70,000 new cases/y; median age at dx ~65 y; ♂ predominance; 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 ↑ *increasing aggressiveness*	Burkitt's lymphoma	*8q24, c-MYC*
	Diffuse large B-cell lymphoma (DLBCL)	*BCL2, MYC, MLL2, CREBBP, etc.*
	Mantle cell	*t(11; 14) BCL1-IgH* → cyclin D1
	Marginal zone lymphoma (nodal, extranodal [MALT ✓ *H. pylori*], splenic)	*AP12-MALT1 & BCL-10-Ig enh*
	Hairy cell leukemia (⊕ TRAP)	*BRAF V600E*
	Follicular lymphoma	*IGH-BCL2, MLL2*
	CLL/small lymphocytic lymphoma	*IGVH, ZAP70, TP53, SF3B1, etc.*
Mature T cell & NK cell	Peripheral T-cell lymphoma	*TET2 and DNMT3A*
	Mycosis fungoides (cutaneous lymphoma)/ Sézary syndrome (+ LAN)	
	Anaplastic large-cell lymphoma	Some *ALK1* ⊕
	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)

  Initial: RT if localized, rituximab + chemo (bendamustine, CVP, fludarabine), ibrutinib. Obinutuzumab (anti-CD20) + chemo w/ obinutuzumab maintenance ↑ PFS but ↑ toxicity (*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: 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
  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 or systemic high-dose methotrexate if paranasal sinus, testicular, breast, periorbital, paravertebral, or bone marrow involved; ≥2 extranodal sites + ↑ LDH may also warrant
  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 or tisagenlecleucel (*NEJM* 2017;377:2531 & 2545)
  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 prophylaxis & tumor lysis syndrome prophylaxis
  Addition of rituximab improves EFS (*Lancet* 2016;387:2402)
  Lymphoblastic lymphoma (B or T cell): treated like ALL (see "Acute Leukemia")
  High-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 and/or BCL6: previously "double-/triple-hit" lymphoma, assoc. w/ poor prognosis

Prognosis

- Indolent: typically incurable, but long median survival
- Aggressive: ↑ chance of cure, but overall worse prognosis

Follicular Lymphoma International Prognostic Index (FLIPI) (*Blood* 2004;104:1258)		
Factors: age >60, stages III/IV, Hb <12 g/dL, >4 nodal areas, LDH >nl		
# Factors	5-y Overall Survival	10-y Overall Survival
0–1	90%	71%
2	78%	51%
≥3	52%	35%

International Prognostic Index (IPI) for Aggressive NHL (*Blood* 2007;109:1857)		
Factors: age >60, stage III/IV, ≥2 extranodal sites, performance status ≥2, LDH > nl		
# Factors	Complete Response	5-y Overall Survival
0–1	87%	73%
2	67%	51%
3	55%	43%
4–5	44%	26%
Revised IPI Prognosis in Patients Rx'd with CHOP-R		
Factors	% at Dx	4-y Overall Survival

0	10%	94%
1–2	45%	79%
3–5	45%	55%

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 Treat as immunocompetent (CHOP-R), but avoid rituximab if CD4 <100 Alternative regimens include R-EPOCH (etop, pred, vincristine, cyclophos, doxorubicin)
- Burkitt lymphoma (20%): can occur with CD4 >200 Treat as immunocompetent; prognosis is not significantly worse
- Primary CNS lymphoma (16%): CD4 <50, EBV-associated (also seen in Pts w/o HIV). Rx w/ high-dose MTX-based regimen + steroids ± temozolomide ± RT, consider auto HSCT.
- Primary effusion lymphoma (<5%): HHV8 driven; also can be seen in other immuno-supp. Pts such as s/p solid organ transplant or w/ chronic HBV. Treat with standard CHOP (often CD20–) or consider EPOCH, overall poor prognosis.

SMALL LYMPHOCYTIC LYMPHOMA (SLL) OR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Definition (*NEJM* 2005;352:804; *Blood* 2008;111:5446)

- Monoclonal accumulation of functionally incompetent mature B lymphocytes
- CLL (>5000/μL malignant cells) & small lymphocytic lymphoma (SLL; <5000/μL malignant cells, with + LAN ± splenomegaly) classified as same disease
- 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
- ↑ incidence in 1st-degree relatives; no known association with radiation, chemicals, drugs

Clinical manifestations

- Symptoms: often asx & identified when CBC reveals lymphocytosis; 10–20% p/w fatigue, malaise, night sweats, weight loss (ie, lymphoma "B" sx)
- Signs: 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 transformation: ~5% develop Richter's syndrome = transformation into high-grade lymphoma (usually DLBCL) and sudden clinical deterioration

Diagnostic evaluation (see "Lymphoma" for general approach)

- Peripheral smear: lymphocytosis (>5000/μL, 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 (sIg); CD5+, CD19+, CD20(dim), CD23+. CD38+ or ZAP70+ a/w unmutated Ig variable heavy chain region & worse prognosis.
- Bone marrow: normo- or hypercellular; infiltrated w/ small B-cell lymphocytes (≥30%)
- Lymph nodes: infiltrated w/ small lymphocytic or diffuse small cleaved cells = SLL
- Genetics: del 11q22-23 & 17p13 unfavorable; trisomy 12 neutral; del 13q14 and mut *IgVH* 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

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 (*Lancet* 2018;391:1524)

- No treatment unless: Rai stage III/IV, Binet stage C, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections
- First-line: ibrutinib (inhibits Bruton's tyrosine kinase [BTK], which is found in B cells; *NEJM* 2015;375:25 & 2018;379:2517), risk of AF, HTN & bleeding (avoid if on warfarin), PNA, ILD
- Other options: purine analogues: fludarabine ("F"), pentostatin ("P");
  alkylating agents: cyclophosphamide ("C"), bendamustine ("B");
  ± anti CD20 (rituximab, "R"; ofatumumab; obinutuzumab) or CD52 (alemtuzumab)
  ibrutinib + obinutuzumab ↑ PFS vs. chlorambucil + obinutuzumab (*Lancet Oncol* 2019;20:43)
  venetoclax + obinutuzumab ↑ PFS vs. chlorambucil + obinutuzumab (*NEJM* 2019;380:2225)
  ibrutinib + venetoclax under study as 1st-line Rx: 88% with CR (*NEJM* 2019;380:2095)
- Refractory: venetoclax (α-BCL2; *NEJM* 2018;378:1107), acalabrutinib (BTK inhibitor; *NEJM* 2016;374:323), idelalisib (PI3K inhibitor; *NEJM* 2014;370:997)
- 17p- or *TP53* mutation: venetoclax, idelalisib, or ibrutinib ± rituximab (*Lancet Oncol* 2014;10:1090), consider allo-HSCT with reduced intensity conditioning
- Supportive care & managing complications: PCP, HSV, VZV prophylaxis; CMV monitoring for Pts receiving anti-CD52; AIHA/ITP → steroids; recurrent infections → IVIg

Prognosis (*NEJM* 2004;351:893; *JCO* 2006;24:4634)

- Survival varies substantially. Median overall survival ~10 y (*Am J Hematol* 2011;12:985)
- Favorable prognosis: 13q14 deletion (~50% of CLL cases)
- Poor prognosis:
  unfavorable cytogenetics: eg, 17p- or *TP*53 mutation (*JCO* 2010;28:4473), IgH

translocations
unmutated (<2% c/w germline) *IgVH* gene (<8–10 y vs. >20–25 y if mutated)
high (>20–30%) Zap-70 expression (part of T cell receptor; correlated w/ unmutated *IgVH*)
CD38 >30% or CD49d <30%: correlated with unmutated *IgVH* (*Blood* 2008;111:865)
higher β_2-microglobulin levels (correlate with disease stage and tumor burden)

PLASMA CELL DYSCRASIAS

MULTIPLE MYELOMA (MM)

Definition and epidemiology (*NEJM* 2011;364:1046)

- 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)

- HyperCalcemia due to ↑ osteoclast activity
- Renal 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
- Anemia (normocytic) due to bone marrow involvement; rarely, may see AIHA
- Lytic Bone 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)

- MM criteria: clonal BM plasma cells ≥10% or bx-proven plasmacytoma and ≥1 myeloma-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 studies
- Variants
  Smoldering MM: M protein >3 g/dL or plasmacytosis >10%, but no myeloma-defining event or amyloidosis; see below under MGUS for approach
  Solitary bone plasmacytoma: 1 lytic lesion w/o plasmacytosis or other ROTI
  Extramedullary (nonosseous) plasmacytoma: usually upper respiratory tract
  Plasma cell leukemia: plasma cell count >2000/μL in peripheral blood
  Nonsecretory MM (~2% of MM Pts): no M protein, but marrow plasmacytosis & ROTI
- Ddx of M component: MM, MGUS (see below), CLL, lymphoma, sarcoidosis, RA. Polyclonal hypergam can be seen in inflammatory states: HIV, rheumatic dis., cirrhosis.
- Peripheral smear → 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
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 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 radiographs) to identify lytic bone lesions and areas at risk for pathologic fracture; *bone scan is not useful for detecting lytic lesions.* Increasingly, whole-body PET-CT (scalp to toe) or MRI is being 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_2-microglobulin** <3.5 mg/L *and* **albumin** >3.5 g/dL	*All of the following:* 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_2-microglobulin** >5.5 mg/L	*Any of the following:* 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 (*NEJM* 2016;375:754 & 1319; 2018;378:518 & 379:1811)

- Decisions generally dictated by *risk stratification* and *transplant eligibility*
- Rx incl. proteasome inhibitors: bortezomib (V), carfilzomib (K), ixazomib (I); immunomodulators: lenalidomide (R), thalidomide (T), pomalidomide (P); immunotherapy: daratumumab (anti-CD38, Dara), elotuzumab (Elo)
  Other active drugs incl. dexamethasone (D), melphalan (M), panobinostat, cyclophosphamide (CYC);
  CAR-T cells (anti-BCMA) promising (*NEJM* 2015;373:621 & 1207; 380:1726; *Lancet* 2016;387:1551)
- 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).
- If *not* transplant eligible: induction chemo ↑ 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: based on prior response & HSCT eligibility: HSCT (if good prior response, no prior HSCT), Elo-PD, Dara-PD; rarely use Allo-SCT.
- 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

MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE (MGUS)

Definition and epidemiology (*NEJM* 2006;354:1362 & 355:2765)
- M prot. <3 g/dL, marrow plasmacytosis <10%, neither myeloma ROTI nor amyloidosis
- Prevalence ~3% in population >50 y of age, ~5% in >70 y of age, 7.5% in >85 y of age

Management
- ✔ 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

Prognosis (*NEJM* 2018;378:241)
- ~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 MM (not MGUS, but variant of MM that req no Rx)
- 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.

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
- Sx (eg, prog. anemia): rituximab ± chemo (eg, bendamustine, Cy, etc.); data for rituximab + ibrutinib (*NEJM* 2018;378:2399). 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 children ("half" match); early post-tx cyclophosphamide reduces GVH by destroying proliferating alloreactive T-cells
  Umbilical cord blood: HSC processed at birth & stored. Low cell number, need 2 cords in adults. 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 preparative 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, high 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 stem cells (*NEJM* 2012;367:1487)
  Bone marrow (BM): original source of HSCT, now less commonly used than PBSC
  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.
  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.

Complications

- Either direct chemoradiotoxicities associated with preparative regimen or consequences of interaction between donor and recipient immune systems
- 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
- Diffuse alveolar hemorrhage (DAH): Diagnosis: bronchoscopy to exclude infection; ↑ bloody lavage fluid seen with DAH. Treatment: pulse 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 + CsA or tacrolimus) or T-cell depletion of graft
  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)
- 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 ↓ cellular 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
Bacterial infection	Gram ⊕ cocci (coagulase-negative *Staph.*, *S. aureus*, *S. 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		2nd malignancy
	IPS/Interstitial pneumonitis		Chronic GVHD
Immune-mediated	Acute 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 or ganciclovir if CMV ⊕	CMV	100 d or when no longer immunosuppressed
Antibiotics (eg, fluoroquinolone)	Bacterial infxn	While neutropenic
TMP-SMX	PCP	365 d or when off immunosupp.
Allopurinol	Hyperuricemia	Until d –1
Ursodiol	SOS/VOD	60 d

LUNG CANCER

Pathology and Genetics				
	Pathology	**%**	**Typ locat.**	**Genetic Mutations in**
Non-small Cell	Adeno-carcinoma	40	Peripheral	*KRAS* (20–30%), *EGFR* (15–20%, esp. ♀, Asian, never smokers), *HER2* (6%) or rearrang. in *ALK* (~4%), *ROS1* (~2%) and *RET* (~1%)
	Squamous	20	Central	*FGFR1*, *SOX*, *PIK3CA*, *PTEN*, *TP53*, *SOX2*, *DDR2*, *BRAF*
	Large cell	5	Peripheral	
	Other/not classif.	20		
Small cell		15	Central	Complex; most have inactiv. of *TP53* and *RB1*

(*NEJM* 2008;359:1367; *JCO* 2012;30:863; *J Thorac Oncol* 2012;7:924; *Nature* 2011;489:519; *Cell* 2012;150:1107)

Epidemiology and risk factors

- Most common cause of cancer-related death for both men and women in the U.S.
- 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)
  squamous & small cell almost exclusively in smokers
  adenocarcinoma 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

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
  Pleural effusion, pericardial effusion, hoarseness (recurrent laryngeal nerve palsy), dysphagia (esophageal compression), stridor (tracheal obstruction)
  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, bone, liver, adrenal, weight loss
- Paraneoplastic syndromes
  Endocrine:

ACTH (SCLC) → Cushing's syndrome; ADH (SCLC) → SIADH
PTH-rP (squamous cell) → hypercalcemia

Skeletal: digital clubbing (non-small cell), hypertrophic pulm. osteoarthropathy (adenocarcinoma) = symmetric polyarthritis and proliferative periostitis of long bones

Neurologic (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)

Cutaneous: acanthosis nigricans, dermatomyositis

Hematologic: hypercoagulable state (adenocarcinoma), DIC, marantic endocarditis

Screening (*Lancet* 2014;382:732)

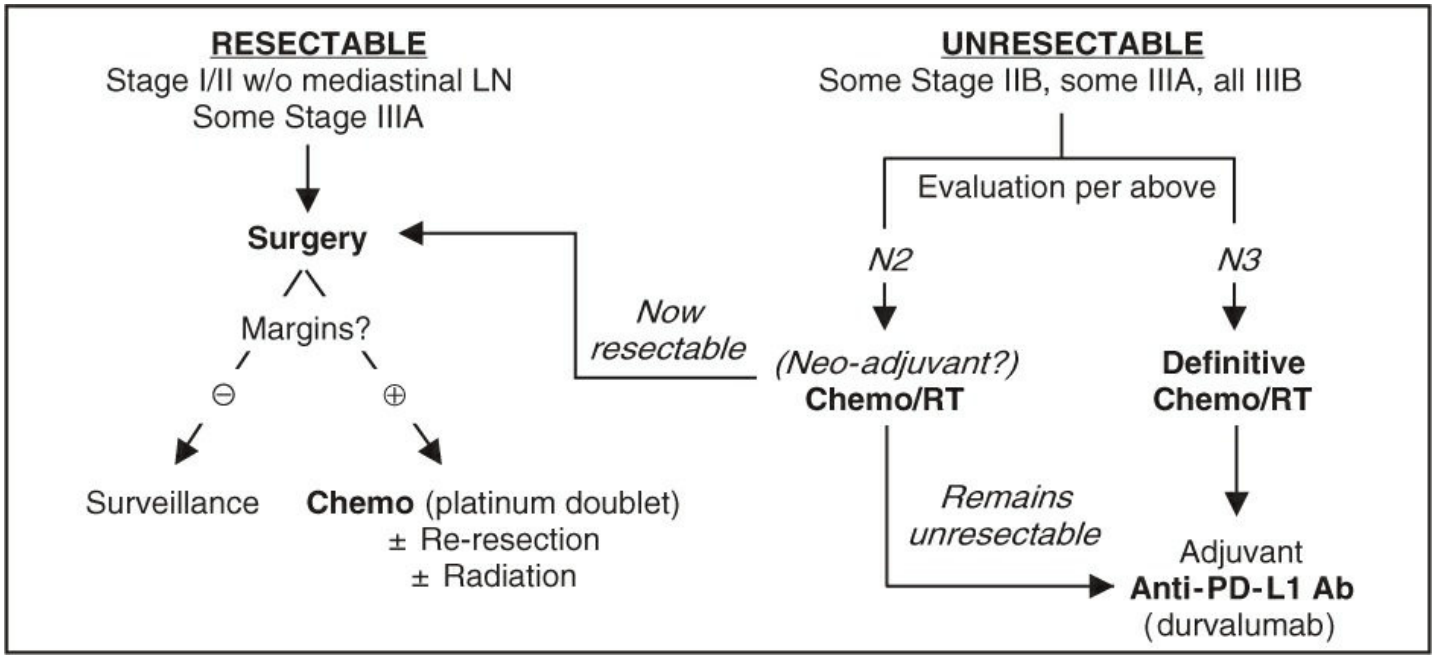
- No benefit to CXR or sputum cytology, even in high-risk Pts
- Annual low-dose chest CT in ≥30 pack-y current or former (quit w/in 15 y) smokers, age 55–74 y → 20% ↓ lung cancer-related mortality (*NEJM* 2011;365:395; 2013;368:1980; USPSTF)
  number needed to screen = 320; high false ⊕ rate
  consider risk scores to target screening (*NEJM* 2013;369:245 & 910; *JAMA* 2016;315:2300)

Diagnostic and staging evaluation (*NCCN Guidelines* v.1.2019)

- Initial imaging: contrast chest CT including liver and adrenals
- Pathology: via bronchoscopy (central lesions) or CT-guided needle bx (peripheral lesions or accessible sites of suspected metastasis); mediastinoscopy (LN bx), VATS (eval. of pleura peripheral lesions), thoracentesis (cell block for cytology)
- TNM 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). 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).
- Pretreatment evaluation
  Intrathoracic: mediastinoscopy (± preceded by U/S-guided transesoph. or transbronch. needle aspiration; *JAMA* 2010;304:2245) or VATS; thoracentesis if pleural effusion
  Extrathoracic: 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)
- Genetics: ✔ *EGFR* mut., *ALK, ROS1, RET, BRAF, NTRK* fusion for adv/metastatic non-squamous dis. (note incidence lower in squamous; only test if nonsmoker, mixed histo)
- PFTs w/ quantitative V/Q if planned treatment includes surgical resection; need to have 30% of normal, predicted lung fxn *after* resection

NSCLC treatment (*Lancet* 2017;389:299; *NEJM* 2017;377:849; *NCCN Guidelines* v.1.2019)

Figure 5-6 NSCLC treatment algorithm



NEJM 2018;379:2342. Encouraging data on PD-1 blockade as *neoadjuvant* therapy (*NEJM* 2018;378:1976).

Stage IV Treatment			
Type	**Genetics**	**%**	**Treatment**
Adeno or Other	EGFR	~15	EGFR TKI ("3rd gen" osimertinib pref.; *NEJM* 2018;378:113)
	ALK	~4	ALK TKI (alectinib pref.: CNS activity; *NEJM* 2017;377:829)
	ROS1	1–2	ROS1 TKI (crizotinib pref.; JCO 2017;35:2613)
	BRAF V600E	1–3	B-Raf inhib. (dabrafenib) + MEK inhib. (trametinib) (*Lancet* Onc 2016;17:984)
	NTRK fusion	<1	Larotrectinib after progression on chemotherapy and immunotherapy (*NEJM*:2018;378:731)
	PD-L1≥50%	30	Anti-PD-1 Ab w/ pembrolizumab; *NEJM* 2016;375:1823)
	No targets		Chemo (carboplatin/pemetrexed) + pembro (*NEJM* 2018;378:2078), *or* Chemo (carbo/paclitaxel) + anti-VEGF Ab (bevacizumab) + anti-PD-L1 Ab w/ atezolizumab (*NEJM* 2018;378:2288)
Squam	PD-L1 ≥50%		Pembrolizumab (*NEJM* 2016;375:1823)
	PD-L1 <50%		Chemo [carbo + (nab-)paclitaxel] + pembro (*NEJM* 2018;379:2040)
Palliative radiation: to control local sx caused by tumor or metastasis			
Solitary brain metastasis: surgical resection + brain radiation may ↑ survival			
Palliative care ↑ survival (*NEJM* 2010;363:733)			

TKI toxicities: rash & diarrhea (common); lung & liver injury (rare but potentially serious)

SCLC staging and treatment (NCCN Guidelines v.1.2019)

- SCLC usually disseminated at presentation but can be very responsive to chemoradiation
- Chemotherapy (platinum + etoposide) is primary treatment modality

- Addition of anti-PD-L1 Ab (eg, atezolizumab) ↑ survival (*NEJM* 2018;379:2220)
- Thoracic radiation added to chemotherapy improves survival in limited-stage disease
- Prophylactic cranial irradiation (PCI) ↑ survival for limited disease in complete remission (*NEJM* 1999;341:476) & ↓ symptomatic brain mets in extensive disease (*NEJM* 2007;357:664)

SCLC Staging Schema and Treatment

Stage	% at dx	Definition	Treatment	Median Survival
Limited	30–40	Confined to ipsilat. hemithorax w/in 1 radiation port	Radiation + chemotherapy ± PCI	1–2 y
Extensive	60–70	Beyond 1 radiation port	Chemotherapy ± PCI	~1 y

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 & ↑ risk of ovarian & prostate ca; ? ↑ colon ca; BRCA2: ↑ *male* breast, prostate & pancreatic ca. Germline loss-of-function mutations in *PALB2* a/w 35% ↑ risk breast cancer by age 70 (*NEJM* 2014;371:497).
- 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 contralat. 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 invasive breast ca & vertebral fx, ↑ risk of stroke & DVT/PE (*NEJM* 2006;355:125); less effective than tamoxifen in prevention of breast ca but lower risk of VTE, cataracts, & uterine ca (*Ann Int Med* 2013;158:604)
- 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 recommends annual mammo beginning at age 45 (consider biennial after age 54)
- USPSTF recommends beginning at 50 and biennially (some may want to begin at age 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)
- Genetic testing: recommended in women with strong FHx (*NCCN* v2.2019)

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 & contralateral 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): marker of ↑ risk of invasive 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
- Biomarkers: estrogen, progesterone receptor (ER/PR) and HER2/*neu* amplification
- Oncotype DX 21-gene expression recurrence score is predictive & prognostic in ER ⊕, HER2 ⊖, node ⊖ cancers (*NEJM* 2018;379:111); also 70-gene profile (*NEJM* 2016;375:717)

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		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)	
LCIS	Close surveillance ± chemoprevention (often tamoxifen) (*JCO* 2015;33:3945)
DCIS	Mastectomy or lumpectomy ± RT ± chemoprevention (*Lancet* 2016;387:849 & 866)
I	Surgery + RT

II	+ adjuvant chemo if ↑ risk: tumor >2 cm *or* ⊕ LN *or* ER/PR ⊖ *or* Oncotype DX ≥31 + 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; *HER2* ⊖ → chemotherapy 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 inhibitor (AI; anastrozole, letrozole, exemestane): adjuvant Rx for post-meno; ↑ OS vs. tam. (*Lancet* 2015;386:1341); 10 y of Rx ↑ DFS vs. 5 y of Rx (*NEJM* 2016;375:209) 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 (preferred 1st-line Rx for metastatic dis.) or fulvestrant ↑ PFS in stage IV vs. AI alone (*NEJM* 2018;379:1926; *JCO* 2017;35:3638) mTOR inhib (everolimus): + AI (exemestane) ↑ OS in stage IV
PIK3CA ⊕	PI3K inhib	Alpelisib added to fulvestrant ↑ PFS in metastatic ER/PR ⊕ (*NEJM* 2019;380:1929)
HER2 ⊕ (*Lancet* 2017;389: 2415)	HER2-targeted	Trastuzumab (anti-HER2): 1st-line Rx combined w/ chemo Pertuzumab (prevents HER2 dimerization): + trastuzumab ↑ PFS in adjuvant & metastatic settings (*NEJM* 2017;377:122) Trastuzumab emtansine (mAb linked to chemo): ↓ risk of recurrence/death if residual disease post neoadjuvant Rx (*NEJM* 2019;380:617); preferred 2nd line Rx for metastatic disease
Stage I–IV (above)	Chemo	Neoadjuvant: conserve breast & evaluate Rx efficacy, equivalent OS as adjuvant (*JCO* 2008;26:778) Adjuvant: calc Oncotype DX score for benefit after surgery in ER/PR⊕ (*NEJM* 2018;379:111); use anthracycline ± taxane
PDL-1 ⊕ triple ⊖	Immune	PDL-1 Ab (atezolizumab) added to nab-paclitaxel (microtubule inhibitor): ↑ PFS & OS in stage IV (*NEJM* 2018;379:2108)
BRCA ⊕	PARP inh	Olaparib & talazoparib (*NEJM* 2017;377:523 & 2018;379:753)
Triple ⊖	Ab-drug conjugate	Sacituzumab govitecan: anti-trop-2 linked to chemo ↑ PFS & OS in heavily pre-Rx'd metastatic disease (*NEJM* 2019;380:741)

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 *against* screening if asx (no ↓ in prostate ca-related mort.)

Diagnostic evaluation, staging, and treatment (*NCCN Guidelines* v4.2018)

- Transrectal ultrasound (TRUS) guided biopsy (6–12 cores)
- Multiparametric MRI (± endorectal coil): improves detection (*NEJM* 2018;378:1767)
- Gleason grade and grouping (histology*): Gleason score* = sum of Gleason grades (1 = best, 5 = worst) of 2 most prevalent patterns in bx; correlates w/ prognosis

Risk Stratification & Treatment of Localized Prostate Cancer (*JAMA* 2017;317:2532)

Risk	T stage	Gleason Score & Path	Imaging	Treatment
Very low*	T1c	Gleason ≤6, <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, tumor, long-term tox of Rx
Low*	T1-2a	Gleason score ≤6, *and* PSA <10 ng/mL		
Intermed*	T2b-T2c	Gleason score 7, *or* PSA 10-20 ng/mL	Bone scan & CT A/P	RP *or* EBRT+ADT (4-6 mo)
High Very high	T3a-T4	Gleason score 8–10, *or* PSA >20 ng/mL		EBRT+ADT (18-36 mo) *or* RP

*In asx Pts w/ life expectancy ≤5 y & very low-to-intermediate risk disease, no workup or Rx indicated until sx. *NEJM* 2016;375:1415 & 2017;376:417 & 2018;378:2465 & 2018;379:2319; *JCO* 2016;34:2182.

Treatment of Metastatic Prostate Cancer (*NEJM* 2018;378:645)	
Androgen deprivation therapy (ADT)	Prostate ca requires androgen signaling for growth. ADT backbone of Rx. Med: 1. Luteinizing hormone-releasing hormone (LHRH) agonist (eg, goserelin) ± 1st-gen anti-androgen (nilutamide, bicalutamide), *or* 2. LHRH antagonist (degarelix) Surg: 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; *or* 2. Docetaxel + ADT (↑ OS vs. ADT alone, espec. in high-volume dis.); *or* 3. ADT + abiraterone/pred (↑ OS vs. ADT alone)
Castration-resistant prostate cancer (CRPC) *Always continue ADT*	Def: All met. HSPC eventually becomes CRPC (ie, progression despite castration level of androgens on ADT), due to re-estab. of androgen signaling via other mech. ∴ more potent anti-androgens are active Rx. Rx: New-gen. anti-androgens: abiraterone (biosynth inhib.), enzalutamide (receptor blocker), & apalutamide (receptor blocker) ↑ PFS & OS Chemo: docetaxel & cabazitaxel +pred/dex Bone-active agents: 1. denosumab or zoledronic acid ↓ skeletal-related events (SREs); 2. radium-223 used in bone-only dis, ↓ SREs & ↑ OS Misc: *Homologous recombination-defic. tumors (BRCA1/2, ATM)*: olaparib; *MSI-H/Lynch synd.*: pembrolizumab; *Cancer vaccine*: Sipuleucel-T

NEJM 2010;363:411 & 2013;368:138 & 2013;369:213 & 2014;371:424 & 2015;373:737 & 2015;373:1697 & 2017;377:338 & 352; 2018;378:1408; 2019;381:13; *Lancet* 2016;387:1163; *JCO* 2017; 35:2189.

Prognosis

- PSA level, Gleason grade and age are predictors of metastatic disease
- In surgically treated Pts, 5-y relapse-free survival >90% if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
- Metastatic disease: median survival ~44–57 mo (*NEJM* 2015;373:737)

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.

Genetic Risk Factors

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*, *MLH1*). 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
Inflammatory bowel disease	0.3%/y	↑ risk with ↑ extent and duration of disease	Small bowel, lymphoma, cholan.
MYH-associated polyposis (MAP)	40–100%	Autosomal *recessive*; consider if mult. polyps but ⊖ for FAP	Duodenal, ovarian, bladder, skin

- COX-2 plays a role. ASA rec for 1° prevention if 50–59 y & ≥10% 10-y CRC risk

Screening (*NEJM* 2017;376:149)

- Colonoscopy: preferred; 90% Se for lesions >1 cm. If polyp, re ✔ in 3–5 y. Removal of adenomatous polyps a/w lower CRC mortality (*NEJM* 2012;366:687)
  Average-risk Pts: start at age 50 & repeat q10y preferred
  ↑ *risk Pts*: ⊕ FHx: screen age 40 or 10 y before index dx, then q5y. IBD: 8–10 y after dx, then q1–2y. Suspect familial syndrome: gene counsel, screen 20–25 yo yearly.
- 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).
- Occult blood (FOBT): use 3-card home testing (Se 24%) yearly
- DNA: ↑ Se, ≈ Sp c/w FOBT but less Se than colonoscopy (*NEJM* 2004;351:2704)
- Combo DNA + Hb immunoassay w/ ~90% Se & Sp (*NEJM* 2014;370:1287)

Pathology and genetics (*Cell* 1990;61:759; *Nature* 2014;513:382)

- Adenoma: ↑ risk of malig. if polyps >2.5 cm, villous, or sessile. Adenomas typically observed ~10 y prior to onset of cancer (both sporadic & familial).
- 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%)

Clinical manifestations

- Distal colon: Δ bowel habits, obstruction, colicky abdominal pain, hematochezia
- Proximal colon: iron defic. anemia, dull vague abd pain, liquid stool
- Associated with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis

Staging and treatment (*NCCN Clin Pract Guidelines*; version 1.2019)

- TNM staging: colonoscopy + biopsy/polypectomy + intraoperative + pathologic
- CT scans of chest and abdomen/pelvis for mets
- Baseline CEA: monitor post resection or follow response; *not* for screening
- Chemo options (*Lancet* 2014;383:1490): 5FU/ & leucovorin (LV) foundation. 5FU/LV + oxaliplatin &/or irinotecan (FOLFOX, FOLFIRI, FOLFOXIRI, resp). Capecitabine oral 5FU prodrug. TAS102 (trifluridine + tipiracil) in progressive disease (*NEJM* 2015;372:1909).
- Biologics: *anti-VEGF* (bevacizumab) added to chemo ↑ OS in all subsets of mCRC; *anti-EGFR mAb* (cetuximab or panitumumab) only in unmutated KRAS/NRAS/BRAF (*NEJM* 2013;369:1023); *multikinase inhibitor* (regorafenib) generally in chemo (& biologic) refractory setting (*Lancet* 2013;381:303); anti PD-1 & PD-1 + CTLA-4 in MSI-H met CRC.

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

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
- Mutations in adenoca.: *KRAS* (>90%), *p16* (80–95%), *p53* (50–75%), *SMAD4* (~55%)

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 radiating to back, ↓ weight & appetite
- New-onset atypical DM (25%); migratory thrombophlebitis (Trousseau's syndrome)
- Exam: RUQ/epigastric nontender mass, palpable gallbladder (Courvoisier's sign); hepatomegaly; ascites; L supraclav. node (Virchow's) & palpable rectal shelf (non-spec.)
- Laboratory tests may show ↑ bilirubin, ↑ alk phos, anemia

Diagnostic and staging evaluation (*NCCN Guidelines* v.1.2019)

- Pancreatic protocol CT scan (I^+ w/ arterial & venous phase imaging) or MRI w/ contrast
- *If no lesion seen* → EUS, ERCP, or MRCP
- Biopsy pancreatic lesion via EUS-guided FNA (preferred in potential surgical candidates) or CT-guided (potential risk of seeding) or biopsy of possible metastasis
- ✔ CA19-9 preop (nb, can be ↑ in benign liver/biliary dis.); may be useful to trend postop

Clinical (Radiologic) Staging Non-Metastatic Panc Adenoca (~40% of cases)	
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 used to be recent 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 (± olaparib); gemcita. + nab-paclitaxel (*NEJM* 2013;369:1691)
  Poor PS: gemcitabine; capecitabine; continuous infusion 5-FU
- Palliative and supportive care
  obstructive jaundice or gastric outlet obstruction: endoscopic stenting or surgical bypass
  pain: opiates, celiac plexus neurolysis, XRT; wt loss: enzyme replacement, nutrition c/s

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 (*NEJM* 2004;351:1218; *Oncologist* 2009;14:125)

- 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 → ductal dilation; ? prog to CA (5–20 y); surgery based on age, size, location, dysplasia

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 Pts w/ cirrhosis, chronic HBV or HCV infection)

- 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

Diagnosis

- At least 3-phase contrast-enhanced CT or MRI; no biopsy or PET required for HCC dx
- Of note, only 15% of liver masses are HCC; metastatic dis. from other 1° more common

Clinical manifestations

- Exam: nonspecific, c/w liver dysfxn (eg, hepatomegaly, ascites, jaundice, encephalopathy)
- Labs: as above, c/w liver dysfunction (eg, coagulopathy, low albumin, elevated LFTs)

Treatment (*NEJM* 2019;380:1450)

- If localized disease, goal is cure
  - Resection: typically ablation of HCC; surgery generally only considered for solitary lesions in Pts w/ preserved liver fxn & adequate postop liver volume
  - Liver transplant: 1 lesion ≤5 cm or 3 lesions ≤3 cm, no vasc invasion or mets
- Palliative
  - Transarterial embolization (TAE), ± chemo (TACE) or radioembolization
  - Systemic therapy: kinase inhibitors (lenvatinib, sorafenib), PD-1 inhib (nivolumab) ä OS in advanced HCC (*Lancet* 2017;389:2492 & 2018;391:1163)

ONCOLOGIC EMERGENCIES

FEVER AND NEUTROPENIA (FN) (*NCCN Guidelines* v.1.2019)

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
- Most episodes thought to result from seeding of bloodstream by GI flora
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- GNRs (esp. *P. aeruginosa*) were historically most common
- 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 fluoroquinolone if neutropenic; no mortality Δ (*NEJM* 2005;353:977 & 988)
- Fungal: consider during neutropenia in blood cancers (posa/fluconazole, micafungin)
- Viral: consider during active Rx in blood cancers (acyclovir, famciclovir, valacyclovir)

Diagnostic evaluation

- Exam: skin, oropharynx, lung, perirectal area, surgical & catheter sites; avoid DRE
- Labs: CBC with differential, electrolytes, BUN/Cr, LFTs, U/A
- Micro: blood (peripheral & through each indwelling catheter port), urine, & sputum cx; for localizing s/s → ✔ stool (*C. difficile*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s → CNS, sinus, chest or abdomen/pelvis imaging
- 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.1.2019)

- Empiric regimens should include antipseudomonal activity; consider VRE coverage if ⊕
- Low risk: PO abx or home IV abx may be considered in select Pts;
  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
- Vancomycin if HoTN, PNA, clinically apparent catheter-related or soft-tissue infxn, gram ⊕ BCx, mucositis on quinolone ppx & ceftazidime for viridans strep; d/c when BCx ⊖ × 48 h

Modification to initial antibiotic regimen based on site-specific evaluation

- Mouth/esophageal (ulcer, thrush): consider anaerobic, 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
- Antifungal Rx added for neutropenic fever ≥5 d despite abx. Liposomal amphotericin B, caspofungin, micafungin, anidulafungin, voriconazole, & posaconazole are options.

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

Role of hematopoietic growth factors (*NCCN Guidelines* 2.2018)

- Granulocyte (G-CSF) and granulocyte-macrophage (GM-CSF) colony-stimulating factors can be used as 1° prophylaxis when expected FN incidence >20% or as 2° prophylaxis after FN has occurred in a previous cycle (to maintain dose-intensity for curable tumors). CSFs ↓ rate of FN but have not been shown to affect mortality (*Cochrane* 2014 CD003039).
- Colony-stimulating factors can be considered as adjuvant therapy in high-risk FN Pts

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* Δ*s*), weakness, autonomic dysfunction (urinary retention, ↓ anal sphincter tone), sensory loss

Diagnostic evaluation

- Always take back pain in Pts with solid tumors very seriously
- 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
- Urgent whole-spine MRI (Se 93%, Sp 97%); CT if unable to get MRI

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); rare with solid tumors; rarely due to spontaneous 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
- Rasburicase (recombinant urate oxidase) 0.15 mg/kg or 6-mg fixed dose (except in obese Pts) & aggressive hydration prior to beginning chemotherapy or RT (see below)

Treatment

- *Avoid* IV contrast and NSAIDs; treat hyperK, hyperphos, and symptomatic hypocalcemia
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP for goal 80–100 cc/h
- Consider alkalinization of urine w/ isotonic $NaHCO_3$ to ↑ UA solubility, ↓ urate nephropathy risk (controversial: avoid w/ rasburicase; may cause met. alkalosis or $Ca_3(PO4)_2$ precip.)
- Rasburicase (0.1–0.2 mg/kg) for ↑↑ uric acid esp. in aggressive malig (*JCO* 2003;21:4402; *Acta Haematol* 2006;115:35). *Avoid in G6PD deficiency* b/c causes hemolytic anemia. Consider G6PD testing in Jehovah's witnesses espec. if African American (12% prevalence).
- Hemodialysis may be necessary; early renal consultation for renal insufficiency or ARF

CHEMO AND IMMUNORX 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, ✔ EF pre-Rx
	Tyrosine kinase inhib (TKI)	QTc prolongation, CMP, angina
	Cyclophosphamide	Myopericarditis (esp. in BMT)
	Cisplatin	HypoMg → arrhythmia, ischemia
Pulmonary (*Sem Oncol* 2006;33:98)	Busulfan	~8% fibrosis or DAH; if severe → steroids
	Bleomycin	~10% IPF; d/c drug, Rx: steroids
	TKI (esp. dasatinib)	Pleural effusion
	Cyclophosphamide	Pneumonitis, progressive fibrosis; Rx: d/c
	Bevacizumab	Pulm hemorrhage (esp. NSCLC)
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;" Ppx: vit E (*JCO* 2003;21:927)
	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
Dermatologic	TKI (eg, imatinib)	Dermatitis, can be severe (eg SJS)

Immune checkpoint inhibitors (*ICI; Science* 2018;359:1350)

- mAb against co-inhibitory signaling molecules, which cancers can use to prevent antitumor immunity
- Targets & drugs include
  - Programmed cell death protein 1 (PD-1; T & pro-B cells): nivolumab, pembrolizumab
  - Prog. death-ligand 1 (PD-L1; tumor & immune cells): atezolizumab, avelumab, durvalumab
  - Cytotoxic T-lymphocyte-assoc. protein 4 (CTLA-4; T cells): ipilimumab
- Toxicity (*NEJM* 2018; 378:158): increased w/ combination of CTLA-4 + PD-1/PD-L1

Most commonly colitis (CTLA-4), pneumonitis (PD-1/PD-L1), hepatitis (CTLA-4), dermatitis, hypothyroidism (PD-1) / hypophysitis (CTLA-4)
Rarely: myocarditis (can be fulminant), myositis, myelitis, uveitis, diabetes

- Treatment: *multidisciplinary care*; hold ICI; give steroids, r/o infection. If severe, consider TNF-α inhibitor for colitis, mycophenolic acid for hepatitis, hormones for endocrinopathy

Chimeric antigen receptor (CAR)-T cells (*Science* 2018;359:1350)

- Autologous T cells w/ modified/chimeric receptor for Ag recognition and T cell activation w/o MHC or 2nd co-stim signal.
- CD19 CAR-T cells targeting B-cell malig. most developed: tisagenlecleucel, axicabtagene ciloleucel

CAR- T Toxicity		
Syndrome	Mechanism & Manifestations	Treatment
Cytokine release syndrome (CRS)	Due to proliferating CAR-T. Fevers to shock.	Anti-IL-6 (tocilizumab or siltuximab) + steroids if severe
CAR-T-cell-related encephalopathy syndrome (CRES)	Cerebral edema due to CAR-T in CNS. Delirium, aphasia, seizures, or death.	Steroids, ativan/keppra for seizures.
Hemophagocytic lymphohistiocytosis (HLH)	Rare hyper-inflammation. Ferritin >10k & liver/kidney/lung toxicity.	CRS Rx, etoposide ± intrathecal cytarabine if not improving (*Nat Rev Clin Onc* 2018;15:47)

NOTES

PNEUMONIA

Microbiology of Pneumonia	
Clinical Setting	Etiologies
Community-acquired (CAP) (*NEJM* 2014;371:1619 & 373:415; *Lancet* 2015;386:1097)	*No pathogen identified in 50–60%*, virus alone in ~25%, bacteria alone in ~10%, virus-bacteria coinfection in <5% Viruses: influenza, RSV, hMPV, rhinovirus (unknown significance), parainfluenza virus, coronavirus *S. pneumoniae* (most common bacterial cause) *S. aureus* (esp. postinfluenza) *Mycoplasma*, *Chlamydia* (esp. in young & healthy) *H. influenzae*, *M. catarrhalis* (esp. in COPD) *Legionella* (esp. in elderly, smokers, ↓ immunity, TNF inhibitors) *Klebsiella* & other GNR (esp. in alcoholics & aspiration)
Hospital-acquired or ventilator-assoc. (HAP/VAP)	*S. aureus*, *Pseudo.*, *Klebsiella*, *E. coli, Enterobacter*, *Acinetobacter, Stenotrophomonas.* IV abx w/in 90 d RF for MDR. Viral~ 20% cases (*Chest* 2017; 154:1)
Immunosuppressed	*Above* + PCP, fungi, *Nocardia*, non-TB mycobacteria (NTM), CMV
Aspiration (*NEJM* 2019;380:651)	*Chemical pneumonitis* due to aspiration of gastric contents *Bacterial pneumonia* ≥24–72 h after aspiration event outPt: oral flora (strep, *S. aureus*, anaerobes) inPt or chronically ill: GNR (*Pseudomonas*) and *S. aureus*

Clinical manifestations

- Presenting features are variable and depend upon several host factors (esp. age)
- Classically: fever, cough w/ purulent sputum, consolidation on CXR
- Atypical pathogens (*Legionella, Mycoplasma, Chlamydia*, virus): historically classified as "atypical" b/c they failed to grow on routine cx. Presentation varies from insidious to acute; imaging features vary from interstitial infiltrates to tree-in-bud opacities, to dense consolid.
- Clinical and imaging features do NOT distinguish "typical" from "atypical"
- Aspiration pneumonitis/PNA: can be infectious or non-infectious; may p/w acute inflammatory syndrome (fever, ↑ WBC, etc.) or insidious course
- HAP/VAP: develops w/in 48 h after admission or mechanical ventilation, respectively

Diagnostic studies

- Sputum Gram stain/Cx: reliable if high quality (ie, sputum not spit; <10 squamous cells/lpf) & if PNA should be purulent (>25 PMNs/lpf). Yield ↓ >10 h after abx (*CID* 2014;58:1782).
- Blood cultures (*before antibiotics!*): ⊕ in ~10% of inPts, depending on pathogen
- 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 immunocompromised hosts. Levels harder to interpret in CKD. False ⊕ in cardiac arrest, shock, surgery.
- CXR (PA & lateral; see Radiology inserts) → tap effusions if >5 cm or severe PNA

- Other: S_aO_2 or P_aO_2, arterial pH (if severe), CBC w/ diff, Chem-20; HIV test (if unknown)
- Other micro based on clinical suspicion (paired serologies available for most atypicals):
  Mycoplasma: PCR of throat or sputum/BAL *before* first dose abx
  Legionella urinary Ag (detects *L. pneumophila* L1 serotype, 60–70% of clinical disease)
  S. pneumoniae urinary Ag (Se 70%, Sp >90%)
  MTb: (induced) sputum AFB stain ×3 q ≥8h (w/ ≥1 early morning specimen). Mycobacterial cx (*empiric respiratory isolation while pending*); MTb DNA PCR if smear ⊕.
- Viral testing (DFA or PCR) on nasopharyngeal swab or sputum
- Bronchoscopy: consider if immunosupp., critically ill, failing to respond, VAP, suspected TB or PCP, or inadequate or ⊖ sputum cx. Some pathogens need specific cx media (eg, *Legionella* on BCYE).
- Reasons for failure to improve on initial Rx:
  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 CT (dx tap ± chest tube if effusion present, esp. if loculated)
  Metastatic infection (eg, endocarditis, meningitis, 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)
- CURB-65: confusion, BUN >20, RR >30, BP <90/60, age >65 If score 0–1: Rx as outpt; 2: Rx as inpt; >3 consider ICU (*Thorax* 2013; 58:377)

Treatment (*CID* 2007;44 Suppl:S27; *JAMA* 2016;315:593; *NEJM* 2019;380:651)		
Scenario	Regimen	Special Considerations
CAP (outPt)	Azithro *or* doxy	*Avoid* azithro/doxycycline if >25% resist- ance locally. Use FQ OR B-lactam + azithro/doxy.
CAP (ward)	Resp FQ *or* [3rd-gen ceph + azithro]	Doxycycline can replace azithro Omadacycline ≈ FQ (*NEJM* 2019;380:517)
CAP (ICU)	Resp FQ + [3rd-gen ceph *or* amp-sulbactam]	Only cover MRSA or Pseudomonas if risk factors. If resp FQ contraindic., use azithro
HCAP (incl. VAP)	[Pip-tazo *or* cefepime *or* carbapen.] + [vanco or linezolid]	May add resp FQ (or azithro) when concerned re: atypicals
Aspiration	Treat if abnl CXR (or if need to be intubated or develops septic shock) Amox-clav, amp-sulbactam, FQ, carbapenem If hosp-acquired and concern for multidrug-resistant pathogens: [pip-tazo, cefepime, or carbapenem] + [AG or colistin]	

- Avoid quinolones if suspect TB
- Steroids: not standard practice, but appear to ↓ mortality, mech vent, & ARDS (*Cochrane*

2017;12:CD007720). Consider in severe CAP (F_iO_2 >0.5 + ≥1 of: pH<7.3; lactate >4; CRP >150). *Avoid* in suspected or known influenza. Dosing: pred 50 mg PO ×7 d or methylpred 0.5 mg/kg IV BID ×5 d.

- Duration: for CAP, 5 d if stable & afebrile for 48–72 h; for HAP/VAP, 8 d (*CID* 2017; 65:8)
- When possible, de-escalate abx based on sensitivities

Prognosis

- For low-risk Pts, can discharge immediately after switching to PO abx (*CID* 2007;44:S27)
- CXR resolves in most by 6 wk; consider f/u to r/o underlying malig (esp. if >50 y or smoker)

Prevention

- All persons >65: give PCV13 vaccine followed by PPSV23 vaccine 1 y later. If PPSV23 already received, give PCV13.
- Age 19–64 w/ CHF/CMP, lung disease (including asthma), cirrhosis, DM, EtOH, or smoker: give PPSV23.
- Any age w/ immunocomp., CSF leak, cochlear implant, asplenia: give PCV13 followed by PPSV23 8 wks later.
- Smoking cessation counseling
- VAP precautions: HOB >30°, chlorhexidine rinse; aspiration precautions in high-risk Pts

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VIRAL RESPIRATORY INFECTIONS

URI, bronchitis, bronchiolitis, pneumonia (*Lancet* 2011;377:1264)

Microbiology & epidemiology (http://www.cdc.gov/flu/weekly)

- Typical pathogens
  short, mild = rhinovirus, coronavirus
  longer, more severe or complicated = influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, metapneumovirus. Can be esp. severe in immunosupp.

Diagnosis

- Sx: fever, cough, myalgias, SOB, wheezing, sore throat, rhinorrhea, malaise, confusion
- Respiratory viral panel on nasal washing or sputum/BAL
- Rapid influenza *nasopharyngeal swab* preferred to nasal swab (Se 50–70%, Sp >90%)
- RT-PCR for influenza A/B (>95% Se & Sp)

Treatment (*NEJM* 2017;390:697)

- Influenza: neuraminidase inhib. (oseltamivir, zanamivir), which are effective vs. A & B (↓ sx by ~1 d), but resistance emerging.
- Oseltamivir dosed 75 mg PO bid × 5 d. Must start w/in 48 h of sx for low-risk; for critically ill or immunosupp., start ASAP even if >48 h.
- Baloxavir superior to oseltamivir in ↓ sx & viral load on 1st day of Rx, but risk of resistance emerges w/in Pts (*NEJM* 2018; 379:913)
- RSV: Can consider inhaled ribavirin in immunosupp. (eg, BMT, lung tx); limited adult data

Prevention

- Inactivated influenza vaccine: incl. H1N1. Rec for *all* >6 mo of age and esp. if pregnant, >50 y, immunosupp., or HCW (*MMWR* 2012;61:613)
- Isolation, droplet precautions for inPts strongly recommended
- Prophylaxis for high-risk contacts of confirmed influenza: oseltamivir 75 mg PO daily × 10 d

FUNGAL INFECTIONS

Fungal diagnostics

- Antigen detection
  - 1,3-β-D glucan (Se 77%, Sp 86%): Candida, Aspergillus, Histo, Coccidio, PCP. *Cannot* detect Mucor, Rhizopus, Blasto, Crypto. False ⊕ w/ IVIG, albumin, HD, gauze.
  - Galactomannan (Se 40%, but *improved to 85% w/ BAL*; Sp 89%) detects Aspergillus. Test *serum* if heme malig or HSCT. Do not use for screening or Rx monitoring in solid organ Tx, chronic granulomatous dis., or Rx/ppx for Asperg. (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): serum Ag >90% Se & Sp in invasive infxn, less for pulm only
  - 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: only useful for *Coccidio*
- Biopsy (histopathology): no grinding of tissue if Zygomycetes suspected

Candida species

- Microbiology: normal GI flora; *C. albicans* & nonalbicans spp.
- Risk factors: 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: *never a contaminant!* R/o retinal involvement (ophtho consult in all cases as req ↑ Rx duration); endocarditis rare but serious (esp. w/ nonalbicans & prosthetic valve). May present with erythematous papules or pustules in immunocompromised.
  - Hepatosplenic: occurs w/ neutrophil recovery

Treatment (*CID* 2016;62:409)	
Mucocutaneous	Clotrimazole, nystatin, fluconazole, itraconazole
Candiduria *(if pyuria or sx of infxn)*	Fluconazole or intravesical ampho if sx, severely immunosupp. or will undergo GU procedure
Candidemia w/o	Echinocandin (mica 1st line) *or* fluc *or* ampho; *remove intravascular catheters if possible*.

neutropenia	*Test for azole resist.*
Febrile neutropenia	Echinocandin *or* ampho

Cryptococcus (*CID* 2010;50:291)

- Epidemiology: immunosupp. (esp. AIDS) most susceptible; can occur in healthy host, esp. elderly, EtOH, DM. Consider *C. gattii* (typically in healthy host).
- Clinical manifestations
  - CNS (meningitis): HA, fever, meningismus, ↑ ICP, CN abnl, ± stupor, often subacute. Dx: CSF CrAg, India ink stain, fungal cx. Cell counts vary; serum CrAg >1:8 Se/Sp in AIDS.
  - Other sites: pulm, GU, cutaneous, CNS cryptococcoma. *With any crypto dx, LP all Pts.*
- Treatment
  - CNS: if ↑ ICP, repeat large-volume LPs or temp. lumbar drain; few require VP shunt
  - CNS Rx has induction (ampho ± flucytosine x2 wks), consolidation and maintenance (fluconazole) phases (*NEJM* 2013;368:1291). If r/o CNS disease, then fluconazole. Dosing and duration vary by host.
  - Non-CNS disease (pulm, skin, bone, blood) in HIV ⊖ Pts: consider fluconazole

Histoplasmosis (*CID* 2007;45:807)

- Endemic to central & SE US, but sporadic cases throughout U.S.
- Clinical manifestations
  - Acute: often subclinical, but may see mild to severe PNA ± cavitary & hilar LAN
  - Chronic pulm: ↑ productive cough, wt loss, night sweats, apical infiltrates, cavitation
  - Disseminated (typically in immunosupp.): fever, wt loss, HSM, LAN, oral ulcers, skin lesion, fibrosing mediastinitis, reactive arthritis, pericarditis
- Treatment: itraconazole (monitor levels); ampho ± steroids if severe or immunosupp

Coccidioidomycosis (*CID* 2016;63:112)

- Endemic to SW U.S. (San Joaquin or "Valley" fever)
- Clinical manifestations
  - Acute: 50–67% subclinical; PNA w/ cough, chest pain, fever, arthralgias, *fatigue*
  - Chronic pulm: nodule(s), cavity or progressive fibrocavitary PNA (can be asx or sx)
  - Disseminated (typically in immunosupp.): fever, malaise, diffuse pulmonary process, bone, skin, & meningeal involvement
- Treatment: monitor mild disease closely q3–6mo; for severe disease: fluconazole, itraconazole or amphotericin

Blastomycosis (*CID* 2008;46:1801)

- Endemic to south central, SE, and Midwest U.S.
- Clinical manifestations
  - Acute: 50% subclinical; cough, multilobar PNA; can progress to ARDS
  - Chronic pulm: cough, wt loss, malaise, CT w/ masses & fibronodular infiltrates
  - Disseminated: (25–40% of all but ↑ in immunosupp.): verrucous & ulcerated skin lesions, bone, & GU involvement; CNS rare unless immunosupp.
- Treatment: itraconazole (monitor levels); ampho if severe, disseminated or immunosupp.

Aspergillosis (*CID* 2008;46:327; *NEJM* 2009;360:1870)

- ABPA; hypersensitivity pneumonitis
- Aspergilloma: usually in pre-existing cavity (from TB, etc.); most asx, but can lead to hemoptysis; sputum cx ⊕ in <50%; CT → mobile intracavitary mass with air crescent
  Rx: antifungals w/o benefit; embolization or surgery for persistent hemoptysis
- Necrotizing tracheitis: white necrotic pseudomembranes in Pts w/ AIDS or lung Tx
- Chronic necrotizing: mild immunosupp.; sputum production, fever, wt loss; CT: infiltrate ± nodule ± thick pleura; lung bx → invasion
- Invasive: seen if immunosupp. (neutropenia for >10 d, transplant, high-dose corticosteroids, AIDS); s/s PNA w/ *chest pain & hemoptysis;* CT: nodules, halo sign (cavitates w/ Rx → air crescent sign); dx w/ galactomannan >0.5 (serum or BAL)
- Rx (necrotizing/invasive): voriconazole (or isavuconazole) superior to ampho; ✔ drug levels

Zygomycetes (eg, *Mucor, Rhizopus*)

- Epidemiology: diabetes (70%, esp. DKA), heme malignancy, s/p transplant, chronic steroids, deferoxamine or iron overload, trauma, h/o voriconazole Rx or Ppx
- Clinical: rhinocerebral = periorbital/forehead pain (more extensive than orbital cellulitis), ± fever (may appear nontoxic at first), exophthalmos, ↓ EOM, CNs (V > VII); nasal turbinates ± black eschar but exam can be quite nl. Also, pulm (PNA w/ infarct & necrosis); cutaneous (indurated painful cellulitis ± eschar); GI (necrotic ulcers).
- Treatment: debridement + Rx (ampho, posaconazole, or isavuconazole); high mortality

INFXNS IN IMMUNOSUPPRESSED HOSTS

Overview

- Many Pts have ≥1 risk (eg, DM, ESRD, transplant, extremes of age)
- 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, chronic steroids, posttransplant, DM, ESRD)	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

- Lower: urethritis, cystitis (superficial infection of bladder)
- Upper: pyelonephritis (inflam of renal parenchyma), renal/perinephric abscess, prostatitis
- Uncomplicated: confined to bladder. No upper tract or systemic infection signs.
- Complicated: extends beyond bladder (fever, rigors, malaise, flank pain, CVA tenderness, pelvic/perineal pain in male). Men, those w/ nephrolithiasis, strictures, stents, urinary diversions, immunocompromised, poor controlled DM, are not automatically complicated. Follow closely w/ low threshold to escalate Rx. Pregnant & renal Tx *are* 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, but high risk for yeast (24%), MDR PsA, *Klebs*, *Enterococcus*
- 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: similar to cystitis except *urethral discharge* can be present
- Prostatitis: chronic: similar to cystitis except *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 (intrarenal, perinephric): identical to pyelonephritis w/ *persistent fever despite 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: $\geq 10^5$ CFU/mL in women, $\geq 10^3$ CFU/mL in men. Counts may vary depending on dilution & stage of infxn; interpret in context of sx and host.
  - Pyuria & ⊖ UCx = sterile pyuria → urethritis, nephritis, renal tuberculosis, foreign body

- Catheter-associated: requires (1) s/s (incl atypical) + (2) urine Cx w/ 1 species ≥10^3 coloni from clean urine sample (after replacing Foley). Pyuria alone *not* sufficient to dx UTI in this setting (may be colonization, do not Rx or screen for asx bacteruria).
- Blood cultures: obtain in febrile Pts; consider in complicated UTIs
- For all men w/ UTI, consider prostatitis: ✔ prostate exam; UCx including 1st void, midstream, and ideally prostatic expressage & postprostatic massage UCx
- Abdominal CT: r/o abscess in Pts with pyelo who fail to defervesce after 72 h
- Urologic w/u (renal U/S w/ PVR, abd CT, voiding cystography) if recurrent UTIs in men

Treatment of UTIs (*CID* 2010;50:625; *JAMA* 2014;312:1677)	
Scenario	Empiric Treatment Guidelines (choice can be individualized)
Cystitis *(JAMA* 2014;16:1677)	Uncomp: nitrofurantoin 100 mg × 5 d *or* TMP-SMX DS PO × 3 d *or* fosfomycin (3 g × 1). Refer to dosing guidelines for ↑ Cr. Complicated: FQ or TMP-SMX PO × 7–14 d FQ or TMP-SMX superior to β-lactams (*NEJM* 2012;366:1028) Asx bacteriuria in pregnancy or prior to urologic surgery → abx × 3 d
Catheterized	Await cultures if HD stable & remove (or exchange) catheter
Urethritis	Treat for both *Neisseria* and *Chlamydia* *Neisseria:* CTX 250 mg IM × 1 and 1 g azithro PO × 1 *Chlamydia:* doxy 100 mg PO bid × 7 d *or* azithro 1 g PO × 1 *M. genitalium:* 1 g azithro PO × 1
Prostatitis	FQ or TMP-SMX PO × 14–28 d (acute) or 6–12 wk (chronic)
Pyelonephritis	OutPt: FQ × 7 d *or* TMP-SMX PO × 14 d (*Lancet* 2012;380:452) InPt: CTX *or* aminoglycoside × 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

SOFT TISSUE AND BONE INFECTIONS

SKIN AND SOFT TISSUE INFECTIONS (SSTI; *CID* 2014;59:e10)

Clinical

- Cellulitis: infxn of dermis/sc fat, w/ erythema, edema, warmth, pain (rubor, tumor, calor, dolor)
- Erysipelas: infxn of upper dermis (more superficial than cellulitis), often caused by strep, w/ raised erythematous lesion w/ clear demarcation from normal skin
- Impetigo: infxn of superficial layers, often caused by staph, typically in children, w/ purulent lesions, often on face/extrem, ± bullae, ± gold crust
- Lymphangitis: proximal red streaking ± regional lymphadenopathy
- Toxic shock syndrome can occur w/ staph or strep infxn. Fever, HA, N/V, diarrhea, myalgias, pharyngitis, diffuse rash w/ desquamation, HoTN, shock. BCx may be ⊖.

Microbiology (*CID* 2014;59:e10)

- Primarily strep and staph, including MRSA; may include GNRs in diabetics/immunosupp.
- MRSA (*NEJM* 2005;352:1485 & 2006;355:666) causes up to 75% of purulent skin/soft tissue infxns, depending on local epi (rapidly increasing), often assoc. w/ purulent drainage or exudate. Often TMP-SMX sensitive; variably clindamycin sensitive (may falsely appear susceptible on lab testing, requires confirmation w/ D-test; *NEJM* 2007;357:380).
- Bites: skin (strep, staph) and oral flora (incl 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.	[Pip/tazo *or* Carbapnem] ± Vanco
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
	Erysipelothrix	Rapid onset, risk of endocarditis	PCN/Amox or FQ
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
- Largely clinical diagnosis; BCx low yield (~5–10%) but useful if ⊕
- Aspirate of bulla or pus from furuncle or pustule 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	PCN, diclox, cephalosporin or clinda
		Mod	PCN, CTX, cefazolin or clinda
		Severe	Vanc + pip/tazo (± clinda for anti-toxin)
Yes	*S. aureus* (incl. MRSA) >> β-hemolytic *Strep.*	Mild	I&D ± [clinda or TMP-SMZ] (*NEJM* 2017;376:2545)
		Mod	TMP-SMX or doxy; some data for clinda (*NEJM* 2015;372:1093), but MRSA sensitivity variable
		Severe	Vanc, dapto, linezolid (± clinda for anti-toxin)

Mild: no systemic signs of infection; moderate: systemic signs; severe: SIRS or immunocompromised

- 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. Take pictures & draw margins to track progress.

NECROTIZING SOFT TISSUE INFECTIONS (*NEJM* 2017;377:2253)

Definition
- Includes cellulitis, fasciitis, myositis, myonecrosis (gas gangrene).
- Fulminant tissue destruction, systemic toxicity & high mortality. Surgical emergency.

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
- 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 (fever, hemodynamic instability) ± crepitus
- Rapid progression of clinical signs
- May see bullae, change in skin color (purple-red to blue-gray)
- Pain out of proportion to apparent cellulitis; skin hyperesthetic and later anesthetic

Diagnosis

- Clinical dx sufficient to initiate urgent surgical exploration
- Aspiration of necrotic center; BCx; Gram stain; lactic acid and CK for 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
- Antibiotics: [vancomycin or linezolid] + [pip/tazo or carbapenem] + clinda for toxin inhibition Consider vanc + cefepime + metronidazole + clinda to avoid nephrotoxicity from pip/tazo Consider IVIG for GAS toxic shock; consult ID

DIABETIC FOOT INFECTIONS

Leading cause of DM-related hosp. days & nontrauma amputations

Microbiology and severity

- Mild (superficial ulcer, no involvement of deeper structures, erythema <2 cm): usually *S. aureus* or aerobic streptococci
- Moderate (ulcer with involvement of deeper structures, erythema >2 cm): more likely to be chronic and polymicrobial (PsA, enterococci, *Enterobacter*, anaerobes)
- Severe (moderate + systemic sx infx): anaerobic streptococci, *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). Avoid superficial swabs (*only* helpful if ⊕ for *S. aureus* and mild infxn).
- 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 below).

Treatment (*CID* 2012;54:e132)

- Mild infxn: oral abx. Target skin flora (diclox, cephalexin, or amox/clav); use TMP-SMX or doxy for MRSA.
- Mod/severe infxn: IV abx. Target GPCs (vano, linezolid, or dapto) + GNRs (CTX, levo, or amp/sulb) ± anaerobes (metronidazole or clinda). Add PsA coverage (cefepime or pip-tazo) if: severe, immunocomp, neutropenic, water exposure, burn, puncture, nosocomial.
- 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

OSTEOMYELITIS

Infection of bone due to hematogenous seeding or direct spread from contiguous focus

Microbiology (*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): 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, usually febrile (*NEJM* 2010;362:1022)

Diagnosis (*JAMA* 2008;299:806)

- Goal is to obtain cx data of causative organism to avoid long-term empiric abx
- Bone biopsy or tissue cx obtained surgically or via percutaneous biopsy (aspiration bx Se 30–74%) 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; *JAMA* 2008;299:806)
- Imaging
  - Plain radiographs: normal early in disease; lytic lesions seen after 2–6 wk
  - MRI: most sensitive 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. 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

EPIDURAL ABSCESS

Etiology

- Hematogenous spread ($^2/_3$): skin infection, soft tissue (dental abscess) or endocarditis
- Direct extension (⅓): vertebral osteo, sacral ulcer, spinal anesthesia or surgery, LP

- Risk factors: diabetes, renal failure, alcoholism, IVDU, immunosupp.
- *S. aureus* most common pathogen, increasing incidence of MRSA

Clinical manifestations

- Back pain (unremitting including midline) + often fever ± nerve root or cord signs

Diagnostic studies

- MRI
- Aspiration of abscess fluid for Gram stain & cx or operative Gram stain & cx
- Blood cx (frequently ⊖)

Treatment

- Antibiotics ± 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, may see paraplegia 48–72 h after first signs)

INFECTIONS OF THE NERVOUS SYSTEM

ACUTE BACTERIAL MENINGITIS

Clinical manifestations (*NEJM* 2006;354:44; *Lancet* 2012;380:1684)

- Fever (77%), headache (87%), stiff neck (31%), photosensitivity, Δ MS (69%) (defined as GCS <14), seizures (5%); 2 of 4 (fever, HA, stiff neck, Δ MS) present in 95%
- Presentation may be *atypical* (eg, lethargy w/o fever) in elderly and immunosupp.

Physical exam

- Nuchal rigidity (Se 31%), Kernig's sign (Pt supine, hip flexed at 90°, knee flexed at 90°; ⊕ if passive extension of knee → resistance), Brudzinski's sign (Pt supine and limbs supine; ⊕ if passive neck flexion → involuntary hip and/or knee flexion)
  nb, Kernig's or Brudzinski's signs ⊕ in only ~10% of Pts (*Lancet* 2012;380:1684)
- ± Focal neuro findings (~30%; hemiparesis, aphasia, visual field cuts, CN palsies)
- ± Funduscopic findings: papilledema, absent venous pulsations
- ± HEENT findings: sinus tenderness, clear rhinorrhea (CSF leak)
- ± Skin findings: petechial rash (*N. meningitidis*), genital or oral ulcers (HSV)

Microbiology in Bacterial Meningitis (*NEJM* 2011;364:2016)	
Etiology	Comments
S. pneumoniae (30–60%)	Assess for distant infxn (eg, Osler's triad = meningitis, PNA, IE) Drug-resistant *S. pneumoniae:* ~40% PCN-resistant (even *intermediate* resistance problematic) ~<10% 3rd-gen. cephalosporin-resistant Vaccine may have reduced rate of invasive disease
N. meningitidis (10–35%)	Primarily in those <30 y; may be a/w petechiae or purpura. Deficiencies in terminal complement predispose to recurrent meningococcemia & rarely meningitis. Vaccine rec for all adolescents, college freshmen living in dorm, military recruits, s/p splenectomy or C5-9 deficiency
H. influenzae (<5%)	↓ Incidence in children b/c vaccine. Look for risk factors in adults (eg, CSF leak, neurosurgical procedure, trauma, mastoiditis).
L. monocytogenes (5–10%)	↑ Incid in elderly, alcoholics or Pts w/ cancer, immunosupp. or iron overload. Outbreaks a/w contaminated dairy & raw vegetables. Despite name, a/w *poly-predominant* pleocytosis.
GNRs (1–10%)	Usually health care associated, postprocedure or in elderly or immunosuppressed
Staphylococci (5%)	Seen with indwelling CSF shunt (*S. epidermidis*) or following neurosurgery or head trauma (*S. aureus*)
Mixed infection	Suspect parameningeal focus or CSF leak
Fungal	Seen if immunosuppressed or after neurosurgery

Sequential approach to bacterial meningitis

(1) Stat BCx → antibiotics + corticosteroids (see below)
(2) Consider CT head (if indicated, see below)
(3) LP (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 (*CID* 2004;39:1267)
- Lumbar puncture (*NEJM* 2006;355:e12)
  CSF Gram stain has 30–90% Se; cx 80–90% Se if LP done prior to abx
  opening pressure typically ↑ in bact meningitis; must measure w/ Pt's legs extended
  rule of 2s: CSF WBC >2k, glc <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
- Additional CSF studies based on clinical suspicion: AFB smear & cx, India ink prep, cryptococcal Ag, fungal cx, VDRL, PCR (HSV, VZV, enteroviral), cytology
- 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

Treatment of Bacterial Meningitis (*Lancet* 2012;380:1693)	
Clinical Scenario	Empiric Treatment Guidelines*
Normal adult	Ceftriaxone 2 g IV q12h + vancomycin 15–20 mg/kg IV q12h If >50 y or alcoholic: add ampicillin 2 g IV q4h for *Listeria* β-lactam allergy: substitute cipro 400 mg q8h or aztreonam 2 g q6h for CTX. Substitute TMP/SMX for amp.
Immunosuppressed	Ampicillin + ceftazidime 2 g IV q8h + vancomycin
CSF shunts, recent neurosurgery, or head trauma	Vancomycin + ceftazidime 2 g IV q8h (*NEJM* 2010;362:146)
Corticosteroids: dexamethasone 10 mg IV q6h × 4 d → ↓ neuro disability & mortality by ~50% w/ *S. pneumo* & GCS 8–11. Consider steroids in all bacterial meningitis prior to organism identification. Must start before or w/ 1st dose of abx (*NEJM* 2002;347:1549). Nb, do *not* give steroids in cryptococcal meningitis (*NEJM* 2016;374:542).	
Prophylaxis: rifampin (600 mg PO bid × 2 d) or ciprofloxacin (500 mg PO × 1) or ceftriaxone (250 mg IM × 1) for close	

contacts of Pt w/ *N. meningitidis* meningitis
Precautions: droplet precautions until *N. meningitidis* is r/o

*When possible, organism-directed Rx, guided by sensitivities or local patterns of drug resistance should be used. In mouse model, Cftx + Ab directed against plgR and PECAM (blood–brain barrier receptors that allow *S. Pneumoniae* to enter) → ↓ bacteria in the brain & less inflammation (*J Infect Dis* 2018; 218:476).

Prognosis

- For community-acquired *S. pneumo* mort. 19–37%; 30% have long-term neuro sequelae

ASEPTIC MENINGITIS

Definition

- CSF pleocytosis w/ ⊖ blood & CSF cx; typically lymphocyte predominant
- Less likely to be bacterial, but can be infectious or noninfectious

Etiologies (*Neurology* 2006;66:75)

- Viral: enteroviruses [most common; if CSF ⊖ & PCR not available, test nonsterile sites (eg, nasopharyngeal, rectum)] to help r/o], HIV, HSV (type 2 > 1), VZV, mumps, lymphocytic choriomeningitis virus, encephalitis viruses, adenovirus, polio, CMV, EBV, WNV
- Parameningeal focus of infection (eg, brain abscess, epidural abscess, septic thrombophlebitis of dural venous sinuses or subdural empyema)
- Partially treated bacterial meningitis
- TB, fungal, spirochetal (Lyme, syphilis, leptospirosis), rickettsial, *Coxiella*, *Ehrlichia*
- Medications: TMP/SMX, NSAIDs, IVIG, PCN, INH, lamotrigine
- Systemic illness: SLE, sarcoidosis, Behçet's, Sjögren's syndrome, RA
- Neoplasm: intracranial tumors (or cysts), lymphomatous or carcinomatous meningitis (CSF cytology or flow may be reactive and dx may require meningeal bx)

Empiric treatment

- No abx if suspect viral (cell count <500 w/ >50% lymphs, TP <80–100 mg/dL, normal glc, ⊖ Gram stain, not elderly/immunosupp.); o/w start empiric abx, wait for cx data
- If suspect MTb: antimycobacterial Rx + dexamethasone (*NEJM* 2004;351:1741)
- If suspect fungal: ampho lipid formulation, ± 5-fluorouracil

ENCEPHALITIS (*NEJM* 2018;379:557)

Definition

- Infection of brain parenchyma with evidence of neurologic dysfunction

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: West Nile, Eastern/Western equine, St. Louis, Japanese, Powassan (*NEJM* 2005;353:287): fever, HA, flaccid paralysis, rash. Risk factors for severe renal dis., cancer,

EtOH, DM, HTN (*Am J Trop Med Hyg* 2012;87:179).
- Enteroviruses (coxsackie, echo): viral syndrome; peaks in late summer/early fall
- Others: CMV, EBV, HIV, JC virus (PML), measles, mumps, rubella, rabies, flu, adenovirus
- Non-infectious: autoimmune/paraneoplastic (anti-NMDAR, anti-Hu, anti-Ma2, anti-CRMP5, anti-mGluR5), endocarditis, brain abscess, toxoplasmosis, TB, toxins, vasculitis, Whipple's disease, subdural hematoma, post-infxn demyelination (eg, ADEM), seizure

Clinical manifestations
- Fever, HA, Δ MS, ± seizures and focal neuro findings (latter atypical for viral *meningitis*)

Diagnostic studies (*CID* 2013;57:1114)
- Lumbar puncture: lymphocytic pleocytosis; PCR for HSV (95% Se & Sp at 2–3 d), VZV, CMV, EBV, HIV, JC, adeno/enterovirus, W. Nile (<60% Se); W. Nile CSF IgM 80% Se
- Consider testing for autoimmune etiologies (anti-NMDAR, etc.) in approp. setting
- MRI (CT if unavail.); HSV w/temporal lobe involvement, W. Nile w/ thalamic hyperintensity
- EEG to r/o seizure; findings in encephalitis are nonspecific (temporal lobe focus in HSV)

Treatment
- HSV, VZV: acyclovir 10 mg/kg IV q8h (often empiric Rx given frequency of HSV/VZV)
- CMV: ganciclovir ± foscarnet; supportive care for most other etiologies

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BELL'S PALSY

Definition & etiology
- Acute idiopathic unilat. facial nerve palsy (CN VII), often presumed HSV-1 reactivation

Clinical manifestations
- Unilateral facial muscle weakness, hyperacusis, ↓ taste/lacrimation/salivation

Diagnosis
- Dx of exclusion: r/o brainstem lesion, Lyme (often bilateral), zoster (incl *sine herpete*), HIV/AIDS, sarcoid (often bilateral)

Treatment (*NEJM* 2007;357:1598; *JAMA* 2009;302:985)
- ~80% recover spontaneously by 9 mo (much lower rate in DM)
- Corticosteroids (prednisolone 25 mg PO bid × 10 d) started w/in 72 h of sx onset improve odds of recovery (note: no conclusive data for use in DM, immunosupp.)
- No conclusive data to support the use of acyclovir or valacyclovir

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ZOSTER

Definition & etiology

- Zoster = herpes zoster = shingles: acute, unilat., painful dermatomal skin eruption
- VZV reactivation in peripheral nerve distribution from latency in dorsal root ganglion

Clinical manifestations

- Neuritic pain in a dermatomal distribution, then acute dermatomal eruption of clustered rash (vesicles > papules/pustules > macules) in varying stages of evolution
- Consecutive dermatomes may be seen in all Pts; more widespread in immunosupp.
- Lesions in V1 distribution of facial nerve require urgent ophthalmologic evaluation
- Post-herpetic neuralgia (PHN) = severe pain lasting >90 d after episode; may last mos to y, more frequent w/ ↑ age and delay of antiviral Rx

Diagnosis

- Appearance of rash; DFA is most Se from scrape of newly unroofed vesicle. Tzanck does not distinguish HSV or VZV, cx insensitive for VZV (unlike HSV).

Treatment

- Rx if can initiate w/in 72 h of skin lesions in healthy Pt or at *any time* in immunosupp
- Valacyclovir or famciclovir × 7–14 d, or until lesions fully crusted; acyclovir 10 mg/kg IV q8h if dissem. or high-risk Pt (medically ill, immunosupp., V1 zoster w/ ophthalmic s/s, etc.)
- Prevention: Shingrix approved for Pts >50 y. 2 doses separated by 2–6 mos (97% effective at preventing shingles, also ↓ post-herpetic neuralgia).

BACTEREMIA & ENDOCARDITIS

BACTEREMIA

Etiologies

- 1° infxn due to direct inoculation of the blood, frequently assoc w/ intravascular catheters. Catheter-related bloodstream infection = same org from peripheral cx *and* cath tip cx *or* cx drawn from catheter (*CID* 2009;49:1).
- 2° infxn due to infection in another site (eg, UTI, lung, biliary tree, skin) spreading to blood

Microbiology

- Coag-neg staph 34%, *S. aureus* 10%, enterococci 16%, *Candida* 12%, GNRs 5%
- *Clostridium septicum*, *Bacteroides*, & *S. bovis* a/w colon ca (*Gastro* 2018;155:383)
- Bacteremia with encapsulated organisms (*S. pneumo, Neisseria, Haemophilus*, Group A strep) may indicate 1° immunodeficiency (*Clin Microbiol Infect* 2017;8:576)

Risk factors for true bacteremia (*JAMA* 2012;308:502)

- Fever, shaking chills and poor food consumption (*J Hosp Med* 2017;12:510), SIRS (96% Se), IVDU, comorbidities, immunosupp, indwelling lines
- Organism
  - more likely pathogenic: *S. aureus*, β-hemolytic strep, enterococci, GNR, *S. pneumo, Neisseria*
  - less likely pathogenic: coag-neg staph (~10%), diphtheroids, *Propionibacterium* (~0%)
- Time to growth: <24 h → higher risk, >72 h → lower risk (except for slow-growing organisms such as HACEK group)
- 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

- Obtain BCx prior to abx if possible, ≥2 sets (2 bottles in each set, each w/ 10 cc blood)
- If proven bacteremia, daily surveillance cxs until 48 hrs of ⊖ cxs. May not need for GNRs (*CID* 2017;65:1776).
- If *S. aureus* or *S. lugdunensis* obtain TEE. TTE for high-grade Strep bacteremia. No need for routine echos for GNR bacteremia.

Treatment

- Antibiotics based on Gram stain/culture results; tailor abx to sensitivities
  - empiric therapy for GPC: vanco to cover coag-neg staph and MRSA while awaiting sensi
- *S. aureus* bacteremia: ID consult associated with lower mortality (*CID* 2015;60:1451).

Short-Term Central Venous Catheter-Related Bloodstream Infections (*CID* 2009;49:1)	
S. aureus	Risk of endocarditis in bacteremia: ~25% (*JACC* 1997;30:1072) D/c CVC, TEE to r/o endocarditis; if TEE ⊖ *and* not immunosupp. *and* no intravasc prosthesis, Rx × 2 wk from first ⊖ BCx. If no echo obtained, Rx × 4–6 wk. Preferred abx: MSSA → nafcillin or cefazolin; MRSA → vancomycin
Coag-neg staphylococci	May consider keeping catheter. Catheter retention does not ↓ rate of bacteremia resolution, but a/w ↑ rate of recurrence (*CID* 2009;49:1187). If catheter left in place, Rx × 10–14 d and consider abx or ethanol lock If catheter d/c, Rx × 5–7 d
Enterococcus	D/c catheter & Rx × 7–14 d
GNR	Rx × 7–14 d. Abx based on sensitivities. D/c catheter if *Pseudomonas.*
Fungi	D/c catheter & Rx × 14 d from first ⊖ BCx

- Persistently ⊕ BCx: d/c indwelling catheters, consider metastatic infxn, infected thrombosis or infected prosthetic material (joint, abscess, vascular graft, PPM, etc.)

BACTERIAL ENDOCARDITIS

Definition

- Infection of endothelium of heart (including but not limited to the valves)

Predisposing conditions

- Abnormal valve
  - *High risk:* prior endocarditis, prosthesis, cyanotic congenital heart (unrepaired), VADs, rheumatic heart disease, AoV disease (incl. bicuspid)
  - *Medium risk:* MV disease (including MVP w/ MR or thickened leaflet), HCMP
- Risk of bacteremia: IVDU, indwelling venous catheters, poor dentition, hemodialysis, DM, prosthetic material in heart (eg, pacemaker, ICD, graft)

Modified Duke Criteria	
Major	Minor
• BCx with common endocarditis pathogen (grown in 2 separate cultures) • *Coxiella* serology ≥1:800 • Endocardial involvement, w/ either: echocardiogram w/ vegetation, abscess, or prosthetic dehiscence new valvular regurgitation	• Predisposing condition (see above) • 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
Definitive (ie, highly probable): 2 major *or* 1 major + 3 minor *or* 5 minor criteria Possible: 1 major + 1 minor *or* 3 minor criteria	

Se ~90%, Sp >95%, NPV ≥92% (*CID* 2000;30:633). *Serologic or molecular tests for other known agents of Cx ⊖ endocarditis (see below) not yet included as major criterion, but may help dx.

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 manifestations (*Lancet* 2016;387:882)

- Persistent bacteremia: fever (80–90%), rigors, night sweats, anorexia, wt loss, fatigue
- Valvular or perivalvular infection: CHF, conduction abnormalities
- Septic emboli: stroke, PE (if right-sided), mycotic aneurysm, MI (coronary artery embolism), CNS, kidneys, spleen, joints
- Immune complex phenomena: arthritis, glomerulonephritis, ⊕ RF, ↑ ESR
- *Subacute* (less-virulent pathogens) can p/w fatigue, nonspecific sx in Pts w/o risk factors

Physical exam

- HEENT: Roth spots (retinal hemorrhage + pale center), petechiae (conjunctivae, palate)
- Cardiac: murmur (85%), new valve regurgitation (40–85%) ± thrill (fenestrated valve or ruptured chordae), muffled sounds (PV). *Frequent exams* for Δ murmurs, s/s CHF.
- Extremities
  Janeway lesions (septic emboli → nontender, hemorrhagic macules on palms or soles)
  Osler's nodes (immune complexes → tender nodules on pads of digits)
  proximal nail bed splinter hemorrhages (8–15%); petechiae (33%); clubbing; arthritis
- Δ MS or focal deficits, vertebral tenderness
- Devices: erythema, tenderness or drainage at catheter site, PM/ICD pocket tenderness

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 ⊖.
- ECG (on admission and at regular intervals) to assess for new conduction abnormalities
- Echocardiogram: *TTE in all*. Obtain TEE if (i) TTE nondx (ii) TTE ⊖ but high suspicion, (iii) high-risk (prosthetic valve, prior IE, congenital heart dis.), or (iv) suspect progressive or invasive infxn (eg, persistent bacteremia or fever, new conduction abnl, etc.)

Method	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)

- Addition of PET/CT or MRI helpful to assess for periannular complications in PVE
- Brain/spine imaging necessary in those who develop severe HA, neurologic deficits, meningeal signs. Consider in any patient with left-sided endocarditis (*Circ* 2015;132:1435).
- 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.

Treatment (*Circ* 2015;132:1435)	
Organism	Specific Considerations
Empiric	NVE or PVE >12 mo post-op: Vanc + CTX PVE <12 mo post op: Vanc + CTX + gent
Strep	*S. bovis* a/w colon cancer. Penicillin, Amp, CTX
Staph	• MRSA: vanc or dapto; MSSA: nafcillin or cefazolin • Obtain ID consult • Vanc inferior to beta lactam for long-term MSSA Rx • For PCN allergy w/ MSSA, undergo desensitization • Do not use cefazolin for CNS involvement b/c poor penetration • Rif (+ AG × 2 wk to prevent resistance) should be added in PVE • *S. lugdunensis* is *virulent* and should be treated like *S. aureus*
Enterococcus	Ampicillin + [CTX or gent]; VRE needs linezolid or dapto
GNRs	HACEK: CTX. *Pseudomonas*: 2 anti-Pseudomonal agents [eg, B-lactam + (AG or quinolone)]; consult ID.
Fungi	Liposomal ampho or micafungin. Risk factors: TPN, lines, pacemaker/ICD, prothesis, IVDU. *Ophtho consult for candidemia.*
Early surgical consult for any prosthetic valve infection regardless of organism	

- De-escalate abx to organism-directed therapy once sensitivities return
- Repeat BCx q24–48h until Pt defervesces and BCx ⊖
- Anticoag. controversial; d/c for ≥2 wk if PVE and CNS embolic event. Can continue antiplatelet Rx if no CNS event in all comers, but no proven benefit to adding.
- Monitor for complications of endocarditis (CHF, conduction block, new emboli, etc., which can occur even on abx) and of abx Rx (interstitial nephritis, ARF, neutropenia, etc.)
- Duration of Rx: usually 4–6 wk

  After ≥10d IV abx, if doing well, and depending on organism, Pt, & abx choices, may consider Δ'ing to PO in consultation with ID (*NEJM* 2019;380:415)

  Uncomplicated right-sided NVE or PCN-S strep spp → 2 wk may be comparable

Indications for surgery (*EHJ* 2015;36:3075)

- Severe valvular dysfunction → refractory CHF: *emergent* if refractory cardiogenic shock (ie, despite ICU-level Rx); *urgent* (w/in days) if persistent refractory heart failure; *elective* (w/in wks) if asx severe AI or MR. Consult cardiac surgery early.

- Uncontrolled infxn (typically urgent surgery w/in days): periannular abscess (10–40% NV 60–100% PVE), heart block, fistula, worsening conduction, PVE w/ dehiscence, ↑ veg. size or persistent sepsis (eg, ⊕ BCx after ~1 wk of appropriate IV abx & no drainable metastatic focus or other identifiable cause; complicated if due to septic emboli to lung)
- Organism: consider surgery for *S. aureus*, fungal or multiRx-resistant organisms
- Prosthetic valve: dysfunction or dehiscence
- Systemic embolism (20–50%): risk 4.8/1000 Pt days in 1st wk, 1.7/1000 thereafter. Urgent surgery if L-sided w/ >10 mm veg & severe AI/MR (*NEJM* 2012;366:2466) or if recurrent emboli, embolism & >10 mm veg, or >15 mm veg despite approp. abx.
- Cerebral emboli no longer considered contraindic to surgery unless severe stroke or hemorrhage (then ideally wait 1 mo) (*Stroke* 2006;37:2094)

Prognosis

- NVE: non-IVDU *S. aureus* → 30–45% mortality; IVDU *S. aureus* (often right-sided) → 10–15% mortality; SBE → 10–15% mortality
- PVE → 23% mortality

Endocarditis Prophylaxis (*Circ* 2007;116:1736)	
Cardiac conditions*	Prosthetic valve; previous NVE; 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, HCMP)
Procedures*	Dental: manipulation of gingival tissue or periapical region of teeth or perf oral mucosa (eg, extraction, periodontal, implant, root canal, cleaning) Respiratory: incision or biopsy of respiratory mucosa (no prophylaxis for GI or GU procedures)
Regimens	Oral: amoxicillin 2 g 30–60 min before Unable to take PO: amp 2 g IM/IV or cefazolin or Cftx 1 g IM/IV PCN-allergic: clinda 600 mg PO/IM/IV

*Pts should meet both indications (high-risk condition & high-risk procedure) to qualify for Ppx

TUBERCULOSIS

Epidemiology

- U.S.: 10–15 million infected (15× ↑ risk if foreign-born or minority); worldwide: ~2 billion
- Multidrug-resistant (MDR) TB: resistant to INH & rifampin. Can occur as 1° infxn.
- Extensively drug-resistant (XDR) TB resistant to INH, RIF, FQ, and injectables
- Risk factors (*NEJM* 2011;364:1441)
  - *Acquisition:* immigrant from high-prevalence area, homeless, IVDU or medically underserved, resident or worker in jail or long-term facility, healthcare worker, close contact to Pt w/ active TB
  - *Reactivation:* risk is 5% in first 2 yr, 5–10% over lifetime, but higher if HIV ⊕, immunosupp. incl. biologics, CKD (HD), uncontrolled DM, cancer, transplant, malnourished, underweight, smoker, IVDU, alcohol

Microbiology & natural history

- Transmission of *Mycobacterium tuberculosis* via small-particle aerosols (droplet nuclei)
- 90% of infected normal hosts will never develop clinically evident disease
- Localized disease: healing & calcification *or* progressive 1° TB (at site of infection)
- Hematogenous spread: latent infection ± reactivation TB *or* progressive dissem. TB

Screening for latent TB

- Whom to screen: high-prevalence and high-risk populations (HIV ⊕ Pts should be tested as part of initial evaluation and annually thereafter)
- How to screen
- IFN-γ release assays (IGRA): Ag-stimulated IFN-γ release from patient's T-cells. Preferred to PPD due to ↑ Sp in BCG vaccine Pts (*Annals* 2008;149:177).
- Tuberculin skin test (TST or also known as PPD): inject purified protein interdermally then examine for wheal 48–72 hrs later. Interpret based on max diameter of induration.

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 w/ apical fibrosis c/w TB
>10 mm	All other high-risk or high-prevalence populations Recent conversion (↑ in induration by >10 mm in last 2 y)
>15 mm	Everyone else
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	↑ induration 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.

- Neither screening test rules in/out active TB. Use both IGRA & PPD combined to ↑ Se (to 80–90%). Relies on host immune system, therefore limited Se in immunocompromised (*J Clin Epi* 2010;63:257; *CID* 2011;52:1031).

Clinical manifestations (*Lancet* 2016;387:1211)

- Primary TB pneumonia: middle or lower lobe consolidation, ± effusion, ± cavitation
- TB pleurisy: can occur w/ primary or reactivation. Due to breakdown of granuloma w/ spilling of contents into pleural cavity and local inflammation. Pulmonary effusion ± pericardial and peritoneal effusions (tuberculous polyserositis).
- Reactivation TB pulmonary disease: apical infiltrate ± volume loss ± cavitation
- Miliary TB: acute or insidious; due to hematogenous dissemination; usually in immunosupp, DM, EtOH, elderly or malnourished. Constitutional sx (fever, night sweats, weight loss) usually prominent. Pulm disease w/ millet seed-like lesions (2–4 mm) on CXR or chest CT (latter more Se) present in 60–80% of those w/ miliary TB.
- Extrapulmonary TB: lymphadenitis, pericarditis, peritonitis, meningitis, nephritis ± sterile pyuria, osteomyelitis (vertebral = Pott's disease), hepatitis, splenitis, cutaneous, arthritis
- TB and HIV: HIV ⊕ at ↑ risk infxn, progressive 1° infxn & reactivation. Risk of progression from infxn to disease >8–10%/y, higher risk with ↓ CD4. Reinfection (also w/ MDR) significant, esp. in hyperendemic areas.

Diagnostic studies for active TB (*high index of suspicion is key!*)

- AFB smear (rapid dx) and culture (↑ Se & allows sensitivity testing) of sputum, BAL, pleura, etc.; *avoid FQ* if considering TB (can compromise dx yield)
- Gene Xpert PCR (rapid dx) can also detect rifampin resistance; validated on nonbloody sputum only. Sp 98% & Se 74% independent of HIV status (*AJRCCM* 2014;189;1426).
- PCR: 94–97% Se c/w smear; 40–77% Se c/w culture (*JAMA* 2009;301:1014)
- CXR: classically fibrocavitary apical disease in reactivation vs. middle & lower lobe consolidation in 1° TB but distinction imperfect. HIV ⊕ assoc. w/ nonapical disease regardless of timing (*JAMA* 2005;293:2740).
- Adenosine deaminase testing: useful in extrapulmonary sites; best validated for ascites

Treatment of latent TB

- Treat Pts who are ⊕ based on guidelines or any exposed HIV ⊕ or immunocompromised Pt (*NEJM* 2015;372:2127; *Eur Respir J* 2015;46:1563)
- R/o active disease in any Pt w/ suggestive s/s before starting INH (cough, fever, nightsweats), CXR (though may be nl in immunosupp.)

Scenario	Prophylaxis Regimen
PPD/IGRA ⊕ (regardless of HIV status), or contact case INH resistant	1st line: Rifampin × 4 mo (non-inferior to INH, greater adherence and lower hepatotoxicity) (*NEJM* 2018;5:440). *Alternative:* [INH 5 mg/kg + vitamin B6 × 9 mo] *or* [INH + Rifapentine weekly × 12 wk]
Contact case known or suspected to have MDR TB	No proven regimen: ? PZA + EMB, ? PZA + FQ

(INH, isoniazid; RIF, rifampin; PZA, pyrazinamide; EMB, ethambutol; FQ, fluoroquinolone)

- ✔ LFTs monthly if receiving INH (risk ↑ w/ age; *Chest* 2005;128:116): if 5× ULN *or* sx → stop TB meds & re-eval

Patient isolation

- Decision based on likelihood. 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, AFB smear neg ×3, or TB treated for 2 wk & AFB neg

Treatment of active tuberculosis (*NEJM* 2015;373:2149; *Lancet* 2016;387:1211)

- Treatment requires several drugs to prevent resistance (see below)
- Suspect MDR TB if prior TB Rx, travel to area w/ ↑ rates of MDR (India, China, Russia, South Africa), exposure to person w/ likely MDR-TB, poor Rx adherence, INH resis. in community ≥4% (includes most of U.S.), extrapulm. TB, HIV ⊕ (*NEJM* 2008;359:636)
- Screen for HIV. If ⊕ → consult ID re: timing of concurrent HIV Rx
- "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 ARVs, Pts taken off immunosuppression). *Must r/o Rx failure* (repeat Cx, imaging, etc.).

Antituberculous Medications		
Drug	Dose	Adverse Effects*
Isoniazid (INH)	300 mg PO qd	Hepatitis, periph neuropathy (↓ risk by suppl. vit B_6), drug-induced lupus
Rifampin (RIF)	600 mg PO qd	Orange tint of body fluids, GI upset, hepatitis, hypersensitivity, fever, drug interactions, avoid EtOH
Pyrazinamide (PZA)	25 mg/kg PO qd	Hepatitis, hyperuricemia, arthritis
Ethambutol (EMB)	15–25 mg/kg PO qd	Optic neuritis
Streptomycin (SM)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Amikacin (AMK)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Quinolone (moxifloxacin)	400 mg PO qd	GI upset, tendinopathy, ↑ QTc

*Risk of hepatitis ↑ w/ pre-existing liver disease. Consult ID if mod to severe liver disease, and consider holding/replacing PZA or INH.

Scenario	Antituberculous Treatment Regimens
Pulmonary TB ≥4% INH-resist. in community (includes most of U.S.)	INH + RIF + PZA + (EMB) until suscept. known If *sensitive* to INH & RIF → INH + RIF + PZA × 2 mo, *then* → INH + RIF × 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*

Individualize duration based on host, disease form, and rate of clinical/microbiologic improvement

HIV/AIDS

Definition & Clinical Manifestations

- Acute HIV: mono-like syndrome → rash, lymphadenopathy, fever, oral ulcers, pharyngitis, myalgias, diarrhea. Presents ~2–6 wk after infxn.
- AIDS: HIV + CD4 <200/mm^3 *or* AIDS-defining opportunistic infection (OI) or malignancy

Epidemiology

- ~1 million Americans living w/ HIV (1 in 8 unaware); ~36 million worldwide
- Highest at risk are men who have sex with men (MSM) and African Americans
- Routes: sexual (risk is 0.1–1% per sex act w/o ARV), IVDU, transfusions, needlesticks (0.3%), vertical (15–40% w/o ARV)

Prophylaxis (*NEJM* 2015;373:2237; *Lancet* 2016;387:53; *J Infect Dis* 2018;218:16)

- Preexposure (PrEP): TDF/FTC qd effective & safe in high-risk, adherent populations. Use in heterosexuals or MSM w/: (1) serodiscordant partner, (2) inconsistent condom use, or (3) STI w/in 6 mo; or IVDU w/ equipment sharing or high-risk for HIV (*JAMA* 2019;321:2203). On-demand PrEP effective option for MSM (44–86% ↓). ✔ renal fxn, STIs, & HIV q3 mo.
- Postexposure (PEP): present <72 hr after high-risk exposure from HIV+ source (case-by-case decision if HIV status unknown). Test baseline HIV, STIs, HBV, HCV. Rx: 2 NRTIs (usually TDF/FTC) + RAL or DTG × 4 wk. Consider initiating PrEP.
- Treatment is prevention: early Rx of HIV ⊕ Pt prevents transmission to partners (*NEJM* 2016;375:830). Risk of transmission w/ unprotected sex w/ undetectable viral load is ~0% (*JAMA* 2016;316:171; *Lancet HIV* 2018;5:e438).

Screening and Diagnosis

- Screen all ages 13–64 once in lifetime & every pregnancy. High risk (IVDU, sex workers, MSM >1 partner) screen annually (*JAMA* 2018;320:379).
- 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 in plasma; assay range is 20–10 million copies/mL; ~2% false ⊕, but usually low # copies; in contrast, should be very 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 (*JAMA* 2018;320:379)

- Document HIV infection; counsel re: treatment options, adherence, & disclosure
- Lab evaluation: CD4 count, HIV VL & genotype, CBC w/ diff., Cr, lytes, LFTs, A1c, & fasting lipids; PPD or IGRA, toxo, syphilis, *Chlamydia* & gonorrhea screens, Hep A/B/C serologies; G6PD (if PCP ppx), Pap smear/anal pap in ♀/♂; ± CMV IgG, baseline CXR

- Initiate ARV early (same day prior to labs/genotype and w/ *guidance from HIV specialist*) regardless of CD4 level because ↓ mortality (*NEJM* 2015;373:795)
- Regimens include: 2 NRTI (eg, TAF + FTC) + *either* int. inhib 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 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/riton. (LPV/r; Kaletra) ritonavir (RTV; Norvir)	*Class:* GI intol; hepatotoxicity; inhibit CYP450 (caution w/ statins); T2DM; truncal obesity; hyperlipid (less w/ ATV); MI (*NEJM* 2007;356:1723) ATV: crystalluria → nephrolithiasis DRV: rash (10%); possible sulfa cross-reactivity
FI	enfuvirtide (T20; Fuzeon)	Injection site reaction
EI	maraviroc (MVC; Selzentry)	Dizziness, hepatotoxicity; ✔ CCR5 tropism assay
II	bictegravir (BIC; Biktarvy) dolutegravir (DTG; Tivicay) elvitegravir (EVG; Vitekta) raltegravir (RAL; Isentress)	Class: diarrhea & other GI intol; ↑ CPK DTG ↑ metformin levels; monitor glc DTG a/w neural tube defects
B*	ritonavir (r); cobicistat (COBI)	Drug interactions (inhibit CYP450)

NRTI, nucleoside/tide reverse transcriptase inhibitor; NNRTI, nonnucleoside RTI; PI, protease inhibitor; FI, fusion inhibitor; EI, entry inhibitor (CCR5 antagonist); II, integrase inhibitor; *booster to give w/ other ARVs; several multiclass combination 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 wk of ARVs ↓ risk for TB-associated IRIS (*NEJM* 2018;379:1915).

Approach to previously established HIV ⊕ Pt

- H&P (mucocutaneous, neurocognitive, OIs, malignancies, STDs); meds
- Review ARVs (past and current); if any must be interrupted, *stop all* to ↓ risk of resistance
- Failing regimen = unable to achieve undetectable viral load, ↑ viral load, ↓ CD4 count or clinical deterioration (with detectable viral load consider genotypic or phenotypic assay)

OI Prophylaxis (https://aidsinfo.nih.gov/guidelines & *JAMA* 2018;320:379)		
OI	Indication	1° Prophylaxis
Tuberculosis	⊕ PPD (≥5 mm)/IGRA *or* high-risk exposure	Rifampin × 4 mo (noninferior to INH, but ✔ for drug interactions) *or* INH + vit B_6 × 9 mo
Pneumocystis jiroveci (PCP)	CD4 <200/mm^3 *or* CD4 <14% *or* thrush	TMP-SMX DS or SS qd or DS tiw *or* dapsone 100 mg qd *or* atovaquone 1500 mg qd *or* pentamidine 300 mg inh q4wk
Toxoplasmosis	CD4 <100/mm^3 *and* ⊕ *Toxo* IgG	TMP-SMX DS qd *or* dapsone 50 mg qd + pyrimeth. 50 mg qwk + leucovorin 25 qwk

MAC	Ppx no longer rec. if effective ART initiated
Stop 1° prophylaxis if CD4 >initiation threshold >3–6 mo on ARVs	
Stop 2° prophylaxis (maintenance therapy for prior OI; drugs and doses differ by OI) if clinical resolution or stabilization and CD4 thresholds have been exceeded × 3–6 mo	

COMPLICATIONS OF HIV/AIDS

CD4 Count	Complications
Any CD4 count	Influenza, HAV, HBV, HPV, VZV, *S. pneumo*, TB
<500	Constitutional sx; noninfectious disease (CVD, bone, oncologic) Mucocutaneous: Kaposi's sarcoma; seborrheic dermatitis; oral hairy leukoplakia; lymphoma; candidiasis; HSV Recurrent bacterial infections, TB (pulm and extrapulm); neurosyphilis
<200	*PCP, Toxo, Bartonella, Crypto, Histo* (if endemic), *Coccidio*
<50–100	CMV, MAC, CNS lymphoma, PML, death (<50 is medical emergency) Invasive aspergillosis, bacillary angiomatosis (dissem. *Bartonella*)

Fever

- 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, chem, LFTs, BCx, CXR, UA, mycobact. & fungal cx, ✔ meds, ? ✔ chest & abd CT
  - CD4 <100–200 → serum crypto Ag, LP, urinary *Histo* Ag, CMV PCR
  - pulmonary s/s → CXR; ABG; sputum for bacterial cx, PCP, 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

Cutaneous

- Seborrheic dermatitis; eosinophilic folliculitis; warts (HPV); HSV & VZV; MRSA skin & soft tissue infxns; scabies; candidiasis; eczema; prurigo nodularis; psoriasis; drug eruption; subungual onychomycosis (at nail bed)
- 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

Ophthalmologic

- CMV retinitis (CD4 usu <50); Rx: gan- or valganciclovir, ganciclovir implant or cidofovir
- HZV, VZV, syphilis (any CD4 count, *treat as neurosyphilis*) or *Toxo:* CD4 usually <100

Oral

- Aphthous ulcers; KS; thrush (oral candidiasis): curd-like patches typically w/ burning or pain; oral hairy leukoplakia: painless proliferation of papillae w/ adherent white

coating usually on lateral tongue, caused by EBV but not precancerous

Endocrine/metabolic

- Hypogonadism; adrenal insufficiency (CMV, MAC, TB, HIV or med-related); wasting osteopenia/porosis (at all CD4 counts); fragility fractures
- Lipodystrophy: central obesity, peripheral lipoatrophy, dyslipidemia, hyperglycemia

Cardiovascular (*JACC* 2013;61:511)

- CAD (HIV incr risk indep of classic risk fx); dilated CMP; pulm HTN; pericarditis/effusion
- Higher rates of VTE, stroke, worse outcomes after MI (*JAIDS* 2012;60:351; *Circ* 2013;127:1767)

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, non-TB mycobacteria, aspergillus, other fungal, bacterial (incl MRSA, *Nocardia, Rhodococcus*)
Pleural effusion	TB, bacterial or fungal, KS, lymphoma

- *Pneumocystis jiroveci* (PCP) pneumonia (CD4 <200) (*NEJM* 1990;323:1444)
  constitutional sx, fever, night sweats, dyspnea on exertion, nonproductive 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 are 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), 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, Entamoeba, etc.); *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)

- Anemia: ACD, BM infiltration by infxn or tumor, drug toxicity, hemolysis
- Leukopenia; thrombocytopenia (bone marrow involvement, ITP); infection, ↑ globulin

- Non-Hodgkin lymphoma: ↑ frequency with any CD4 count, but incidence ↑ with ↓ CD4
- 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 (a/w HBV/HCV), gastric

Neurologic

- Meningitis *Crypto* (dx w/ CSF; serum CrAg 90% Se), bact (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 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

- AIDS dementia complex: memory loss, gait disorder, spasticity (usually at CD4 ↓)
- Depression: ↑ rates of suicide/depression
- Myelopathy: infxn (CMV, HSV), cord compression (epidural abscess, lymphoma)
- Peripheral neuropathy: meds, HIV, CMV, demyelinating

Disseminated *Mycobacterium avium* complex (DMAC)

- Fever, night sweats, wt loss, HSM, diarrhea, pancytopenia. Enteritis and mesenteric lymphadenitis if CD4 <150, bacillemia if <50. Rx: clarithro/azithro + ethambutol ± rifabutin.

Cytomegalovirus (CMV)

- Usually reactivation with ↓ CD4. Retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis. CMV VL may be ⊖. 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	<10%	++	+	+++	+++
Ehrlichiosis (HME)	25%: maculopapular, petechiae	+++	++	++++	++++
Anaplasmosis (HGA)	<5%	+++	+	+++	++++
Babesia	–	+	++++ (lysis)	++++	+++

–: <15%, +: 15–25%, ++: 25–50%, +++: 50–75%, ++++: >75%

LYME DISEASE

Microbiology

- Spirochete *B. burgdorferi* (consider coinfection w/ *Anaplasma, Babesia, B. miyamotoi*)
- Transmitted by ticks (*Ixodes*, deer tick); infxn usually requires tick attached >36–48 h

Epidemiology

- Most common vector-borne illness in U.S.; peak incidence in summer (May–Aug)
- Majority of cases in MN, WI, New England, northern mid-Atlantic, northern CA
- Humans contact ticks usually in fields with low brush near wooded areas

Clinical Manifestations	
Stage	Manifestations
Stage 1 (early localized) 3–30 d after bite	Pathogenesis: local effects of spirochete. *General:* flu-like illness *Derm* (~80%): erythema migrans (EM) = erythematous patches w/ central clearing, ~6–38 cm in size & often not "annular"
Stage 2 (early dissem.) wks to mos after bite	Pathogenesis: spirochetemia and immune response *General:* fatigue, malaise, LAN, HA; fever uncommon *Derm:* multiple (1–100) annular lesions ≈ EM *Rheum* (~10%): migratory arthralgias (knee & hip) & myalgias *Neurologic* (~15%): cranial neuropathies (esp. CN VII), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis *Cardiac* (~8%): conduction block, myopericarditis
Stage 3 (late persistent) mos to yrs after bite	Pathogenesis: immune response *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

(*CID* 2006;43:1089; *Lancet* 2012;379:461; *NEJM* 2014;370:1724)

Diagnostic studies

- *EM present:* confirmed in appropriate geographic setting; no need for testing (likely sero ⊖)
- *EM absent* (ie, stage 2 or 3 disease): 2-step testing
  1st step: ELISA screen (false ⊕ common, false ⊖ w/ early abx or <6 wk after tick bite)
  2nd step: if ⊕ ELISA, confirm with Western blot (↑ Sp)
- ✔ CSF if suspected neuro disease: ⊕ CSF Ab if $(IgG_{CSF}/IgG_{serum})/(alb_{CSF}/alb_{serum}) > 1$

Treatment (*NEJM* 2014;370:1724; *JAMA* 2016;315:1767 & 2461)

- Prophylaxis: tick avoidance, protective clothing, tick ✔ q24h, DEET
  Chemoprophylaxis w/ doxycycline 200 mg PO × 1 *only* if *all* of the following:
  1. *Ixodes scapularis* tick attached ≥36 h
  2. Local Lyme carriage in ticks ≥20% (peak season in endemic area)
  3. Abx can be given w/in ≤72 h of tick bite
  4. No contraindication to doxy (eg, preg, allergy, age <8 y)

  If criteria 1–4 met, NNT to prevent 1 case ~50; w/o doxy, risk of Lyme after tick bite 1–3%
  Regardless of Ppx, monitor for fever, flu-like sx, rash (erythema migrans) × 30 d
- Abx (ISDA 2019): *if* clin. manifest. *and* ⊕ serology in endemic area (unless isol. EM)
  Isolated EM: doxy 100 mg PO bid × 10 d (altern: cefurox or amox × 14 d or azithro × 7 d)
  Arthritis: doxy 100 mg PO bid × 28 d (alternative: cefurox or amox × 28 d)
  Carditis or meningitis: CTX 2 g IV q24h or doxy 100 mg PO bid (IV vs. PO depends on severity, clinical improvement) × 2–3 wk
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias

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BABESIOSIS

Microbiology & epidemiology

- Infxn w/ parasite *Babesia microti* (U.S.), transmitted by *Ixodes* ticks; also a/w transfusion
- Europe & U.S. (more commonly MN, WI, coastal areas & islands of MA, NY, NJ, RI, CT)
- Peak incidence June–August (*MMWR* 2012;61:505)

Clinical manifestations (typically 1–4 wk after tick exposure; <9 wk if transfusion)

- Range from asx to fevers, sweats, myalgias, & HA to severe hemolytic anemia, hemoglobinuria, & death (degree of parasitemia correlates roughly with severity)
- Risk factors for severe disease: asplenia, ↓ cellular immunity, TNF inhib, ↑ age, pregnancy

Diagnosis (*NEJM* 2012;366:2397)

- Clinical syndrome + blood smear w/ intraerythrocytic parasites
- Repeat smears (q12–24h) if sx persist despite negative initial smear
- PCR serum if smear ⊖ and high clinical suspicion, serum IgG can help but some false ⊕

Treatment (*JAMA* 2016;315:1767)

- Atovaquone & azithro for mild/mod illness; call ID if severe (azithro/atovaquone/clinda)
- Duration depends on host; immunosupp Pts often need longer Rx
- Exchange transfusion if parasitemia >10%, severe hemolysis or SIRS

EHRLICHIOSIS/ANAPLASMOSIS

Microbiology

- Gram ⊖ obligate intracellular bacterium; human monocytic ehrlichiosis (*E. chaffeensis*, HME); human granulocytic anaplasmosis (*A. phagocytophilum*, HGA)
- Transmission: HME by *Amblyomma americanum*, *Dermacentor variabilis;* HGA by *Ixodes*

Epidemiology

- HGA cases typically in New Engl, 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 wk of tick exposure)

- Asx or nonspecific: fever, myalgias, malaise, HA, cough, dyspnea; onset often acute
- Laboratory: leukopenia, thrombocytopenia, ↑ aminotransferases, LDH, Aφ, renal insuff
- More severe disease can occur with bacterial superinfection in HGA

Diagnosis

- Acute: intraleukocytic morulae on peripheral blood smear (rare); PCR; later: serology

Treatment (*JAMA* 2016;315:1767)

- Start Rx based on clinical suspicion; definitive dx requires PCR (may not detect all spp.)
- Doxycycline 100 mg PO bid (often × 10 d); should defervesce in ≤48 h, else reconsider dx

ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

Microbiology & epidemiology

- Infection with *Rickettsia rickettsii* (Gram ⊖ obligate intracellular bacterium)
- Transmitted by *Dermacentor variabilis, D. andersoni* (dog tick); peak in spring/early summer
- Occurs in mid-Atl, SE, Midwest, New Engl, NW, Canada, Mexico, Central & S. America
- Consider other rickettsial spp.: *R. akari* (Rickettsial pox), *R. conorii* (Mediterranean spotted fever), *R. africae* (African tick bite fever), *R. felis* (Flea rickettsiosis)

Clinical manifestations (typically w/in 1 wk of tick exposure)

- Nonspecific: fever, HA, ΔMS, myalgias, N/V, occasionally abdominal pain
- Rash (2–5 d *after* onset) = *centripetal:* starts on ankles and wrists → trunk, palms, & soles; progresses from macular to maculopapular to petechial
- Severe cases → vasculitis, hypoperfusion/shock, end-organ damage; more likely in elderly
- Up to 75% mortality if untreated, 5–10% even w/ Rx (esp. if delayed) (*NEJM* 2005;353:551)

Diagnosis

- Usually a clinical dx; *requires early clinical suspicion* given risks of delayed Rx
- Acute illness dx by skin bx for rickettsiae (Se ~70%); 7–10 d after sx onset, serology ⊕

Treatment

- Doxycycline 100 mg PO bid *(give empirically if clinical suspicion)*

TULAREMIA

Microbiology

- Infxn w/ *Francisella tularensis* via contact w/ animal tissue, aerosol, tick/insect bite

Clinical manifestations (typically w/in 2–10 d of exposure)

- Acute onset of fever, HA, nausea; ulcer w/ black eschar at site of entry; LAN; PNA

Diagnosis & treatment

- Hazardous and difficult to Cx, alert lab. Serology ⊕ by wk 2. PCR by research lab.
- Streptomycin or gentamicin × 7–14 d; empiric Rx may be needed given challenges in dx

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); less likely to mount fever if: chronic renal or liver disease, extremes of age, protein calorie malnutrition, immunosuppression, steroid use
- Exposures: travel, occupation or hobbies, animals and insects, sexual contacts, TB; consider age, geography, season and incubation time in relation to exposures
- Physical exam: complete exam w/ focus on mucous membranes & conjunctiva; cardiac murmurs; liver and spleen size; skin, genitals, lymph nodes, & joints; complete neuro exam incl cranial nerves and meningeal signs
- If rash: location, duration, progression/Δ in appearance, was prodrome present

FEVER OF UNKNOWN ORIGIN (FUO)

Definition & etiologies

- 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 (*Archives* 2003;163:545; *Medicine* 2007;86:26)
Infection ~30%	Tuberculosis: disseminated or extrapulm disease can have normal CXR, PPD, sputum AFB; bx (lung, liver, bone marrow) for granulomas has 80–90% yield in miliary disease Abscess: dental, paraspinal, hepatic, splenic, subphrenic, pancreatic, perinephric, pelvic, prostatic abscess or prostatitis, appendicitis Endocarditis: consider HACEK orgs, *Bartonella*, *Legionella*, *Coxiella* Osteomyelitis, sinusitis, Lyme, 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%	Drugs, 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

Workup

- Focus by H&P, incl: CBC w/ diff, lytes, BUN, Cr, LFTs, ESR, CRP, ANA, RF, cryoglobulin, LDH, CK, SPEP, 3 sets BCx (off of abx), U/A, UCx, PPD or IGRA, HIV Ab ± PCR, heterophile Ab (EBV serologies if), CMV antigen, Hep serologies if LFTs abnl
- Stop unnecessary meds (only 20% with a med cause have eos or rash), reassess 1–3 wk
- Imaging: CXR, chest & abd CT, consider tagged WBC, gallium scan, PET, TTE, LENI
- Consider temporal artery bx if ↑ ESR and age >60, particularly if other s/s
- Consider BM aspirate & bx (esp. if signs of marrow infiltration) or liver bx (esp. if ↑ Aϕ): even w/o localizing s/s, yield may be up to 24% (path and cx) (*Archives* 2009;169:2018)
- Pursue abnormalities raised by above w/u (eg, bx, MRI, etc., for dx, *not* screening)

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic)
- Empiric glucocorticoids not indicated unless strong suspicion for specific rheumatologic dx
- 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, lytes, BUN/Cr, LFTs, LDH, CK, U/A, HIV 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 1/2, *Mycoplasma*, syphilis, tick-borne diseases, etc.
  Non-infxn etiol: meds (eg, NSAIDs, sulfa), malignancy, autoimmune & rheum 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 swab PCR, antigen tests and possibly skin biopsy ± exam of vesicular or bullae fluid if present
- Etiologies more broad in immunosupp. Pts, dx testing should be earlier and more extensive; higher risk of critical illness due to disseminated or rapidly progressive infxns

Variable	Possible Etiology
Summer/fall > other seasons	Enterovirus
Winter	Parvovirus, Meningococcemia
Spring/summer	Measles/rubella, Lyme, RMSF
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, HSV2
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

FEVER IN A RETURNED TRAVELER

Region or Exposure	Common Etiologies
Sub-Saharan Africa	Malaria >> dengue, rickettsial disease, enteric disease
Southeast Asia	Dengue > malaria, enteric disease (*S. typhi*), Chikungunya
Central & S. America	Enteric disease, malaria, dengue, Zika
Caribbean & Mexico	Dengue >> Chikungunya > malaria. Also consider Zika.
Middle East	Middle East Respiratory Syndrome
Freshwater swimming	Schistosomiasis, leptospirosis
Unpurified drinking water	Enteric disease (*E. coli* >> *S. typhi*, *Campylobacter*, hepatitis E > *Vibrio cholerae*), amebic liver abscess
Lacking immunizations	HAV/HBV, *S. typhi*, influenza, measles, rubella, yellow fever
Animal bite	Rabies
African "safari"	Rickettsial disease, African trypanosomiasis
Adult <30 years	Mononucleosis (EBV or CMV)

(*NEJM* 2017;376:548)

- Pts visiting friends and relatives abroad are most likely to contract illness during travel
- Emerging pathogens: Influenza occurs year-round in the tropics. Chikungunya and dengue w/ ↑ areas of transmission, hemorrhagic fevers primarily in Central Africa.
- Consider domestic infxns, STIs, & non-infxn causes. Enteric parasites rarely cause fever.

Select clinical manifestations

- Ebola: fever in traveler from area with active transmission of Ebola w/in 21 d: isolate & contact state health department (http://www.cdc.gov/vhf/ebola)
- Malaria: nonspecific symptoms including diarrhea, myalgias, cough, altered mental status
- Dengue: nonspecific symptoms including headache, severe myalgias, rash/petechiae
- Chikungunya: nonspecific symptoms including joint pain, moderate myalgias, fever
- Typhoid (*Lancet* 2015;385:1136): constipation, abd pain, possible rash, relative bradycardia
- Rickettsial disease: headache, myalgias, lymphadenopathy, possible rash/eschar
- Zika: fever, rash, arthralgia, H/A, conjunctivitis (http://www.cdc.gov.zika)

Workup

- Routine testing: CBC w/ diff, lytes, 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.

NOTES

PITUITARY DISORDERS

HYPOPITUITARY SYNDROMES (*Lancet* 2016;388:2403)

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
- 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 and including ADH
- Mass effect: headache, visual field Δs, cranial nerve palsies, galactorrhea

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, weight gain
- 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)

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, *mild* hypernatremia (*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, diploplia, 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 normal trophic pituitary hormone
  Acute: target gland hormonal studies may be *normal*
  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 (*JAMA* 2017;317:516)

- 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: syndromes due to oversecretion of hormones (see below)
  ± 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 hormonal effects, can f/up q3–6mo

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, nasal congestion

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; *NEJM* 2006;355:2558; *JCEM* 2014;99:3933)

- 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: *no 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 co-secretion), pegvisomant (GH receptor antagonist), radiation
- Prognosis: w/o Rx 2–3× ↑ mortality, risk of pituitary insufficiency, colon cancer

Cushing's disease (↑ ACTH): 10–15% 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) Pheochromocytoma (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)
2B (*RET* proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Mucosal and gastrointestinal neuromas

Autoimmune Polyglandular Syndromes (APS) (*NEJM* 2018;378:1132)	
Type	Features
I (child onset)	Mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency
II (adult onset)	Adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1

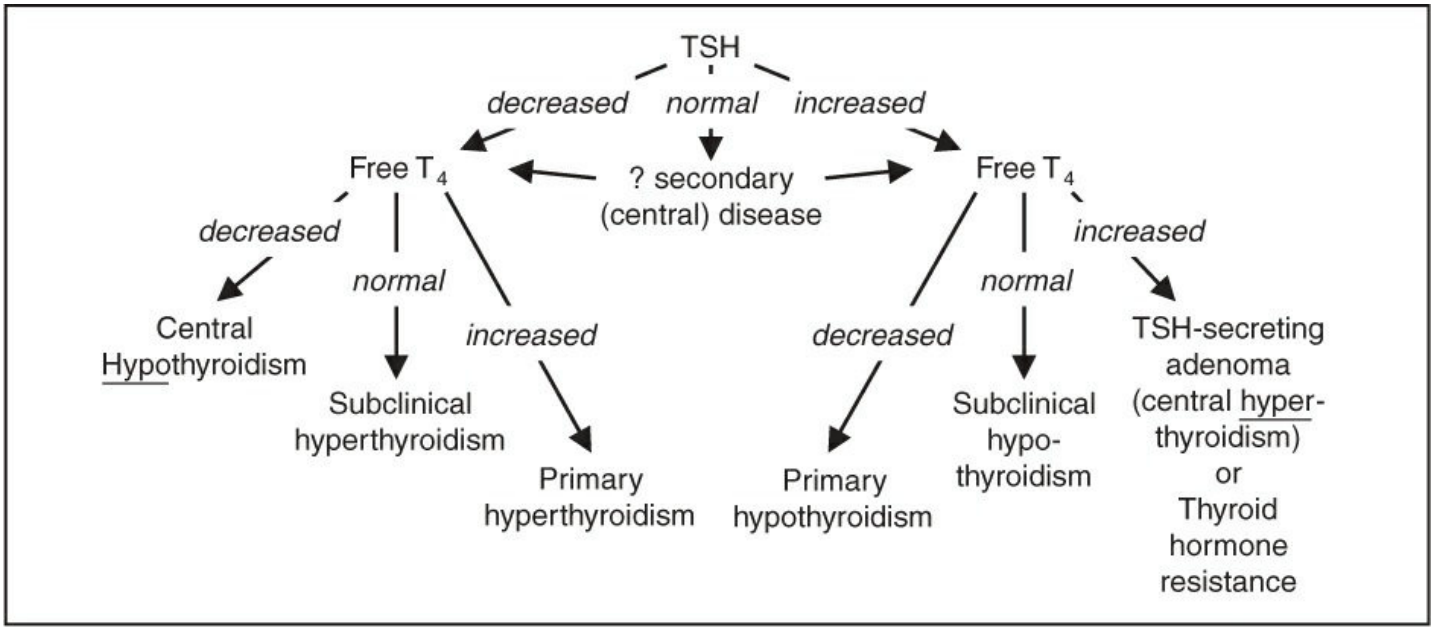
THYROID DISORDERS

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. May not be accurate 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 T3 (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 T4 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 (TSI)	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, nephritic syndrome, cirrhosis, acromegaly, antiepileptics, hereditary
Radioactive iodine uptake (RAIU) scan	Useful to differentiate causes of hyperthyroidism ↑ uptake: Graves' disease, 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

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 patchy 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* 2009;151:ITC61)

- 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: hypothermia, hypotension, hypoventilation, Δ MS (including coma) hyponatremia, hypoglycemia; often precipitated by infection or major cardiopulmonary or neurologic illness (*Med Clin North Am* 2012;96:385)

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

- Levothyroxine (1.5–1.7 µg/kg/d), re ✔ TSH q5–6wk & titrate until euthyroid (can take mos)
- *Lower starting dose* (0.3–0.5 µg/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; *Med Clin North Am* 2012;96:385)

- 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 5–8 µg/kg T_4 IV, then 50–100 µg IV qd; b/c peripheral conversion impaired, may also give 5–10 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

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), hCG-secreting tumors (eg, choriocarcinoma), large deposits of metastatic follicular thyroid cancer

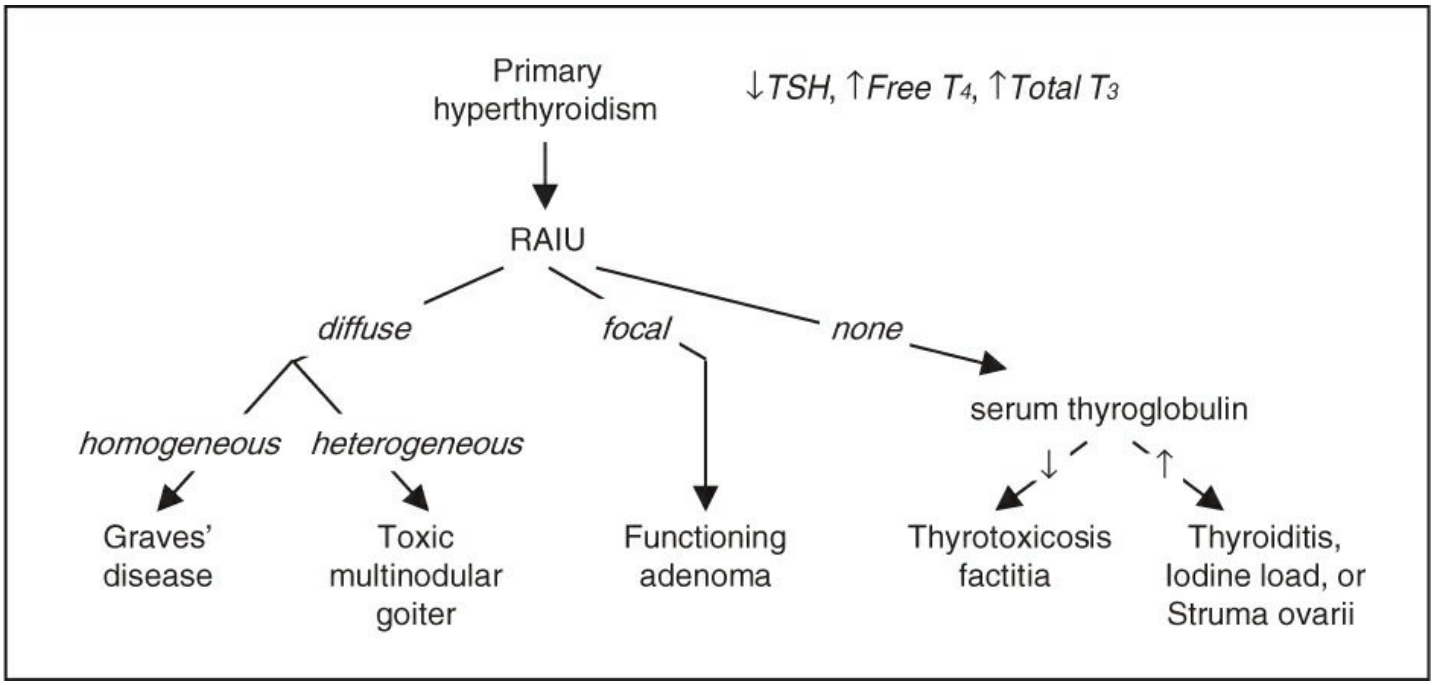
Clinical manifestations

- 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), palpation thyroiditis, post-radiation

Treatment (*Thyroid* 2011;21:593)

- β-blockers: control tachycardia (propranolol also ↓ $T_4 \rightarrow T_3$ conversion)
- Graves' disease: either antithyroid drugs or radioactive iodine (*JAMA* 2015;314:2544)
  - methimazole: 70% 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
- Ophthalmopathy: can worsen after RAI; prophylax w/ prednisone in high-risk Pts; can be Rx'd w/ 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 in hyperthyroidism; *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 (↓ $T_4 \rightarrow T_3$)

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: ↓ $T_4 \rightarrow T_3$ conversion, ↑ $rT_3 \rightarrow$ ↓ T_3; in severe illness: ↓ TBG & albumin, ↑↑

$rT_3 \rightarrow \downarrow\downarrow T_3$, ↑ degradation of T_4, central ↓ TSH → $\downarrow\downarrow T_3$, $\downarrow\downarrow T_4$, ↓ 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

AMIODARONE AND THYROID DISEASE

Overview (*JCEM* 2010;95:2529)

- 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

THYROID CANCER (*NEJM* 2015;373:2347; *Thyroid* 2016;26:1)

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 <20 or >70 y, ♂, h/o neck XRT, hard & immobile mass, cervical LAN, dysphonia
- 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 if medium or high risk (*Lancet* 2013;381:1046 & 1058)

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 North Am* 2008;37:525)
- ♀:♂ 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
- Neuroendocrine tumor of C cells, peak incidence 40 to 60 y, a/w MEN2A and MEN2B
- Most commonly solitary nodule; calcitonin production 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) (*NEJM* 2017;376:1451)

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%): ACTH-secreting pituitary adenoma (usually microadenoma) or hyperplasia
- Adrenal tumor (15–25%): adenoma or (rarely) carcinoma
- Ectopic ACTH (5–10%): SCLC, carcinoid, islet cell tumors, medullary thyroid cancer, pheo

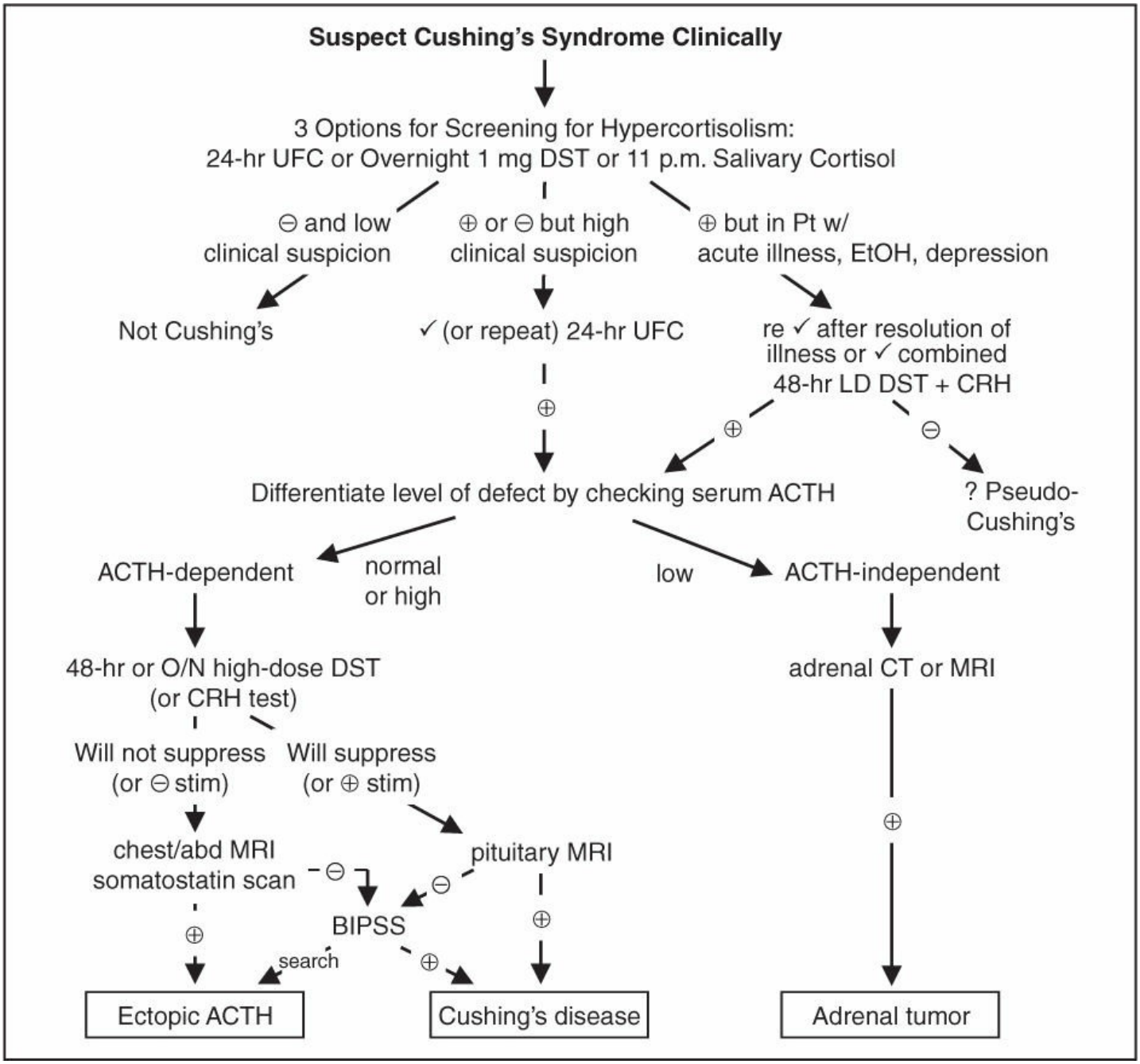
Clinical manifestations (*Lancet* 2006;367:13)

- *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 (*JCEM* 2008;93:1526)



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 = abnl if level ↑; 24-h UFC = 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; ✔ 24-h UFC at base. & during last 24 h of dex (suppress if <10% of base)
48-h HD DST = 2 mg q6h × 2 d; ✔ 24-h UFC as per LD DST
O/N HD DST = 8 mg at 11 p.m.; ✔ 9 a.m. serum cortisol (suppression if <32% of baseline)
CRH test = 1 μg/kg IV; ✔ cortisol and ACTH (⊕ stim if > 35% ↑ in ACTH or >20% ↑ in cortisol above baseline)
BIPSS, bilat. Inferior petrosal sinus vein sampling; ✔ petrosal:pewwripheral ACTH ratio (⊕ = 2 basal, >3 after CRH)

Treatment of Cushing's syndrome (*JCEM* 2015;100:2807)

- Surgical: resection of pituitary adenoma, adrenal tumor or ectopic ACTH-secreting tumor, or bilat surgical adrenalectomy if unable to control source of ACTH
- Medical: cabergoline, pasireotide, mitotane, ketoconazole, or metyrapone 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%), carcinoma glucocorticoid-remediable aldosteronism (GRA; ACTH-dep. rearranged promoter)
- Secondary (extra-adrenal disorders, ↑ aldosterone is renin-dependent)
  Primary reninism: renin-secreting tumor (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)

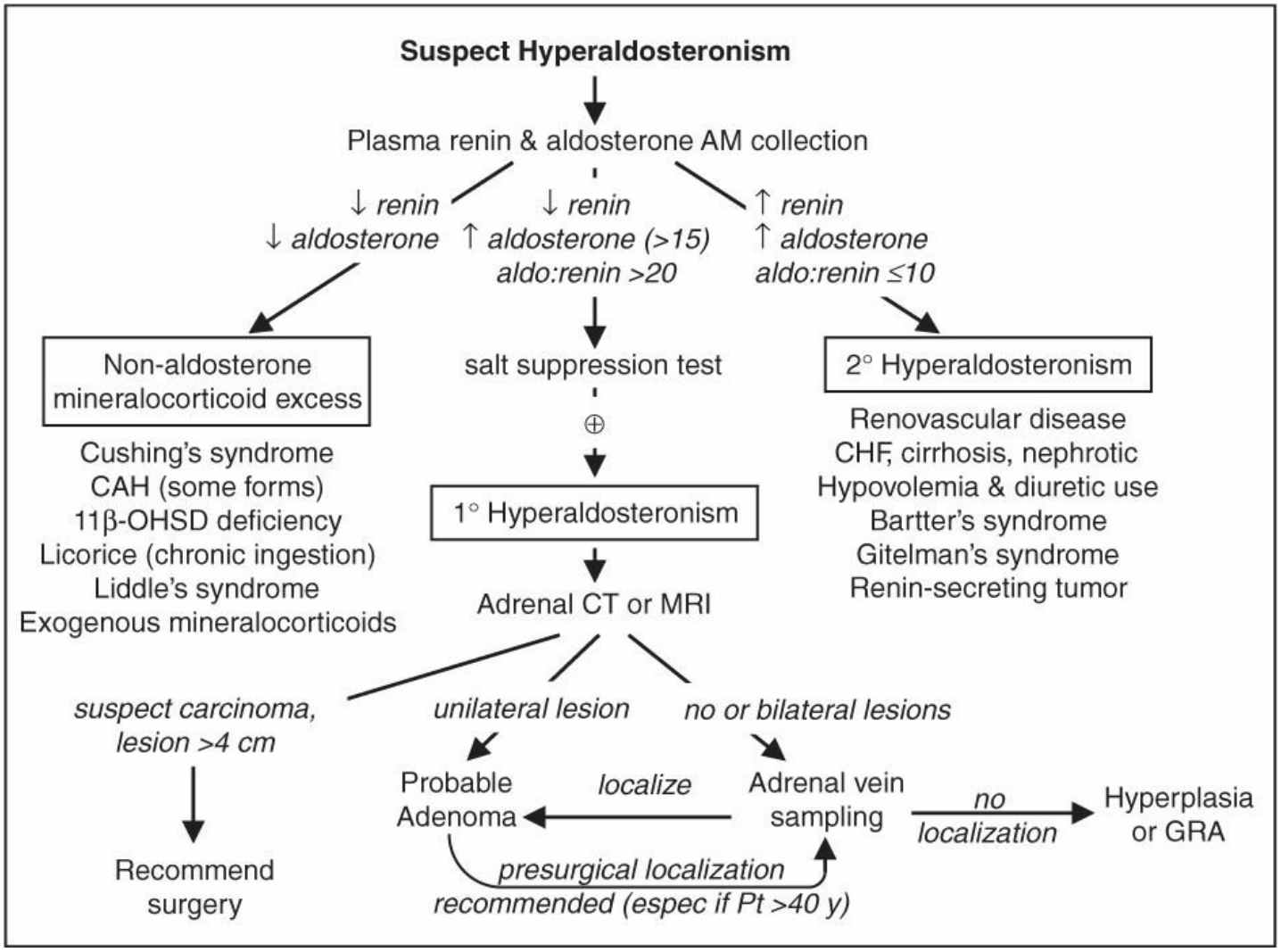
Clinical manifestations

- Mild-to-moderate HTN (11% of Pts w/ HTN refractory to 3 drugs; *Lancet* 2008;371:1921) 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

Diagnostic studies (*JCEM* 2008;93:3266; *SCNA* 2014;94:643)

- 5–10% of Pts w/ HTN; ∴ screen if HTN + hypoK, adrenal mass, refractory/early onset HTN
- Screening: aldo (>15–20 ng/dL) *and* plasma aldo:renin ratio (>20 if 1°) obtain 8 a.m. paired values (*off* spironolactone & eplerenone for 6 wk); Se & Sp >85%
- 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 (*Surg Clin N Am* 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 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* 2014;383:2152)

- Primary or secondary: weakness and fatigability (99%), anorexia (99%), orthostatic hypotension (90%), nausea (86%), vomiting (75%), hyponatremia (88%)
- 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 (see Appendix for examples of test results)
- 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 (⅔ a.m., ⅓ 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 perform ACTH stim ASAP 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 50–100 mg IV q8h; prior to ACTH stim test, use dexamethasone 2–4 mg IV q6h + fludrocortisone 50 μg daily
- Controversial data for empiric steroids in all critically ill Pts (see "Sepsis")

Adrenal crisis in adrenal insufficiency (*Lancet Diabetes & Endo* 2015;3:216)
- Precipitants: bilateral adrenal hemorrhage or infarction, pituitary infarction, pre-existing adrenal insufficiency + serious infection or GI illness
- Presentation: shock + anorexia, N/V, abd pain, weakness, fatigue, confusion, coma, fever
- Lab findings: hyponatremia, hyperkalemia (1°)
- Rx: hydrocortisone 50–100 mg IV q8 + IVF; do not delay for dx tests

PHEOCHROMOCYTOMA & PARAGANGLIOMA

Clinical manifestations (five Ps) (*Lancet* 2005;366:665)
- Neuroendocrine neoplasm leads to inappropriate and paroxysmal release of adrenergic agents including epinephrine, norephinephrine, and rarely dopamine
- Pressure (hypertension, paroxysmal in 50%, severe & resistant to Rx, occ orthostatic)
- Pain (headache, chest pain)
- Palpitations (tachycardia, tremor, wt loss, fever)
- Perspiration (profuse)
- Pallor (vasoconstrictive spell)
- Paroxysms can be triggered by meds (eg, β-blockers) abdominal manipulation
- Associated with MEN2A/2B, von Hippel Lindau, NF1, familial paraganglioma (mutations in succinate dehydrogenase gene B, C and D) or *TMEM127* mutations
- Up to 40% of pheos/paragangliomas thought to have underlying genetic etiology; genetic testing frequently recommended

Diagnostic studies (*JCEM* 2014;99:1915)
- 24° urinary fractionated metanephrines: 85–97% Se, 69–95% 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-free metanephrines: 89–100% Se, 79–97% Sp (*JAMA* 2002;287:1427). 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 generally better than 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 if bilateral disease, young Pt, ⊕ FHx, extra-adrenal

Treatment
- α-blockade first (usually phenoxybenzamine) ± β-blockade (often propranolol) → surgery
- Preoperative volume expansion is critical due to possible hypotension after tumor excision

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), nonclassical CAH, other endocrine tumor, carcinoma

Hormonal workup (*NEJM* 2007;356:601; *EJE* 2016;175:G1)

- 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-free 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 >6 cm or ↑ size on repeat scan; 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, yearly fxnal testing for 4 y w/ follow-up imaging at 6, 12, & 24 mo reasonable approach, but controversial

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	↑
	↑ or nl	Familial hypocalciuric hypercalcemia	↓	nl	nl
	↓	Malignancy	var.	var.	var.
		Vitamin D excess	↑	↑	var.
		Milk-alkali syndrome, thiazides	↓	nl	nl
		↑ Bone turnover	↑	var.	var.
↓	↑↑	Pseudohypoparathyroidism	↑	nl	↓
	↑	Vitamin D deficiency	↓	↓↓	nl / ↓
		Chronic renal failure (2° hyperpara)	↑	var.	↓
	var.	Acute calcium sequestration	var.	var.	var.
	↓	Hypoparathyroidism	↑	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;379:105; *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
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 (*JCEM* 2015;100:2024)	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: 24-h U_{Ca} >200 mg → HPT; 24-h U_{Ca} <100 mg & FE_{Ca} <0.01 → FHH
  ↓ PTH: ✔ PTHrP, Aϕ, & search for malig (eg, CT, mammogram, SPEP/UPEP) and ✔ vit D: ↑ 25-(OH)D → meds; ↑ 1,25-$(OH)_2$D → granuloma (✔ CXR, ACE, r/o lymph)

Acute Treatment of Hypercalcemia

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
Calcitonin	h	2–3 d	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

(*BMJ* 2015;350:h2723)

Treatment of asymptomatic 1° HPT (*JCEM* 2014;99:3561)

- 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

Calciphylaxis (calcific uremic arteriolopathy)

- Calcification of media of small- to med-sized blood vessels of dermis & SC fat
- Ischemia & skin necrosis. See "Chronic Kidney Disease" for further details.

HYPOCALCEMIA

Etiologies of Hypocalcemia	
Category	Etiologies
Hypoparathyroidism (*NEJM* 2019;380:1738)	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 (*JCEM* 2011;96:3020)	Ia and Ib: PTH end-organ resistance (∴ ↑ serum PTH) Ia: + skeletal abnormalities, short stature, & retardation Pseudopseudohypoparathyroidism = Ia syndrome but *nl* Ca & PTH
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)
Chronic renal failure	↓ 1,25-$(OH)_2$D production, ↑ PO_4 from ↓ clearance
Accelerated net bone formation	Postparathyroidectomy, Paget's disease (*NEJM* 2013;368:644), 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 (↓ vit D & ↑ PTH in renal failure): osteomalacia [↓ mineralization of bone due to ↓ Ca and 1,25-$(OH)_2$D] & osteitis fibrosa cystica (due to ↑ PTH)

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)

- 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* 2019;42:S13)

- 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), TZD (60% ↓; *Lancet* 2006;368:1096)

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 type 2 diabetes" or "Flatbush diabetes"): most often seen in nonwhite, ± anti-GAD Ab, eventually may not require insulin (*Endo Rev* 2008;29:292)
- Mature-Onset Diabetes of the Young (MODY): autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*NEJM* 2001;345:971)
- Secondary causes of diabetes: exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), endocrinopathies (Cushing's disease, acromegaly), gestational, drugs (protease inhibitors, atypical antipsychotics)

Clinical manifestations

- Polyuria, polydipsia, polyphagia with unexplained weight loss; can also be asymptomatic

Diabetes Treatment Options	
Medication (↓ Hb_{A1C})	Comments
Metformin (~1–1.5%)	↓ hepatic gluconeogenesis. Mild wt ↓. *1st line for T2D.* Rare lactic acidosis. Caution if GFR 30–45; contra. if <30. Poss CV benefit.
DPP-4 inhibitors (~0.5–1%)	Block degrad. GLP-1 & GIP → ↑ insulin. ↑ risk of HF w/ saxagliptin (*NEJM* 2013;369:1317), not w/ others.
GLP-1 receptor agonists	↑ glc-depend insulin secretion. Wt ↓, N/V.

(~1–1.5%)	↓ CVD/MI/stroke, espec. if ASCVD. ↓ prog of albuminuria.
SGLT-2 inhibitors (~0.5–1%)	↑ glucosuria. Wt ↓. Genital infxn. ↓ CVD/HHF. ↓ CVD & MI if ASCVD. ↓ prog. of renal disease.
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-glucosidase inhib. (0.5–1%)	↓ intestinal CHO absorption. Abd pain, flatulence.
Pramlintide (~0.5%)	Delays gastric emptying & ↓ glucagon. N/V
Insulin (variable)	Hypoglycemia; wt gain. Mandatory in T1D; consider in T2D if oral Rx inadequate.
Gastric bypass	Wt ↓↓↓; can cause remission DM (*NEJM* 2014;370:2002)

(*Diabetes Care* 2019;42:S90; *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
  diffuse glomerular basement membrane thickening/nodular pattern (Kimmelstiel-Wilson)
  usually accompanied by retinopathy; lack of retinopathy suggests another cause
  treatment: strict BP control using ACE inhibitors or ARBs (*Mayo Clin Proc* 2011;86:444), SGLT-2 inhib (*NEJM* 2016;375:323 & 2019;380:2295), 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* 2019;42:S61, S81, S103)

- ✔ 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 & macrovascular

complic. ↓ by strict glycemic control in T1D (*NEJM* 2005;353:2643) & T2D (*NEJM* 2015;372:2197).

- 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 "Lipids")
- ASA in 2° prevention; ? role in 1°, balancing ↓ MACE & ↑ bleeding (*NEJM* 2018;379:1529)
- Dilated retinal exam and comprehensive foot exam yearly

Management of hyperglycemia in inPts (for ICU: see "Sepsis") (*ClinTher* 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 w/ known insulin needs do not rely on sliding scale alone* (*Diabetes Care* 2018;41:S144).
- 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 μ/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: can later develop nonanion gap acidosis due to urinary loss of ketones (HCO_3 equivalents) and fluid resuscitation with 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; ↑ BUN & Cr (dehydration ± artifact due to ketones interfering w/ some assays)
- 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)

Typical DKA "Flow Sheet" Setup

VS	UOP	pH	HCO_3	AG	Ketones	Glc	K	PO_4	IVF	Insulin

Note: Main ketone produced is β-OH-butyrate (βOHB), *but ketone measured by nitroprusside is acetoacetate (Ac-Ac). As DKA is treated, βOHB → Ac-Ac, ∴ AG can decrease while measured ketones can increase.*

Treatment of DKA (*BMJ* 2015;28:351)	
R/o possible precipitants	Infection, intra-abdominal process, MI, etc. (see above)
Aggressive hydration	NS 10–14 mL/kg/h, tailor to dehydration & CV status
Insulin	10 U IV push followed by 0.1 U/kg/h Continue insulin drip until AG normal If glc <250 and AG still high → add dextrose to IVF and continue insulin to metabolize ketones AG normal → SC insulin (overlap IV & SC 2–3 h)
Electrolyte repletion	K: add 20–40 mEq/L IVF if serum K <4.5 insulin promotes K entry into cells → ↓ serum K careful K repletion in Pts with renal failure HCO_3: ? replete if pH <7 or if cardiac instability PO_4: replete if <1

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;37:3214)

- 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

- No ketoacidosis; usually ↑ BUN & Cr; [Na] depends on hyperglycemia & dehydration

Treatment

- Rule-out possible precipitants; ~15% mortality due to precipitating factors
- Aggressive hydration: initially NS, then 1/2 NS, average fluid loss up to 8–10 L
- Insulin (eg, 10 U IV followed by 0.05–0.1 U/kg/h)

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 in diabetics

- Excess insulin, oral hypoglycemics, missed meals, renal failure (↓ insulin & SU clearance)
- β-blockers can mask adrenergic symptoms of hypoglycemia

Etiologies in nondiabetics

- ↑ insulin: exogenous insulin, sulfonylureas, insulinoma, anti-insulin antibodies
- ↓ glucose production: hypopituitarism, adrenal insufficiency, glucagon deficiency, hepatic failure, renal failure, CHF, alcoholism, sepsis, severe malnutrition
- ↑ IGF-II: non-islet tumor
- Postprandial, esp. postgastrectomy or gastric bypass: excessive response to glc load
- Low glc w/o sx can be normal

Evaluation in nondiabetics (*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 = lipids (cholesteryl esters & triglycerides) + phospholipids + 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 >1000 mg/dL; xanthelasma (yellowish streaks on eyelids)
- Metabolic syndrome (≥3 of following): waist ≥40″ (♂) or ≥35″ (♀); TG ≥150; HDL <40 mg/dL (♂) or <50 mg/dL (♀); BP ≥130/85 mmHg; fasting glc ≥100 mg/dL (*Circ* 2009;120:1640)
- Lp(a) = LDL particle bound to apo(a) via apoB; genetic variants a/w MI (*NEJM* 2009;361:2518)

Dyslipidemias

- 1°: *familial hyperchol.* (FH, 1:500): defective LDL receptor; ↑↑ chol, nl TG; ↑ CAD; *familial hypertrig.* (FHTG, 1:500): ↑ TG, ± ↑ chol, ↓ HDL, pancreatitis; and many others
- 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**	**↑ HDL**	**↓ TG**	**Side Effects/Comments**
Statins	20–60%	5–10%	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)
Ezetimibe	~24%	—	—	Well tolerated
PCSK9i	~60%	5–10%	15–25%	mAb inj SC q2w or q4w; siRNA under development
Fibrates	5–15%	5–15%	35–50%	Myopathy risk ↑ w/ statin. ↑ Cr; ✓ renal fxn q6mo.
Ω-3 FA	5% ↑	3%	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)

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 >500–1000 mg/dL w/ fibrates or Ω-3 FA to ↓ risk of pancreatitis; genetically-mediated lower levels a/w ↓ risk of CAD (*NEJM* 2014;371:22); modest benefit of fibrates on CV outcomes (*NEJM* 2010;362:1563 & 2013;368:1800); high-dose Ω-3 FA (4 g/d of EPA) ↓ CV outcomes in Pts w/ ASCVD or DM (*NEJM* 2019:380:11)
- Lp(a): consider ↓ to <50 mg/dL in intermed- to high-risk Pts (*EHJ* 2010;31:2844)

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
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
Low	**<30%**			10	10–20	20	20–40	1

APPROACH TO RHEUMATIC DISEASE

Approach to patient with joint pain

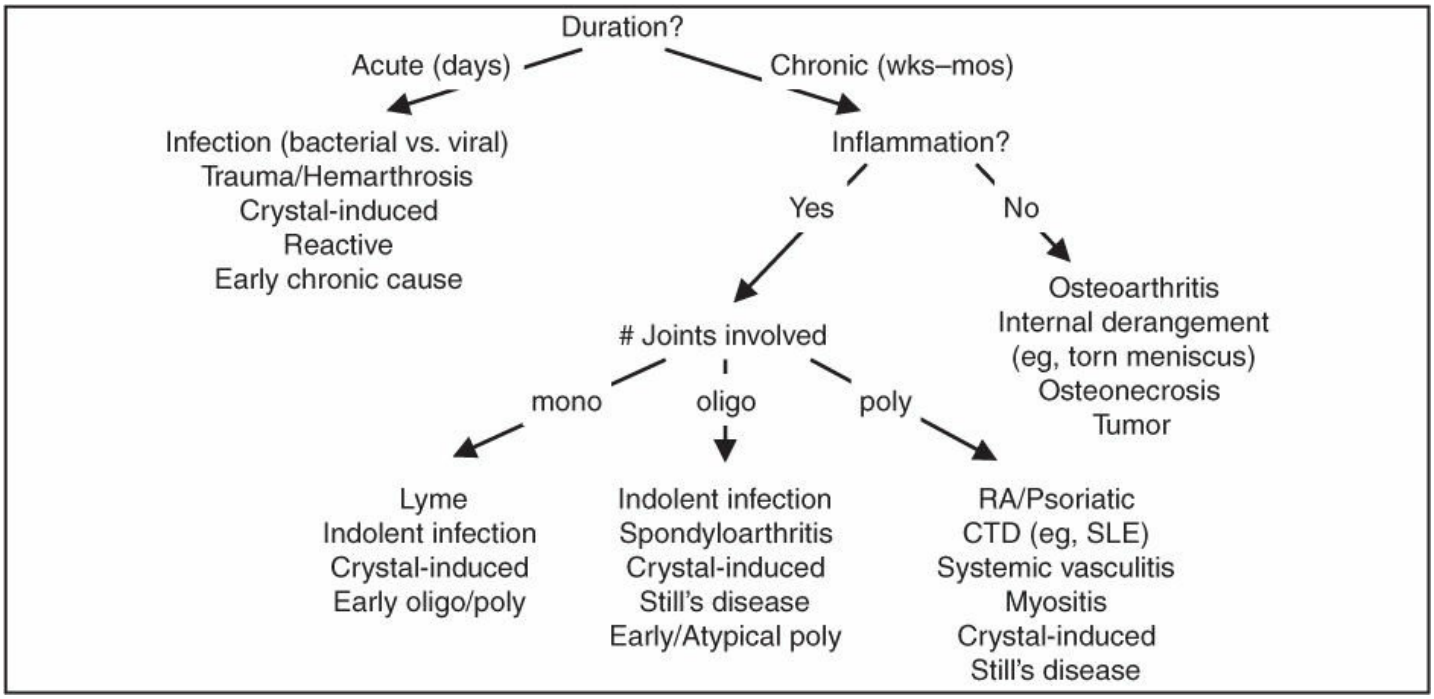
- Articular vs. periarticular (bursitis, tendinitis) source of pain: typically active ROM more painful than passive ROM in periarticular process
- Inflammatory vs. noninflammatory pain: *features of inflammatory pain* include swelling, warmth or redness in specific joint, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise. Assess for extra-articular features.
- Physical exam: localize complaint, identify objective signs of inflammation, and assess number and pattern of affected joints
- The physical exam is only *50–70% sensitive* for detecting inflammatory arthritis

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.

Radiologic 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
Inflammation	⊖	⊕	⊕	⊕
Pathology	Degeneration	Pannus	Microtophi	Enthesitis
# of joints	Poly	Poly	Mono to poly	Oligo or poly
Typical joint involvement	Hips, knees, spine, 1st CMC DIP, PIP	MCP, PIP wrists, feet, ankles, knees	MTP feet, ankles, knees	Sacroiliac spine large periph
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	Urate/CPPD crystals tophi	Dactylitis enthesitis (eg, Achilles) bamboo spine syndesmophytes
Extra-articular features		SC nodules pulmonary 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)

- ESR: *indirect* measure of inflammation [↑ RBC aggregation due to acute-phase proteins (fibrinogen & Ig) in blood]; slow to rise; may ↑ w/ age, preg., anemia, obesity. Ddx for >100: malig. esp. MM, lymphoma; GCA or other vasculitis; ESRD; endocarditis, TB, osteo.
- 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; found in autoimmune conditions; most useful in testing for suspected connective tissue diseases
- 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
- "False ⊕" ANA: AIH, PBC, thyroid disease, certain infxns and malignancies, IBD, IPF
- RF and anti-CCP (see "Rheumatoid Arthritis")

DDX & APPROACH TO COMMON INPATIENT RHEUM PRESENTATIONS

Presentation	Rheum Ddx	Rheum Lab Workup
Fever of unknown origin	GCA/PMR, adult-onset Still's, SLE, inflammatory arthritis, Takayasu's, PAN, ANCA ⊕ vasc, cryo, HSP	ESR, CRP, ANA, RF, ANCA, ± cryo
Pulmonary hypertension	Scleroderma (limited > diffuse), MCTD, SLE, PM/DM (less common)	ANA, Scl-70, centromere, RNA Pol III, RNP
Diff alveolar hemorrhage	ANCA ⊕ vasculitis, Goodpasture's, SLE, APS	ANCA, GBM, ANA, C3/C4
Interstitial lung disease	Scleroderma (diffuse > limited), sarcoid, RA, DM/PM, antisynthetase syndrome, Sjögren's, MCTD, SLE (esp. pleura), ANCA ⊕ vasc (esp. MPA)	ANA, Scl-70, RF/anti-CCP, CK, aldolase, ± myositis specific Abs, Jo-1, Ro/La, ANCA
Pleuro- pericarditis	SLE, RA, MCTD, DM/PM, ANCA ⊕ vasc, Sjögren's, PAN	ANA, dsDNA, Sm, RNP, Ro/La, RF, anti-CCP, ANCA
Acute kidney injury (+active sed. or s/s c/w CTD)	SLE (GN or nephrotic), ANCA ⊕ vasc (GN), scleroderma renal crisis (diffuse), Sjögren's (RTA/TIN), PAN (infarct), HSP, Goodpasture's (GN), cryo, APS	ANA, dsDNA, Smith, Ro/La, RNP, C3/C4, Scl-70 & RNA Pol III (SRC), ANCA, GBM, cryos, APS panel
Neuropathy	ANCA ⊕ vasc, SLE, RA, PAN, Sjögren's, cryo, sarcoid	ANA, Ro/La, ANCA, cryo RF/anti-CCP, HCV, HBV

RHEUMATOID ARTHRITIS (RA)

Definition & epidemiology (*Lancet* 2016;388:2023)

- Chronic, symmetric, debilitating, and destructive inflammatory polyarthritis characterized by proliferative synovial tissue (pannus) formation in affected joints
- Pathogenesis involves over-production of TNF, IL-1, and IL-6 (∴ used as drug targets)
- Risk stems from combination of genetic (~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% adults and 5% of ♀ >70 y; ♀ to ♂ ratio = 3:1; peak incidence 50–75 y

Clinical manifestations (*Medicine* 2010;38:167)

- 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 with active disease (*Autoimmun Rev* 2011;11:123)

Extra-Articular Manifestations (EAMs)	
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, airway disease, pleuritis, effusions (low glc), nodules, pulm HTN; precedes joint sx in 20% of cases; RA med toxicity (MTX, ? anti-TNF & anti- CD20) (*Curr Opin Pulm Med* 2011;362:367)
CV	Accel. athero w/ ↑ risk of MI & CV death, pericarditis (effusions in ⅓ of sero ⊕), myocarditis, AF, coronary/systemic vasculitis. (*Arth Rheum* 2015;67:2311)
Nervous	Mono/polyneuritis multiplex, CNS vasculitis, stroke, nerve entrapment
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 (*Curr Opin Rheum* 2009;21:35)

Laboratory & radiologic studies (*JAMA* 2018;320:1360)

- RF (IgM/IgA/IgG anti-IgGAb) ⊕ in ~70% of Pts w/ RA; also seen in other rheumatic diseases (SLE, Sjögren's), infection (SBE, hepatitis, TB), cryo, ~5% of healthy population
- Anti-CCP (Ab to cyclic citrullinated peptide): ⊕ in ~80% of Pts w/ RA, similar Se (~70%), 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 diagnosis synovitis 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), ANA, ↑ 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-⊕ disease (eg, RF or anti-CCP) a/w aggressive joint disease & EAM
- At dx, start *both* rapid-acting agent (to acutely ↓ inflammation) and Disease-Modifying Anti-Rheumatic Drug (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 or leflunomide; consider HCQ if seronegative and mild disease
  - If inadequate response after 3 mo (despite DMARD dose escalation) consider:
    - combination Rx w/ other DMARDs (eg, "triple therapy" w/ MTX, SAS and HCQ)
      or
    - adding biologic (anti-TNF typically 1st line unless contraindication)
    - MTX/SAS/HCQ non-inferior to etanercept/MTX (*NEJM* 2013;369:307)
    - JAK inhib: if fail biologics vs. initial DMARD (*NEJM* 2017;376:652; *Lancet* 2018;391:2503 & 2513)
- Given ↑ r/o early CV morbidity/mortality, try to ↓ risk w/ lifestyle mgmt, lipid & DM screening

RA Therapeutics (*Arth Rheum* 2016;68:1)		

Class	Drug	Side Effects
Traditional DMARDs	Methotrexate (MTX) Leflunomide Sulfasalazine (SAS)	MTX: GI distress, stomatitis, ILD, myelosuppression, hepatotoxicity Supplement MTX ± SAS w/ folate ✔ *G6PD prior to SAS*
Biologic DMARDs (all anti-TNF ≈ efficacy; if inadequate resp to anti- TNF try non-TNF)	Anti-TNF: etanercept, infliximab, adalimumab, 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) JAK inhib: tofacitinib (TF), baricitinib, others Rarely: cyclosporine, azathioprine, gold	HCQ: retinopathy, rash JAK inhib: infxn, ↑ Cr, ↑ LFTs, HTN CsA: nephrotox, HTN, gum hyperplasia

(*Lancet* 2013;381:451,918, & 1541; *NEJM* 2012;367:495 & 508, & 369:307; *JAMA* 2016;316:1172)

ADULT-ONSET STILL'S DISEASE & RELAPSING POLYCHONDRITIS

Adult-onset Still's disease (*J Rheumatol* 1992;19:424; *Autoimmun Rev* 2014;13:708)

- Rare autoinflammatory synd; ♂ = ♀ w/ typical onset 16–35 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 (*Rheum Dis Clin NA* 2013;39:263)

- Inflammatory destruction of cartilaginous structures; onset usually age 40–60 y, ♂ = ♀
- Subacute onset of red, painful, and swollen cartilage; ultimately atrophic & deformed
- Common clinical features: bilateral auricular chondritis; nonerosive inflammatory arthritis; nasal chondritis; ocular inflammation; laryngeal or tracheal chondritis; cochlear and/or vestibular dysfxn
- 40% of cases a/w immunologic disorder (eg, RA, SLE, vasc., Sjögren's), cancer or MDS
- Clinical diagnosis based on exam with multiple sites of cartilaginous inflammation
- 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
- Therapy guided by disease activity and severity: steroids 1st line; NSAIDs, dapsone for sx control of arthralgias and mild disease; MTX, AZA, or biologics for steroid-sparing; cyclophosphamide for organ-threatening disease

CRYSTAL DEPOSITION ARTHRITIDES

Comparison of Gout and Pseudogout		
	Gout (*NEJM* 2011;364:443)	Pseudogout (*Rheum* 2009;48:711)
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: Hyperparathyroidism, Hypo-magnesemia, Hemochromatosis
Crystal	Monosodium urate (MSU)	Calcium pyrophosphate dihydrate
Polarized microscopy*	Needle-shaped, negatively birefringent (yellow)	Rhomboid-shaped, weakly positively birefringent (blue)
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 (*Lancet* 2016;388:2039)

- Humans lack enzyme to metabolize urate (end-product of purine metabolism)
- MSU crystal deposition promotes inflammation in joints and peri-articular tissue;
- ♂ > ♀ (9:1); peak incidence 5th decade; most common cause of inflammatory arthritis in ♂ over 30 y; *rare* in premenopausal ♀ (estrogens promote renal urate excretion)

Etiologies (*Ann Rheum Dis* 2012;71:1448)

- 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 (*Lancet* 2008;372:1953)

Diagnosis

- ↑ UrA is not diagnostic: 25% of measurements nl during flare; ± ↑ WBC & ESR
- Arthrocentesis is gold standard: negatively birefringent needle-shaped MSU crystals
- 2015 ACR/EULAR Classification Criteria (*Ann Rheum Dis* 2015;74:1789) used 1° in research

Acute treatment (*Ann Rheum Dis* 2017;76:29)

- No superior option; start w/in 24 h of sx onset; continue until acute flare resolves; for severe cases, consider combination therapy; rest and ice; w/o treatment self-limited in 3–10 d
- Continue urate-lowering therapy during attack if already taking

Acute Treatment for Gout		
Drug	Initial Dose	Comments
NSAIDs (nonselect or COX-2)	Full anti-inflammatory dose → tapering	Gastritis & GIB; avoid in CKD & CVD ≈ efficacy among NSAIDs never compared with colchicine
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); ↓ dose in renal insufficiency (however, not nephrotoxic) a/w BM supp., myopathy, neuropathy
Corticosteroids (PO, IA, IV, IM) *or* Corticotropin	eg, prednisone ~0.5 mg/kg/d × 5–10 d ± taper	Rule out joint infection 1st Comparable to NSAID as 1st-line treatment Corticosteroid injection if <3 joints
IL-1 inhibitors (*Curr Opin Rheumatol* 2015;27:156)	anakinra (100 mg SC qd × 3 d) canakinumab (150 mg SC × 1)	↑↑ cost; anakinra a/w injection site pain (*Arthritis Res Ther* 2007;9:R28) Canakinumab approved in EU (*Ann Rheum Dis* 2012;71:1839; *Arth Rheum* 2010;62:3064)

Chronic treatment (*Ann Rheum Dis* 2017;76:29)

- 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 or < 5 mg/dl if tophi; 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 mo 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 (see above)
- Lifestyle Δs (*Rheum Dis Clin NA* 2014;40:581): ↓ intake of meat, EtOH & seafood, ↑ low-fat dairy products, 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
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; ↓ risk by *starting* w/ dose 100 mg/d if eGFR >40 or 50 mg/d if eGFR ≤40; titrate up by 100 mg/d (if eGFR >40) or 50 mg/d (if eGFR ≤40) q2–5wk until UrA <6 mg/dL (dose can be >300 mg/d even in CKD). *Associated with HLA-B5801*, esp. Han Chinese, Koreans, Thai; screen in these high-risk populations prior to initiating allopurinol (*Curr Opin Rheumatol* 2014;26:16).

CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) DEPOSITION DISEASE/PSEUDOGOUT

Definition

- Deposition of CPPD crystals w/in tendons, ligaments, articular capsules, synovium, cartilage; frequently asymptomatic

Etiologies (*Rheumatology* 2012;51:2070)

- 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 (*Rheum Dis Clin NA* 2014;40:207)

- Chondrocalcinosis: calcification of cartilage, resulting from CPPD deposition in articular cartilage, fibrocartilage or menisci
  ↑ incidence w/ age; 20% >60 y have knee chondrocalcinosis in autopsy studies
- 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
  precipitants: surgery, trauma, or severe illness
- Chronic forms: "pseudo-RA" and pyrophosphate arthropathy (may involve axial skeleton, resembles OA)

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 arthritis (PsA), reactive arthritis (ReA), IBD-associated arthritis, juvenille SpA and undifferentiated

Epidemiology & pathogenesis (*Nat Rev Rheumatol* 2015;11:110)

- Prevalence 0.5–2% 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
AS	♂:♀ = 3:1; onset in teens to mid- 20s (rare after 40 y)	Progressive limitation of spinal motion, "bamboo spine," ⊕ Schober test
Psoriatic arthritis	♂ = ♀; 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	♂ >> ♀; 20–40 y; 10–30 d after GI or GU infxn* in genetically susceptible host	Previously "Reiter's syndrome": arthritis, urethritis, and conjunctivitis. Most resolve w/in 12 mo.
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
- Subtypes also distinguished by *axial* vs *peripheral* predominant involvement

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%	Conjuncti-vitis, 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* 2012;8:253)

- Seronegative: notable for *absence* of rheumatoid factor or autoantibodies; ± ↑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: hyperkeratotic lesions on soles of feet, scrotum, palms, 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 (*NEJM* 2017;376:957; 2018;391:2273 & 2285)

- Monoarticular/oligoarticular (eg, large joint, 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 (*Ann Rheum Dis* 2012;71:319; *Arth Rheum* 2016;68:282)

- Untreated disease may lead to irreversible structural damage and associated ↓ function
- Early physiotherapy beneficial
- Tight control of inflammation improves joint outcomes 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, SAS, 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 manifestations, improves function and may slow progression of structural changes (*Curr Rheumatol Rep* 2012;14:422); adalimumab or infliximab preferred if inflammatory eye disease
- Anti-IL17A (secukinumab, ixekizumab): for both axial and peripheral PsA & for ankylosing spondylitis (*NEJM* 2015;373:1329 & 2534; *Lancet* 2015;386:1137)

- Anti-IL12/23 (ustekinumab): for both axial and peripheral PsA (*Ann Rheum Dis* 2014;73:990)
- PDE-4 inhibitor (apremilast): peripheral arthritis in PsA (*Ann Rheum Dis* 2014;73:1020); associated with GI side effects and significant wt loss
- JAK inhibitor: for anti-TNF resistant peripheral PsA (*NEJM* 2017;377:1525)
- Psoriasis (skin) also responds to anti-TNF, anti-IL17A, anti-IL12/23, PDE-4 inhib, JAK inhib
- Other:
  Abx in reactive arthritis if evidence of active infxn; consider prolonged abx for refractory *Chlamydia* ReA (*Arthritis Rheum* 2010;62:1298)
  Involve ophthalmologist for any evidence of inflammatory eye disease (may benefit from steroid eye drops or intravitreal steroid injections)
  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* (2° to anti-TNF Rx), 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

- 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, osteo)

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, pain
- Infection can track from initial site to form fistulae, abscesses, or osteomyelitis
- *Septic bursitis must be differentiated from septic intra-articular effusion*

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 (*Curr Rheumatol Rep* 2013;15:332)

- Prompt empiric antibiotics guided by Gram stain after surgical drainage. If Gram stain ⊖, empiric Rx w/ vancomycin; add anti-pseudomonal agent if elderly, immunocompromised.

Common Microbes (by Gram stain)		Population	Initial Antibiotic Regimen (tailor based on Gram stain, cx, clinical course)
GPC	*S. aureus* (most common)	Normal joints Prosthetic joints Damaged joints	Vancomycin*
	S. epidermidis	Prosthetic joints Postprocedure	Vancomycin*
	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

* Can later Δ to antistaphylococcal penicillin or cefazolin based on sensitivities

- IV antibiotics × ≥2 wk followed by oral antibiotics; varies by clinical course & microbiology
- Joint must be drained, often serially; arthroscopic drainage for larger joints and as initial treatment but may also be accomplished by 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 typically acquired during implantation; early w/ virulent organisms (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 by orthopedics; ESR & CRP (CRP Se 73–91%, Sp 81–86%; *NEJM* 2009;361:787) can be helpful

- Treatment typically requires prolonged abx & 2-stage joint replacement (joint retention a/w ~40% failure rate; *CID* 2013;56:182) or life-long suppressive abx. *ID and orthopedics consultation required.*

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; ↑ incidence during menses, pregnancy, & postpartum period, SLE; ↑ incidence in homosexual males; rare after age 40 y

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)
  DGI: 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 DGI; 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 azithromycin 1g x 1 dose for *Chlamydia* (fluoroquinolones no longer recommended due to resistance)
- Joint arthroscopy/lavage may be required for purulent arthritis; rarely >1 time

OLECRANON & PREPATELLAR BURSITIS

Epidemiology & risk factors (*Infect Dis North Am* 2005;19:991)

- >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, CPPD), 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 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 1–4 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
SLE	≥95	75	20	25	⊖	⊖	⊖	⊖	45	35
Sjögren's	≥95	rare	⊖	45	⊖	⊖	⊖	⊖	rare	>75
Diffuse SSc	>90	⊖	⊖	rare	40	20	rare	⊖	rare	30
Limited SSc	>90	⊖	⊖	rare	10	rare	60	⊖	rare	30
IM	75–95	⊖	⊖	⊖	rare	⊖	⊖	25	⊖	15
MCTD	≥95	⊖	⊖	rare	⊖	⊖	⊖	⊖	always	50
RA	40	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	70

Centr, centromere; IM, inflammatory myopathies; RF, rheumatoid factor; Sm, Smith; SSc, systemic sclerosis; (*Primer on the Rheumatic Diseases*, 12th ed., 2001; *Lancet* 2013;382:797)

- 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

see "Systemic Lupus Erythematosus" and "Rheumatoid Arthritis" for those diseases

SYSTEMIC SCLEROSIS AND SCLERODERMA DISORDERS

Definition & epidemiology (*Best Pract Res Clin Rheumatol* 2010;24:857)

- Scleroderma refers to the presence of tight, thickened skin
- Localized scleroderma: *morphea* (plaques of fibrotic skin), *linear* (fibrotic bands), "*en coup de saber*" (linear scleroderma on one side of scalp and forehead ≈ saber scar)
- Systemic sclerosis (SSc) = scleroderma + internal organ involvement
  SSc w/ *limited cutaneous disease:* formerly CREST syndrome (see below)
  SSc w/ *diffuse cutaneous disease:* often rapidly progressive disorder affecting skin
  SSc *sine scleroderma* (visceral disease without skin involvement, rare)
- Peak onset of SSc between ages 30–50; ♀ > ♂ (7:1); African American > white
- 1–2/100,000 annual incidence of systemic disease in the U.S.
- Pathogenesis: endothelial injury → ROS production → oxidative stress → perivascular inflammation → fibrosis. Cytokines, growth factors, genetics, environ. factors + antibodies (against PDGF receptor, endo. cells, fibroblasts) all 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 limited to fingers (not beyond 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) = accelerated development of HTN (*relative ↑ in BP as compared with Pt's baseline BP*), MAHA Urine sed. typically bland; "onion-skin" hypertrophy of capillaries Affects 5–10% of Pts, 66% w/in 1st yr (*Rheum* 2009;48:iii32); >15 mg/d prednisone and RNA Pol III Ab a/w ↑ risk of developing SRC Poor prognosis w/ 50% mortality	
GI (>80% of Pts)	GERD and erosive esophagitis Esophageal dysmotility → dysphagia, odynophagia, aspiration Gastric dysmotility → early satiety and gastric outlet obstruction 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	Diffuse
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 = Calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasias	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 (*Semin Arthritis Rheum* 2005;35:35)

- 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 help diagnose disease and be correlated w/ degree of lung & skin fibrosis and disease progression but awaits validation (*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, ∴ must be vigilant
- Frequent (eg, daily) BP ✔ to monitor for HTN suggestive of scleroderma renal crisis

Treatment (*Arthritis Rheumatol* 2018;70:1820)

- *Minimize steroid exposure to reduce risk of renal crisis*
- *Pulmonary* fibrosis: MMF (*Lancet Respir Med* 2016;4:708) vs. cyclophosphamide (NEJM 2006;354:2655); MMF + perfinidone under evaluation (*Rheum Dis Clin NA* 2015;41:237)
  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 and/or H2-blockers for GERD; antibiotics for malabsorption
  hypomotility: metoclopramide or erythromycin; nonoperative Rx of pseudo-obstruction
- Cardiac: NSAIDs ± colchicine superior to steroids for pericarditis
- Arthritis: acetaminophen, NSAIDs, hydroxychloroquine, MTX
- Myositis: MTX, AZA, steroids
- Skin: PUVA for morphea. Pruritus: emollients, topical or oral steroids (↓ dose). Fibrosis: MTX or MMF ? efficacy (*Ann Rheum Dis* 2017;76:1207; *Int J Rheum Dis* 2017;20:481)
- Auto-HSCT promising for severe disease (*NEJM* 2018;378:35)

INFLAMMATORY MYOPATHIES

Definition & epidemiology (*JAMA* 2013;305:183; *NEJM* 2015;372:1734)

- All lead to skeletal muscle inflammation & weakness, variable extramuscular involvement
- Polymyositis (PM): idiopathic diffuse polymyopathy, onset typically 40s–50s; ♀ > ♂
- Dermatomyositis (DM): similar to PM; also occurs in childhood, but differentiated from other myopathies by skin manifestations; malignancy a/w PM (10%) and DM (24%)
- Necrotizing autoimmune myositis (NM): usually in adults; risk factors include statin exposure ⊕ anti-HMGCR), CTD, malignancy, and rarely viral infection
- Inclusion body myositis (IBM): onset after age 50; ♂ > ♀; 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 (*NEJM* 2015;372:1734)

- Muscle weakness: gradual (wks → mos) except in NM, 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 may be *asymmetric and distal*
- 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 ⊕
- 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

- ↑ CK (rarely >100,000 U/L, can be ↑↑↑ in NM), aldolase, SGOT, LDH; ± ↑ ESR & CRP
- Autoantibodies: ⊕ ANA (>75%) (*Curr Rheumatol Rep* 2013;15:335)
  - ⊕ 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
- 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: *T cell–mediated muscle injury;* endomysial inflam. surrounds non-necrotic fibers
  - DM: *immune complex deposition in blood vessels with complement* activation; perimysial, perivascular inflam (B & CD4 T cells), complement in vessels.
  - NM: *necrotic fibers w/ macrophages*
  - IBM: *T cell–mediated muscle injury, vacuole formation;* same as PM with eosinophilic inclusions and rimmed vacuoles (EM)

Treatment (PM & DM, no effective treatment for IBM) (*Autoimmun Rev* 2011;11:6)

- 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 (DM ± PM), rituximab (*Arthritis Rheum* 2013;65:314), 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: discontinue statin if taking; steroids + MTX or IVIG if needed (MUSCLE NERVE 2010;41:185)

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 (*JAMA* 2014;311:1547)	⊖	⊕ (tender points)	⊖	⊖	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)
- More prevalent in ♀ than ♂; typically presents between 40 & 60 y of age

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%), neuropathies (10%), PNS or CNS disease, ILD, PBC
- ↑ risk of lymphoproliferative disorders (~50× ↑ risk of lymphoma and WM in 1° Sjögren's)

Diagnostic studies

- Autoantibodies: ⊕ ANA (95%), ⊕ RF (75%)
  Primary Sjögren's: ⊕ anti-Ro (anti-SS-A, 56%) and/or ⊕ anti-La (anti-SS-B, 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 Rheum* 2016;69:35)

- 3 points: ⊕ anti-Ro; labial saliv. gland bx w/ lymphocytic sialadenitis & score ≥1 foci/4mm^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 (*Arth Res Ther* 2013;15:R172)

- 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

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Definition (*Best Pract Res Clin Rheumatol* 2012;26:61)

- 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): non-specific symptoms that fail to meet criteria for any CTD; 30% go on to develop CTD over 3–5 y (usually SLE)

Clinical & laboratory manifestations (variable clinical course)

- Raynaud's phenomenon typical presenting symptom (75–90%); see below
- 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

RAYNAUD'S PHENOMENON

Clinical manifestations & diagnosis (*NEJM* 2016;375:556)

- 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 dis (athero, Buerger's), trauma Heme (cyro, Waldenström's, APLAS) 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* 2011;23:555; *BMJ* 2012;344:e289)

- 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

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Multisystem inflammatory autoimmune disease with a broad spectrum of clinical manifestations in association with antinuclear antibody (ANA) production

Epidemiology (*Lancet* 2014;384:1878)

- Prevalence 15–50/100,000; predominantly affects women 2nd to 4th decade
- ♀:♂ ratio = 8:1; African American:Caucasian ratio = 4:1
- Complex genetics; some HLA association; rarely C1q & C2 deficiency

Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria		
Clinical Criteria	SLICC Classification Criteria*	Other Clinical Features
Constit (84%)		Fever, malaise, anorexia, ↓ wt
Cutaneous/Oral/ Ophthalmologic (81%)	1. Acute or subacute cutaneous changes 2. Chronic cutaneous changes 3. Oral or nasal ulcers 4. Nonscarring alopecia	Malar rash (spares nasolabial folds), discoid rash (papules w/ keratosis & plugging), bullous SLE, urticaria, TEN Photosens. (n/v, rash, fever) Vasculitis, panniculitis (lupus profundus) Raynaud's, nailfold cap Δs, Sicca syndrome Conjunctivitis, episcleritis
Musculoskeletal (85–95%)	5. Joint disease: synovitis or tenderness & morning stiffness involving ≥2 joints	Arthralgias and myalgias Avascular necrosis of bone
Cardiopulmonary (33%)	6. Serositis: pleuritis (37%) or pleural effusion, pericarditis (29%) or pericardial effusion	Pneumonitis, IPF, shrinking lung, PAH, DAH Myocarditis, CAD Libman-Sacks endocarditis
Renal (77%)	7. Proteinuria (>0.5 g/dL) or RBC casts	Nephrotic syndrome Lupus nephritis (qv)
Neurologic (54%)	8. Seizures or psychosis w/o other cause	Cognitive dysfxn, stroke, cranial or periph neuropathies, transverse myelitis, mononeuritis multiplex
GI (~30%)		Serositis (peritonitis, ascites) Vasculitis (bleeding, perf.) Hepatitis, pancreatitis
Hematologic	9. Hemolytic anemia 10. Leukopenia (<4000/mm^3) *or* lymphopenia (<1000/mm^3) 11. Thrombocytopenia (<100,000/mm^3)	Anemia of chronic disease Antiphospholipid synd (VTE w/ ⊕ ACL Ab, lupus anticoag, and/or B2GPI Ab) Splenomegaly, LAN
Immunologic	12. ⊕ ANA; 13. ⊕ anti-ds-DNA 14. ⊕ anti-Sm; 15. ⊕ APLA 16. ↓ Complement: C3, C4, CH50 17. ⊕ Direct Coombs' (w/o #9)	↑ ESR/CRP, ⊕ anti-Ro/La, ⊕ anti-RNP, ⊕ RF, ⊕ anti-CCP

*Expert opinion, not dx criteria for SLE: ≥4/17 SLICC criteria, including ≥1 clinical & ≥1 immunologic, *or* bx proven SLE

nephritis w/ ⊕ ANA or anti-ds-DNA (*Arth Rheum* 2012;64:2677)

Autoantibodies in SLE (*NEJM* 2008;358:929)			
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 of SLE (*Curr Rheumatol Rep* 2011;13:308; *Arthritis Care Res* 2015;67:1237)		
Drug	Indication	Adverse Effects
Hydroxychloroquine (HCQ)	All Pts b/c ↓ flares (*NEJM* 1991;324:150); monoRx for arthritis, serositis, skin disease	Retinal damage (<1%) Stevens-Johnson; myopathy *Not immunosuppressive*
NSAIDs	Arthritis, myalgias, serositis	Gastritis, UGIB, renal failure
Corticosteroids	Low dose (10–15 mg) for arthritis, serositis; high-dose (1 mg/kg) ± pulse (1 g × 3 d) for major dis (eg, renal, CNS, heme)	Adrenal suppression, DM, cataracts, osteopenia, avascular necrosis of bone, myopathy
Mycophenolate (MMF)	Nephritis (induction/maint) Nonrenal refractory to HCQ	Cytopenias, ↑ LFTs, diarrhea, teratogen
Cyclophosphamide (CYC)	Nephritis CNS disease (induction, minimize exposure)	Cytopenias, infertility, teratogen, myeloproliferative disorders, hemorrhagic cystitis, bladder cancer
Azathioprine (AZA)	Nephritis (maintenance) Non-renal disease refractory to HCQ	Myelosuppression (✔TPMT), hepatotoxicity, teratogen lymphoproliferative disorders
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
Belimumab (*NEJM* 2013;368:1528)	Arthritis, serositis, skin disease (esp. if ⊕ ds-DNA or ↓ C3/C4)	B-cell depletion (< RTX, different mechanism)
Rituximab (RTX)	Refractory SLE, ITP, AIHA	Infusion reaction; serum sickness; PML
Baricitinib (*Lancet* 2018;392:222)	Prelim data: 4 mg w/ efficacy in arthritis, skin disease	Infections (zoster), ↑ LFTs, cytopenias, dyslipidemia

Lupus Nephritis (*Arthritis Care Res* 2012;64:797)		
Class	Presentation	Treatment (all benefit from HCQ)
I: Min. mesangial	Normal U/A & creatinine	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
IV: Diffuse prolif	Hematuria/proteinuria and HTN, ↓ GFR, ± nephrotic	
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

(*Ann Rheum Dis* 2010;69:2083; *NEJM* 2004;350:971 & 2005;353:2219 & 2011;365:1886)

Prognosis (*Arth Rheum* 2006;54:2550; *Rheum [Oxford]* 2016;55:252)

- 5-y survival rate >90%, 10-y survival rate >80%
- Leading causes of morbidity and mortality: infection, renal failure, neurologic and cardiovascular events; thrombotic complications (*Medicine* 2003;82:299)

Drug-induced lupus (DLE) (*Drug Saf* 2011;34:357; *Curr Opin Rheumatol* 2012;24:182)

- 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

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 > HSP
Periph Neurop	No		Yes	Yes	Yes
GI	Uncommon		Yes	Yes	HSP > Cryo
Skin	Rare	None	Common	Common	Common
Granul.	Yes		No	Yes, except MPA	No
Other			Mesenteric aneurysms, testicular involv.	GPA: upper airway EGPA: asthma	HSP: IgA-dep Cryo: 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, HSP, cryoglobulinemia); GN, glomerulonephritis.

LARGE-VESSEL VASCULITIS

Takayasu's arteritis ("pulseless disease")

- Arteritis of aorta and its branches → stenosis/aneurysm → claudication; onset <50 y
- Pattern of involvement: aorta and branches; most often subclavian and innominate arteries (>90%), as well as carotid, coronary, renal, pulmonary (~50%)
- Epidemiology: most common in Asia; ♀:♂ ~9:1; age <50 y
- Clinical manifestations and physical findings (*Circ* 2015;132:1701)
  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 or AZA; anti-TNF (2nd line, *Autoimmun Rev* 2012;11:678); anti-IL-6 ? effective (*J Autoimmun* 2018;91:55); ASA; surgical/endovascular revasc (*Circ* 2008;69:70)
- Monitoring: MRA or PET-CT (*Arth Rheum* 2012;64:866); ESR/CRP (*Ann Rheum Dis* 2009;68:318)

Giant cell arteritis (GCA) (*JAMA* 2016;315:2442)

- Granulomatous arteritis of aorta/branches w/ predilection for temporal artery
- Pattern of involvement: extracranial branches of carotid artery, esp. temporal artery (thus also called temporal arteritis); aorta and/or its branches in 10–80%
- 90% of Pts w/ GCA are >60 y, peak incidence at 70–80 y, extremely rare <50 y; ♀:♂ = 3:1
- 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 studies: ↑ ESR (Se 84%, Sp 30%), ↑ CRP (Se 86%, Sp 30%), anemia

  temporal artery bx *whenever GCA suspected* (Se ≤85%); 1–2 cm ± bilat to ↑ yield (3–7% discordance) (*Ann Rheum Dis* 2009;68:318) → vasculitis & *granulomas*

  if suspect aortitis or lg-vessel involvement (BP Δ or bruits) → MRI/MRA or PET-CT
- Rx: steroids: *do not await bx/path results to begin!* Have at least 2 wk to bx w/o Δ results. Prednisone 40–60 mg/d w/ *slow* taper, ASA daily; consider IV steroid pulse if vision threatened. Adding tocilizumab helps achieve sustained remission (*NEJM* 2017;377:317).
- Polymyalgia rheumatica (*JAMA* 2016;315:2442; *Lancet* 2017;390:1700)

  Seen in 50% of GCA Pts; 15% of Pts w/ PMR develop GCA

  Age ≥50 y; 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 improvement, initiate slow taper. If no improvement, ↑ dose. Consider MTX if at high risk for steroid side effects (*Ann Rheum Dis* 2015;74:1799).
- Follow clinical status & ESR/CRP (*Ann Rheum Dis* 2009;68:318); ~1/3 relapse over 2 y (*J Rheum* 2015;42:1213)

MEDIUM-VESSEL VASCULITIS

Polyarteritis nodosa ("classic" PAN) (*Arth Rheum* 2010;62:616)

- Necrotizing nongranulomatous vasculitis of medium and small arteries (w/ muscular media) w/o glomerulonephritis or capillary involvement (ie, no DAH), not a/w ANCA
- Epidemiology: ♂ > ♀; average age of onset ~50 y; 1° vs. 2° (HBV > HCV; ~10%)
- Clinical manifestations
  - Constitutional 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 studies: ↑ ESR/CRP, ANCA, HBV testing, ↓ C3/C4 if HBV-associated
  - Angiogram (mesenteric or renal vessels) → microaneurysms & focal vessel narrowing
  - CTA may be adequate to make dx, but conventional angiogram is most sensitive
  - Biopsy (sural nerve, skin, or affected organ) → vasculitis of small- and medium-vessel arteries with fibrinoid necrosis *without granulomas*
- Rx: based on severity; steroids ± DMARD (eg, MTX or CYC); antivirals if a/w HBV

ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS

Microvascular vasculitis (eg, capillaries, postcapillary venules, & arterioles)

Disease	Gran	Renal	Pulm	Asthma	ANCA Type[a]	ANCA ⊕
Granulomatosis with polyangiitis[b]	⊕	80%	90% (+ ENT)	—	anti-PR3 (c-ANCA)	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO (p-ANCA)	70%
Eosinophilic granulomatosis with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO (p-ANCA)	50%

[a]Predominant ANCA type; either p- or c-ANCA can be seen in all three diseases (*NEJM* 2012;367:214).

[b]GPA is formerly Wegener's granulomatosis and EGPA is formerly Churg-Strauss.

Differential diagnosis of ANCA (*Lancet* 2006;368:404)

- anti-PR3 (c-ANCA): GPA, EGPA, microscopic polyangiitis (rarely), levamisole (contaminant in cocaine) both c- & p-ANCA ⊕
- anti-MPO (p-ANCA): microscopic polyangiitis, EGPA, GPA, drug-induced vasculitis, nonvasculitic rheumatic dis., levamisole (contaminant in cocaine) both c- & p-ANCA ⊕
- 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 nose, sinuses and/or upper respiratory tract in addition to kidneys, lungs, etc.
- Epidemiology: any age, but ↑ incidence in young and middle-aged adults; ♂=♀
- Clinical manifestations
  - Constitutional: fever, fatigue, malaise, anorexia, unexplained wt loss
  - Respiratory (90%): Upper: recurrent sinusitis, rhinitis, oral/nasal ulcers, nasal crusting, saddle-nose deformity, otitis, hearing loss, subglottic stenosis; Lower: pulm. infiltrates, nodules, pulm. hemorrhage, hemoptysis, pleurisy
  - Renal (80%): RPGN (pauci-immune), RBC casts, dysmorphic RBCs, hematuria
  - Ocular (50%): episcleritis, scleritis, uveitis, orbital granulomas → proptosis, corneal ulcer
  - Neurologic: cranial and peripheral neuropathies, mononeuritis multiplex
  - Skin (50%): palpable purpura, livedo reticularis
  - Hematologic: ↑ 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
- Treatment: assess disease severity with BVAS/WG score (*Arth Rheum* 2001;44:912)
  - 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* CYC 2 mg/kg/d × 3–6 mo or pulse 15 mg/kg q2–3wk] + steroids 1 g IV × 3 d → 1–2 mg/kg/d (*NEJM* 2005;352:351, 2010;363:211, & 2013;369:417; *Annals* 2009;150:670; *Ann Rheum Dis* 2015;74:1178)
    - If RPGN: ± plasma exchange to ? ↓ risk of ESRD (*Am J Kidney Dis* 2011;57:566)
    - *Maintenance:* RTX q6mo superior to AZA or watchful waiting (*Arth Rheum* 2012;64:3760; *NEJM* 2014;371:1771)
  - 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/airway involvement & nongranulomatous
- Epidemiology: ♂ > ♀; avg onset 50–60 y
- Clinical manifestations: similar to GPA *w/o upper respiratory involvement;* Renal (80–100%): glomerulonephritis Pulmonary (25–50%): pulmonary capillary alveolitis, pulmonary fibrosis Constitutional and neuro sx similar to GPA; skin lesions (eg, palpable purpura) in 30–60%
- Dx studies: 70% ⊕ ANCA (almost all anti-MPO)
  - biopsy → necrotizing, nongranulomatous inflammation of small vessels, pauci-immune (minimal deposition of complement or Ig; contrast w/ HSP, cryoglobulinemia, etc.)
  - urine sediment and CXR findings similar to those seen in GPA

- Treatment: as for GPA; ↓ 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
- Epidemiology: rare; can present at any age (typically 30–40 y); a/w HLA-DRB4
- Clinical manifestations (*Curr Rheumatol Rep* 2011;13:489)
  - 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 (5–10 k/μL, 80–100%), biopsy → microgranulomas, fibrinoid necrosis, and thrombosis of small arteries and veins with eosinophilic infiltrates
- Treatment: high-dose steroids + CYC (if severe); anti-IL5 (mepolizumab) for refractory/relapsing (*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

Henoch-Schönlein purpura (HSP)

- IgA-mediated vasculitis w/ predilection for skin, GI tract, and kidneys
- Epidemiology: ♂ > ♀, children > adults, onset in winter > summer
- May develop after upper respiratory tract infection (esp. *Strep*) or 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

Connective tissue disease–associated vasculitis

- Small-vessel vasculitis a/w RA, SLE or Sjögren's syndrome
- Clinical manifestations
  - Distal arteritis: digital ischemia, livedo reticularis, palpable purpura, cutaneous ulceration
  - Visceral arteritis: pericarditis and mesenteric ischemia
  - Peripheral neuropathy

- Dx studies: skin/sural nerve bx, EMG, angiography; ↓ C′ in SLE; ⊕ RF or anti-CCP in RA
- Treatment: steroids, cyclophosphamide, MTX (other DMARDs)

Cutaneous leukocytoclastic angiitis

- Most common type of vasculitis; heterogeneous group of clinical syndromes due to IC deposition in capillaries, venules, and arterioles; includes *hypersensitivity vasculitis*
- Etiologies
  - Drugs: PCN, ASA, amphetamines, levamisole, thiazides, chemicals, immunizations, etc.
  - Infections: *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 HSP)*;* if etiology not clear, consider ANCA, cryoglobulins, hepatitis serologies, ANA, RF
- Treatment: withdrawal of offending agent ± rapid prednisone taper

Behçet's syndrome (*Curr Rheum Opin* 2010;12:429)

- Systemic vasculitis affecting all vessel sizes, a/w painful oral and/or genital ulcers
- Epidemiology: usually young adults (25–35 y); a/w HLA-B51 in areas of highest prevalence on the old Silk Road (Turkey, Middle East, and other Asian countries)
- 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 (*Rheumatology* 2007;46:736; *Ann Rheum Dis* 2008;67:1656 & 2009;68:1528)
  - Mucocutaneous:
    - Mild: topical steroids, colchicine (esp. for erythema nodosum), dapsone, apremilast (PDE-4 inhib) for oral ulcers and ? genital ulcers (*NEJM* 2015;372:1510),
    - 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)

IGG4-RELATED DISEASE

Definition & etiology (*NEJM* 2012;366:539; *Ann Rev Pathol* 2014;9:315)

- Characterized by tumor-like inflammatory lesions that can affect nearly any organ
- Etiology unclear: ? autoimmune; unclear role of IgG4 Ab; Pt may have h/o atopy

Clinical manifestations (*Lancet* 2015;385:1460; *Arth Rheum* 2015;67:2466)

- Commonly pancreatitis, aortitis, cholangitis, sialadenitis, thyroiditis, orbital myositis ± pseudotumor, retroperitoneal fibrosis
- Multiple lesions may be present synchronously or metachronously

Diagnosis (*Ann Rheum Dis* 2015;74:1 & 14)

- Biopsy w/ specific histopathology & immunohistochemistry findings: lymphoplasmacytic infiltrate w/ significant IgG4+ plasma cell infiltrate, fibrosis, obliterative phlebitis
- ↑ serum IgG4 (Se 90%, Sp 60%); *not specific* seen in GPA, bronchiectasis (*Ann Rheum Dis* 2014;74:14)

Treatment (*Arth Rheum* 2015;67:1688)

- Prednisone vs. rituximab (*Ann Rheum Dis* 2015;74:1171)

CRYOGLOBULINEMIA

Definition & types (*Lancet* 2012;379:348; *Oncology* 2013;37:1098)

- 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

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.	

Etiologies

- Hematologic diseases
  Type I: multiple myeloma, MGUS, Waldenström's, chronic lymphocytic leukemia
  Type II: B-cell lymphomas, solid-organ malignancies
- Infections (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)
- Essential (idiopathic) in 10% of cases

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 patients with circulating cryoglobulins are asx

- Type I: hyperviscosity (cold worsens sx) → H/A, visual disturbance, livedo, digital ischemia
- Type II/III: vasculitis (sx not affected by cold exposure)
  - "Meltzer's triad" (purpura, arthralgias, weakness) seen in 25–30% of Pts
  - General: weakness, low-grade fever
  - Dermatologic (54–80%): lower extremity purpura, livedo reticularis, leg ulcers
  - Joint (44–70%): symmetric, migratory arthralgias of small or medium joints
  - Renal (50%): glomerulonephritis (proteinuria, hematuria, ARF, HTN, edema)
  - Neurologic (17–60%): peripheral neuropathy (polyneuropathy > mononeuritis multiplex)
  - Hematologic: anemia, thrombocytopenia, ↑ risk of B-cell lymphoma
  - GI (5%): abdominal pain, hepatosplenomegaly, abnormal LFTs

Diagnostic studies

- ✔ Cryoglobulins; must keep blood *warmed to 37°C at all times* en route to lab; early cooling causes false ⊖ cryoglobulin, loss of RF and ↓↓ complement
- *Cryocrit* is quantification of cryoprotein, does not always correlate w/ disease activity
- False ↑ in WBC or plt on automated CBC, due to cryoprecipitation
- Type I: ✔ serum viscosity, symptomatic if ≥4.0 centipoise; complement levels normal
- Type II: ↓ C4 levels, variable C3 levels, ↑ ESR, ⊕ rheumatoid factor (RF)
  - ✔ HCV, HBV, & HIV serologies in all Pts w/ mixed cryoglobulinemia
  - Bx of affected tissue: hyaline thrombi; vasculitis w/ mixed inflammatory infiltrates of small vessels; leukocytoclastic vasculitis in purpuric lesions

Treatment (*Blood* 2012;119:5996; *Medicine* 2013;92:61)

- Treat underlying disorder:
  - Lymphoproliferative disease: chemotherapy and/or radiation
  - HCV: antivirals ± immunosuppression for severe disease (*NEJM* 2013;369:1035)
  - Connective tissue–related disease: DMARD/steroids ± rituximab
- Type I: plasma exchange if hyperviscosity; steroids, alkylating agents, rituximab, chemo
- Type II: NSAIDs for control of mild symptoms for Pts w/ normal renal function.
  - Rituximab or cyclophosphamide for major organ involvement. For mixed cryo, plasmapheresis or plasma exchange only in severe, life-threatening disease.

AMYLOIDOSIS

Deposition of misfolded and insoluble fibrous proteins in normal organs and tissues

Classification of Amyloidosis			
Type	**Precursor**	**Causative diseases**	**Main organs affected**
AL (Primary) Most common ~2000 cases/y	Monoclonal Ig light chain	MM Light chain disease ($\lambda > \kappa$) MGUS, WM	**Renal, cardiac, GI, neuro, cutaneous,** hepatic, pulmonary
AA (Secondary)	Serum amyloid A (SAA)	Inflam: RA, IBD, FMF Chronic infxns: osteo, TB	**Renal, GI, hepatic,** neuro, cutaneous
Hereditary ↑ incid Afr Am	Mutant TTR, etc.	*Mutant* proteins	**Neurologic, cardiac**
Senile	Normal TTR	*Normal* proteins; 2° aging	**Cardiac**, aorta, GI
Aβ_2M	β_2-microglobulin	Dialysis-associated β_2m (normally renally excreted)	Musculoskeletal
Localized	β-amyloid protein Peptide hormones	Localized production and processing	Neurologic Endocrine

TTR, transthyretin (prealbumin). Adapted from *NEJM* 1997;337:898; 2003;349:583; & 2007;356:2361.

Clinical Manifestations of Amyloidosis (*Lancet* 2016;387:2641)		
System	Manifestations	Amyloid
Renal	Proteinuria or nephrotic syndrome	AL, AA
Cardiac	CMP (either restrictive or dilated); orthostatic hypoTN ↓ QRS amplitude, conduction abnormalities, AF	AL, hereditary, senile
GI	Diarrhea, malabsorption, protein loss Ulceration, hemorrhage, obstruction Macroglossia → dysphonia and dysphagia	All systemic
Neurologic	Peripheral neuropathy with painful paresthesias Autonomic neuro → impotence, dysmotility, ↓ BP Carpal tunnel syndrome	Hereditary, AL, organ-specific, Aβ_2M
Cutaneous	Waxy, nonpruritic papules; periorbital ecchymoses "Pinch purpura" = skin bleeds with minimal trauma	AL
Hepatic & splenic	Hepatomegaly, usually *without* dysfunction Splenomegaly, usually *without* leukopenia or anemia	All systemic
Endocrine	Deposition with rare hormonal insufficiency	Organ-specific
Musculoskel	Arthralgias and arthritis (especially shoulder)	AL, Aβ_2M
Pulmonary	Airway obstruction; pleural effusions	AL, AA
Hematologic	Factor X deficiency	AL

Diagnostic studies

- Biopsy (abdominal SC fat pad, rectal, or affected tissue) → apple-green birefringence on Congo red stain; fat pad bx Se 60–85%, Sp 90–100%
- If suspect AL → ✔ SIEP & UIEP (↑ Se vs. SPEP & UPEP) & free light chains, ± BM bx
- If suspect renal involvement ✔ U/A for proteinuria
- If suspect cardiac involvement ✔ ECG (↓ voltage, conduction abnl), TTE (biventricular valve leaflet & interatrial septum thickening), ↑ wall w/o ↑ volt has 75% Se, 95% Sp; MRI
- Genetic testing for hereditary forms

Treatment of Amyloidosis	
AL	Limited involvement: high-dose melphalan → auto HSCT (*NEJM* 2007;357:1083) Not HSCT candidate: [low-dose melphalan + dexamethasone] or [cyclophosphamide + bortezomib + dexamethasone] (*Blood* 2015;126:612) Relapsed: lenalidomide, thalidomide, or bortezomib (*Blood* 2010;116:1990 & 2014;124:2498)
AA	Rx underlying disease. Colchicine for FMF, esp. to prevent renal disease. ? Anti-cytokine Rx (anakinra or tocilizumab) (*Clin Exp Rheumatol* 2015;33:46)
ATTR	Liver Tx prevents further protein deposition (*Muscle Nerve* 2013;47:157) ↓ hepatic TTR production: siRNA (patisiran) or anti-sense oligo (inotersen) improve neuropathy (*NEJM* 2018;379:11 & 22) Stabilize TTR tetramers (also useful for senile amyloidosis): tafamidis ↑ QoL & ↓ CV hosp & mortality (*NEJM* 2018;379:1007)

- Clearance of amyloid by Ab against serum amyloid P under study (*NEJM* 2015;373:1106)
- Cardiac involvement: diuretics; avoid dig, CCB, and vasodilators; ? ICD for 1° prevention
- Heart, kidney, and liver Tx may be considered in those w/ advanced disease
- Median survival: 12–18 mo for AL (~6 if cardiac); 11 y for AA; variable for others

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)*
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: ↓ PaO2, ↑ PaCO2 GI: liver failure, ↑ NH3 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)
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 0.2mg 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 hypothermia if patient found down or has had head trauma

Targeted temperature management (*Circulation* 2015;132:2448)

- Indications: comatose (GCS <8) w/in 6h after cardiac arrest (not isolated resp. arrest). Studied only in VT/VF, but consider after asystole or PEA, or 6–12h post-arrest.
- Exclusions: pregnancy, CV instability despite pressors/assist devices, other cause of coma, persistent ↓ O_2. Relative contraindications: major head trauma, coagulopathy/bleeding, major surgery <14d, systemic infection/sepsis.
- Target temp: 32–36°C × ≥24h. Initial studies showing benefit targeted 32–34°C, but subsequent study showed ≈ outcomes for 36°C vs. 33°C (*NEJM* 2013;369:2197). Some still target 32–34°C and reserve 36°C for Pts w/ contraindic to more aggressive cooling.
- Method: ice packs to head/neck/torso; cooling blankets; cooling vest or endovascular catheter. Goal to achieve target temp <6h (but no benefit to prehosp cooling; *JAMA* 2014;311:45). Pts should be sedated/paralyzed while cooled. MAP goal >70. Start rewarming 24h after cooling is initiated (rewarm ≤0.5°C per h).
- In Pts not cooled or after rewarming Pts who were cooled: prevent fever (goal <36°C) for ≥48h post arrest
- 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
- 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 >33, diffuse hypoxic injury on MRI. 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, incontinence
    - 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, tox screen, AED levels (valproic acid and phenytoin have therapeutic range; levetiracetam level rarely useful unless ? noncompliance), illicit drug screen
- 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 24h, sleep deprivation and repeated studies ↑ dx yield of EEG.
- Long-term EEG monitoring (hrs to days): if suspicion for non-convulsive 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) or 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, 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
- May consider withdrawal of meds if seizure free (typically for at least 1 y) and normal EEG
- 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
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 glc, metabolic panel, CBC, tox screen, 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	**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 10 mg Up to 10 mg x1 Up to 10 mg IV; up to 20 mg PR
<10	**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		
<30–60	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 sx (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, coingestions, acute liver failure, GIB
- Ten-item scale (CIWA-Ar) used to assess and manage alcohol withdrawal (see Appendix)

Treatment (*NEJM* 2003;348:1786)

- Benzodiazepines (BDZ)
  - Drug: diazepam (long-acting w/ active metab; ↓ risk of recurrent withdrawal), lorazepam (short half-life), 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 q1h until score <8 × 8 h, then q2h × 8 h, and if stable, then q4h (*JAMA* 1994;272:519)
- If refractory to BDZ prn → BDZ gtt, phenobarb, dexmedetomidine, or propofol (& intubation)
- *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
- Prophylaxis: 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 (based on severity of EtOH use) q6h × 24 h, then 25–50 mg q6h × 2 d

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.
- Vertigo Ddx:
  - *Peripheral*
    - 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; if w/ hearing loss = labyrinthitis
  - *Central*
    - 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)
  - Head impulse test: Pt fixates on examiner's nose during rapid passive head turn; presence of "catch-up saccade" supports peripheral dysfunction to side of turn
  - Nystagmus (see table above)
  - Test of skew: vertical refixation saccade on alternating eye cover supports central cause
- Dix-Hallpike test: Pt sitting → lying back w/ 45° 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: ECG, basic labs, if concerning s/s on HINTS → MRI brain
- Treatment: reposition maneuv. for BPPV, vestib. PT; anti-hist., sedatives or anti-emetics

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: dissection, vasculitis, vasospasm, hypercoag, hypoperfusion, 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
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 $ABCD^2$: Age ≥60 y (+1); BP ≥140/90 (+1); Clin features: unilat. weak. (+2), speech impair. w/o weakness (+1); Duration ≥60 (+2) or 10–59 min (+1); DM (+1)

Physical exam

- General: murmurs, carotid & subclavian bruits, peripheral emboli, endocarditis stigmata
- Neurologic exam, NIH stroke scale (http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.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, and not Se for small & brainstem. CTA if considering endovascular intervention.

Acute treatment of ischemic stroke (*Lancet* 2017;389:641; *Stroke* 2018;49:e46)

- 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, ∅ ICH, ∅ 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, ∅ mortality benefit (nb, trial excluded patients with previous strokes + DM)
  Data for TNK, Rx up to 9 h, and for MRI imaging to guide Rx (*NEJM* 2018;378:1573 & 379:611; 2019;380:1795)
- BP: lower to <185/110 to consider lysis; if lyse keep <180/105 × 24 h (consider 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 indicated if w/in 6 h of sx onset, pre mRS 0-1, occlusion in ICA or MCA, NIHSS ≥6 (clinical severity), ASPECTS ≥6 (CT based likelihood of recovery) (*NEJM* 2015;372:11, 1009, 1019, 2285 & 2296; *Lancet* 2016;387:1723). 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: prolonged Holter for AF (eg, 10 d at presentation, 3 & 6 mo detects in 14%); 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 hrs, persists for wks; *PWI* differentiates irreversibly infarcted core vs. viable penumbra; *T1 fat-sat* (neck vessels) if suspicious for dissection

Secondary stroke prevention (*NEJM* 2012;366:1914)

- 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)
  clopidogrel + ASA (vs. ASA alone): Rx for 21 d in minor strokes/TIA → ↓ risk of stroke, ? ↑ ICH; longer Rx not better & ↑ ICH (*NEJM* 2013;369:11 & 2018;379:215; *BMJ* 2018;363:k5108) 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 120–139 mmHg (*JAMA* 2011;306:2137)
- ↓ LDL-C (<< 70 mg/dL): ↓ recurrence w/ statin PCSk9i added to statin (*NEJM* 2017;376:1713)
- Fluoxetine: improved motor recovery after 3 mo (*Lancet Neurol* 2011;10:123)
- 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. stroke rate ≈ (*NEJM* 2016;374:1011 & 1021; *Lancet* 2016;387:1305; *Lancet Neuro* 2019;18:348)

Patent foramen ovale (PFO; in ~27% of population) (*NEJM* 2005;353:2361)

- ↑ stroke risk: ≥4 mm separation, R→L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- If PFO & stroke/TIA: no benefit of warfarin over ASA (*Circ* 2002;105:2625), but consider if at high risk for or has DVT/PE. Closure ↓ recurrence by ≥50% if ↑ risk features (see above) and absence of factors suggesting alternate etiology (*NEJM* 2017;377:1011, 1022, 1033). 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). Consider closure if >7 (*JAHA* 2018;7:1).

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 tx 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 ↑; IPH: no obvious benefit (*Lancet* 2013;382:397)
- 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 n. (carpal tunnel); ulnar n. (elbow or wrist); radial n. (spiral groove); com. peroneal n. (fibular head w/ leg crossing); lat. femoral cutan. n. (inguinal lig)
- Mononeuropathy multiplex (axonal loss of multiple, noncontig. nerves): vasculitic synd. (eg, PAN, Churg–Strauss, Wegener's, 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}, TSH, ESR, SPEP + IF
- EMG/NCS (often no change in 1st 10–14 d or in small-fiber neuropathy)
- Based on H&P: LFTs, 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-BARRÉ SYNDROME (GBS)

Definition & epidemiology (*Nat Rev Neurol* 2014;10:469)
- 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), URI (*Mycoplasma*), gastroenteritis (*Campylobacter*), Lyme, immunizations (no proven risk w/ current), surgery

Clinical manifestations (*Lancet* 2016;388:717)
- 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 (telemetry)
- 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: 1 in 7500; affects all ages, peak incidence 20s–30s (women), 60s–70s (men)
- 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); 20% will only have ocular sx; 15% w/ bulbar (difficulty chewing, dysarthria, dysphagia)
- Limb weakness proximal > distal; DTRs preserved; minimal/no atrophy
- MusK MG (F >> M): mostly cranial/bulbar, neck, and resp weakness
- Exacerb. triggered by stressors: URI, surgery, preg/postpartum, meds (eg, Mg, AG, macro-lides, FQ, procainamide, phenytoin, D-penicillamine). Prednisone can *worsen* sx acutely.
- Myasthenic crisis = sx exacerbation, risk of respiratory compromise
- Cholinergic crisis = weakness due to *overtreatment* with anticholinesterase meds; may have excessive salivation, abdominal cramping and diarrhea; rare at normal doses

Diagnostic studies

- Bedside: ptosis at baseline or after >45 sec of sustained upgaze; improved ptosis with ice pack over eyes for 2–5 min (Se 77%, Sp 98%)
- 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

- Thymectomy if thymoma and in Ab ⊕ Pts w/o thymoma (*NEJM* 2016;375:511)
- Cholinesterase inhibitor (eg, pyridostigmine) is most rapid acting (benefit in 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) + AZA (benefit in 6–15 mo). If no response: mycophenolate, rituximab, MTZ, CsA. Goal to taper off steroids
- Myasthenic crisis: treat precipitant; consider d/c cholinesterase inhibitor if suspect cholinergic crisis. IVIg or plasmapheresis; if no response, high-dose glucocorticoids (in

monitored setting b/c risk for initial worsening). ICU if rapid or severe (follow FVC, NIF).

MYOPATHIES

Etiologies

- Hereditary: Duchenne, Becker, limb-girdle, myotonic, metabolic, mitochondrial
- Endocrine: hypothyroidism, hyperparathyroidism, Cushing syndrome
- Toxic: statins, fibrates, glucocorticoids, zidovudine, alcohol, cocaine, antimalarials, colchicine, penicillamine
- Infectious: HIV, HTLV-1, trichinosis, toxoplasmosis
- 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 (if statin use), 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 (International Headache Society Classification)

- 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). Ppx: CCB (verapamil). Rx: high-flow O_2 (12–15 L/min), sumatriptan.
  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

- 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 (*JAMA* 2006;296:1274 & 2013;310:1248)

- History: onset (sudden vs. gradual), quality, severity, location, duration, triggers, alleviating factors, positional component, hormonal triggers (menstruation), preceding trauma, associated sx (visual Δs, "floaters," N/V, photophobia, focal neurologic sx), medications (analgesics), substance abuse (opioids, caffeine), personal/family hx of HA

- General and neurologic exam (including funduscopic exam, visual fields)
- Warning signs (should prompt neuroimaging)
  Explosive onset (vasc); "worst HA of my life" (SAH, RCVS); *meningismus* (SAH, infxn)
  Positional: lying > standing (↑ ICP); *N/V* (↑ ICP; migraines)
  Visual sx: diplopia, blurring, ↓ acuity (GCA, glaucoma, ↑ ICP); *eye pain* (glaucoma, trigeminal autonomic cephalalgia, optic neuritis)
  Abnl neuro exam (struct. lesion, poss. in migraine); ↓ *consciousness* (± fever): infxn, ICH
  Age >50 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)

- 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(s) 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

- 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: valproic acid, topiramate, β-blockers (propranolol first-line), TCAs, Mg, B2, botox, anti-CGRP & receptor mAbs (femanezumab, erenumab; *NEJM* 2017;377:2113 & 2123)

BACK AND SPINAL CORD DISEASE

Differential diagnosis of back pain

- Musculoskeletal: involving spine (vertebra, facet joints), paraspinal muscles and ligaments, sacroiliac joint, or hip joint. Spondylolisthesis, vertebral fx, OA, inflam. spondyloarthritis (RA, ankylosing spondylitis, reactive, psoriatic), 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
- 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)

- History: location, radiation, trauma, wt loss, cancer hx, fever, immunocompromised, IV drug use, neurologic sx, saddle anesthesia, bowel/bladder sx (retention, incont.)
- 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 (sacroiliac joint syndrome): severe pain on hip external rotation; 70% Se, 100% Sp
  Neurogenic claudication in lumbar stenosis (see table on next page)
- Neurologic exam: full motor (including sphincter tone), sensory (including perineal region; note dermatomal patterns), and reflexes including bulbocavernous, anal wink (S4), and cremasteric (L2)
- Red flags: upper motor neuron signs (hyperreflexia, upgoing toes), cauda equina or conus medullaris syndromes (saddle anesthesia, bowel or bladder dysfunction, reduced rectal tone, loss of sacral reflexes), 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

SPINAL CORD COMPRESSION

Clinical features

- Etiologies: tumor (vertebral mets, intradural meningioma/neurofibroma), epidural abscess or hematoma, vascular malformation (dural AV fistula), degenerative dis. (spondylosis)
- 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 q6h) 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)

- 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
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)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

	Surgery (if other Rx fails)	

Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. (*NEJM* 2007;356:1241 & 2008;358:818)

Evaluation & treatment of nerve root compression (*NEJM* 2016;374:1763)

- MRI if sx not improved after 6 wk of conservative tx; if non-diagnostic, consider EMG/NCS
- Conservative: avoid bending/lifting; soft collar (cervical radiculopathy); NSAIDs; muscle relaxants; lidocaine patch/ointment; Rx neuropathic pain (see "Peripheral Neuropathies"); physical therapy. Insufficient evidence to recommend 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; bowel/bladder dysfunction; failure to respond to conservative Rx after 3 mo

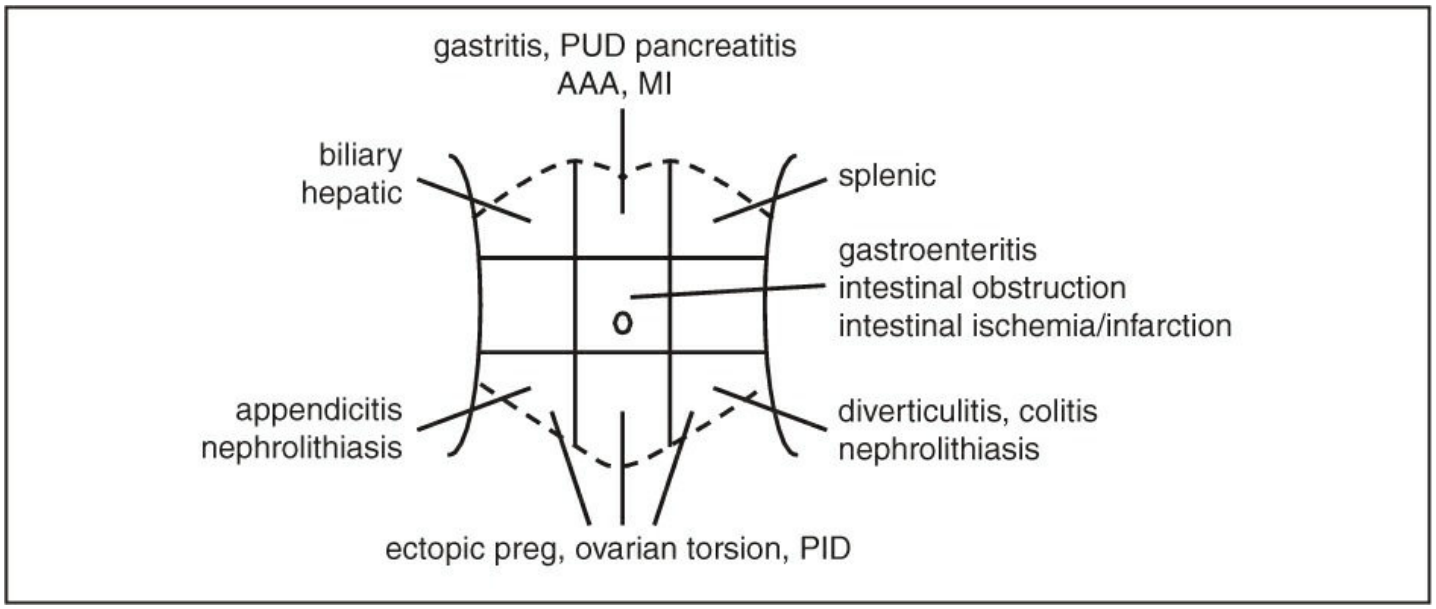
SURGICAL ISSUES

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), 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)
- Acute mesenteric ischemia (esp if afib, "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: KUB (upright) or if stable, CT abd/pelvis 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 esp. 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 presence 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
- Pre-existing 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

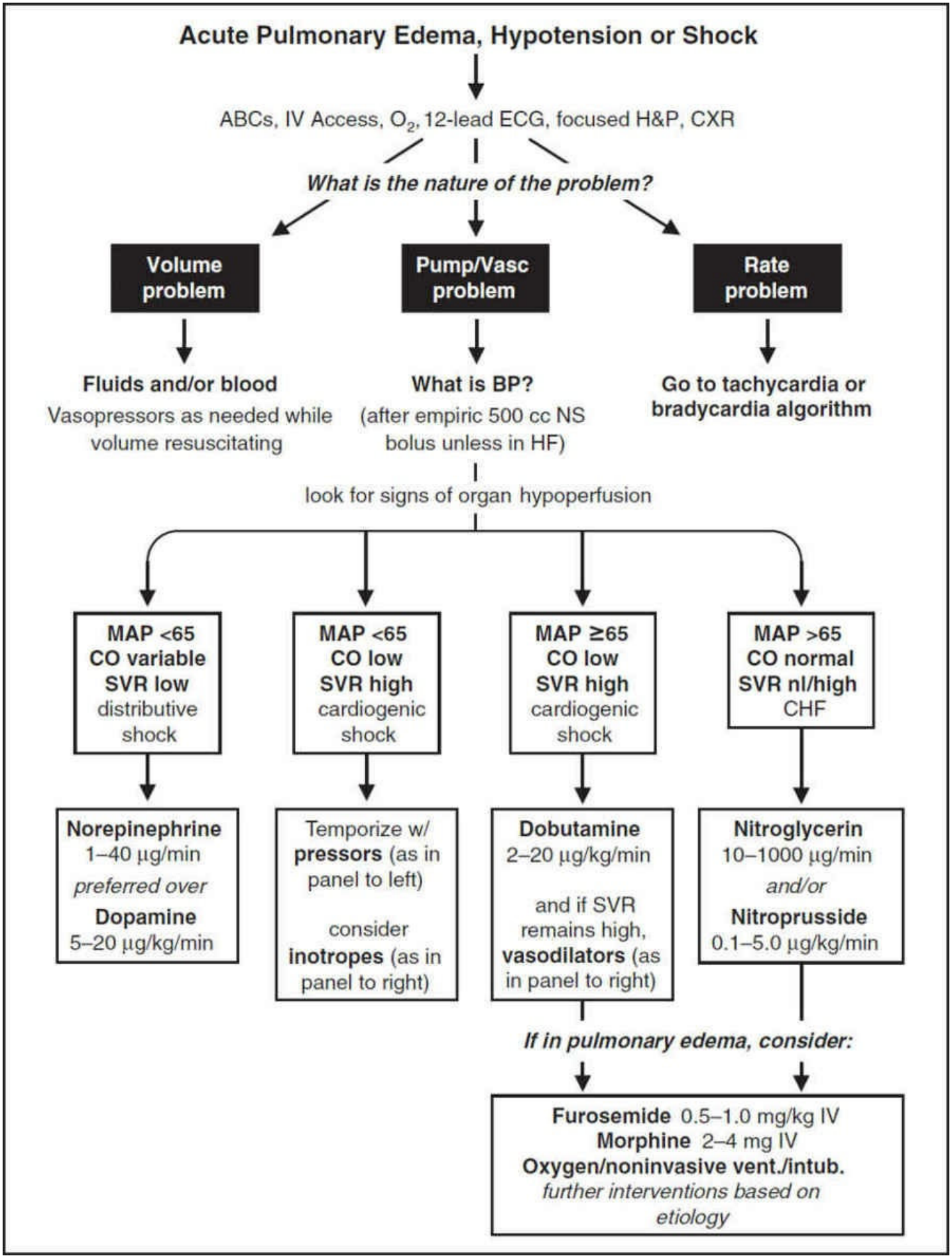
- Chemical splash: alkali worse than acid; immediate eye flush; pH 7.3–7.4 normal
- Acute angle closure glaucoma: fixed mid-dilated pupil, corneal edema, high intraocular pressure (typically >50; normal 8–21). Rx w/ topical drops; may require AC tap/laser.
- Penetrating eye injury: protect eye (no patching), 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	$\alpha_1, \alpha_2, \beta_1, \beta_2$	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 (Class III)	1 mg over 10 min, 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



(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 (eg, penicillin)	Some GPC, GPR, GNC, many anaerobes (not *Bacteroides*)	Group A strep, Enterococci, *Listeria, 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	*E. coli, Proteus, Listeria, H. influenzae Salmonella, Shigella, Enterococci*
Extended (eg, piperacillin)	Penetrate porin channel of Gram ⊖ More resistant to PCNases	Most GNR incl. *Enterobacter, Pseudomonas, Serratia*
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
β-lact. inhib. (eg, sulbactam, clavulanate)	Inhibit plasma-mediated β-lactamases	Adds staph, *B. fragilis*, & some GNR (*H. flu, M. cat*, some *E. coli*); intrinsic activity against *Acinetobacter*

Cephalosporins		
Resistant to most β-lactamases. No activity vs. enterococci.		
Gen.	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
3rd (eg, ceftriaxone, ceftazidime)	Broad activity vs. GNR & some anaerobes. Ceftazidime active vs. *Pseudomonas*.	PNA, sepsis, meningitis
4th (eg, cefepime)	↑ resistance to β-lactamases (incl. of staph and *Enterobacter*)	Similar to 3rd gen. MonoRx for nonlocalizing febrile neutropenia
5th (eg, ceftaroline)	Only class of cephalosporin with MRSA activity. 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 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	Enteric GNR & atypicals. 3rd & 4th gen. ↑ 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	Some enteric GNR, *Stenotrophomonas*, PCP, *Nocardia, Toxo*, most community-acquired MRSA
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (↑ resis. to *B. fragilis*)
Metronidazole	Almost all anaerobic Gram, most anaerobic Gram ⊕
Doxycycline	*Rickettsia, Ehrlichia, Anaplasma, Chlamydia, Mycoplasma, Nocardia*, Lyme
Tigecycline	Many GPC incl. MRSA & VRE; some GNR incl. ESBL but not *Pseudomonas* or *Proteus.*

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
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) = $\frac{MAP - \text{mean RA}}{CO} \times 80$	800–1200 dynes × sec/cm^5
Pulmonary vascular resistance (PVR) = $\frac{\text{mean PA} - \text{mean PCWP}}{CO} \times 80$	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 >1.0 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)

$$\text{or: AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{LVOT}}{V_{AoV}}\right) \quad (\text{all of which can be measured on echo})$$

$$\text{Gorlin equation: Valve area} = \frac{\text{CO}/(\text{DEP or SEP}) \times \text{HR}}{44.3 \times \text{constant} \times \sqrt{\nabla P}} \quad (\text{constant} = 1 \text{ for AS, } 0.85 \text{ for MS})$$

$$\text{Hakki equation: Valve area} \approx \frac{\text{CO}}{\sqrt{\nabla P}}$$

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	*Acute:* pulm edema, infxn (PCP, viral, resolving bact. PNA) *Chronic:* ILD

	visible)	w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF
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 1–2-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 $R \approx 0.8$)

$$P_AO_2 = 150 - \frac{P_aCO_2}{0.8} \text{ (on room air)}$$

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) = (UN_a + U_K) – U_{Cl}

Calculated osmoles $= (2 \times \text{Na}) + \left(\frac{\text{glc}}{18}\right) + \left(\frac{\text{BUN}}{2.8}\right) + \left(\frac{\text{EtOH}}{4.6}\right)$

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 $(FE_{Na}, \%) = \left[\frac{\frac{U_{Na}(\text{mEq/L})}{P_{Na}(\text{mEq/L})} \times 100\%}{\frac{U_{Cr}(\text{mg/mL})}{P_{Cr}(\text{mg/dL})} \times 100\ (\text{mL/dL})}\right] = \frac{\frac{U_{Na}}{P_{Na}}}{\frac{U_{Cr}}{P_{Cr}}}$

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)

$$\text{Free } H_2O \text{ deficit} = TBW \times \left(\frac{[Na]_{serum} - 140}{140}\right) \approx \left(\frac{[Na]_{serum} - 140}{3}\right) \text{(in 70-kg Pt)}$$

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
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
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 ($t_{½}$ 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
Cftx	ceftriaxone
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
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
	carotid sinus massage

CSM	
CT	computed tomogram
CTA	CT angiogram
CTD	connective tissue disease
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
	diffusion capacity of the lung

DLCO	
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
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
FEV1	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
	glomerular filtration rate

GFR	
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 β2-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
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
	left ventricle

LV	
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
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
	non-small cell lung cancer

NSCLC	
NSF	nephrogenic systemic fibrosis
NTG	nitroglycerin
N/V	nausea and/or vomiting
NVE	native valve endocarditis
NYHA	New York Heart Association
O&P	ova & parasites
OA	osteoarthritis
OCP	oral contraceptive pill
O/D	overdose
OG	osmolal gap
OGT	orogastric tube
OGTT	oral glucose tolerance test
OI	opportunistic infection
OM	obtuse marginal cor. art.
OSA	obstructive sleep apnea
OTC	over-the-counter
o/w	otherwise
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
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
	pressure support

PS	
	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
	red blood cell

RBC	
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
SAS	sulfasalazine
SBE	subacute bacterial endocarditis
SBO	small bowel obstruction
	spontaneous bacterial peritonitis

SBP	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
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
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
T3RU	T3 resin uptake
TAA	thoracic aortic aneurysm
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
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
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 thromboembolism
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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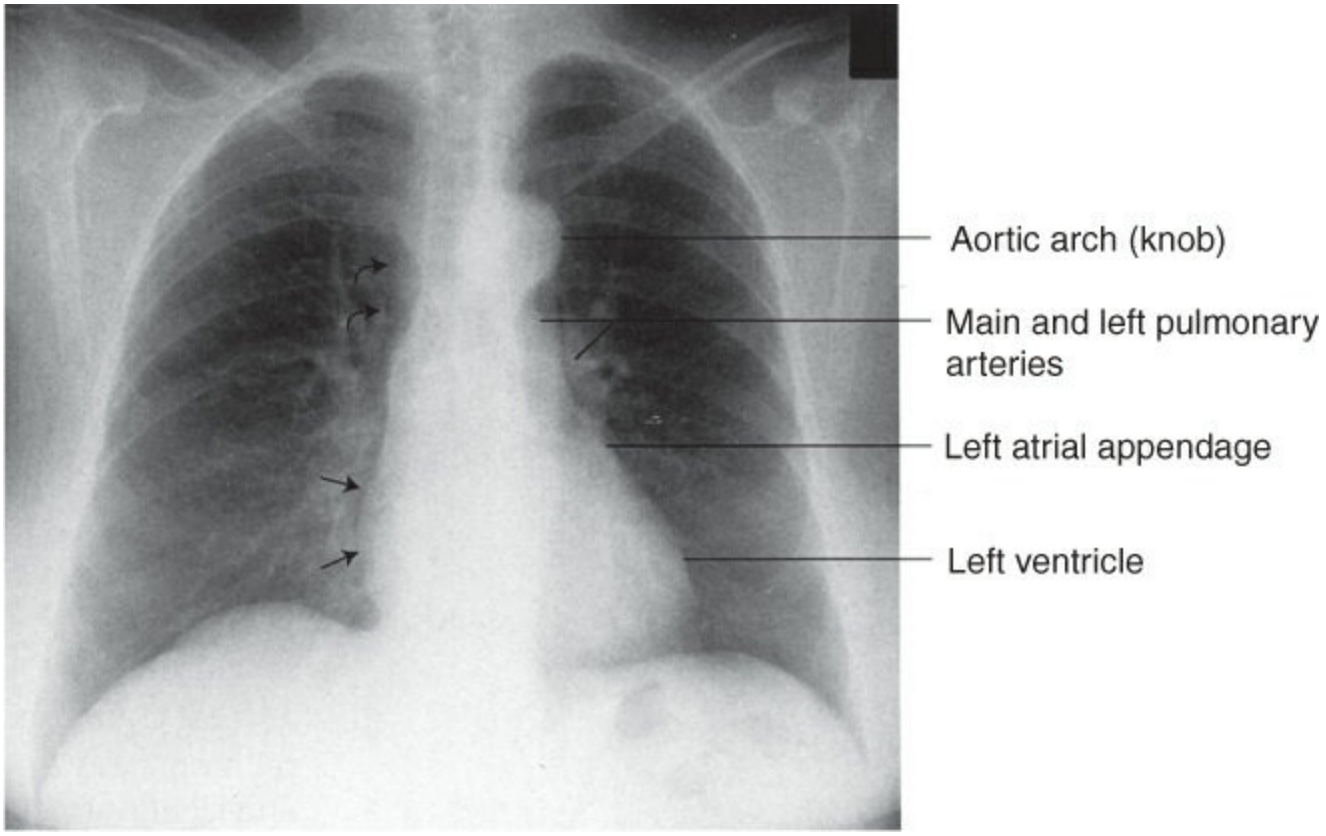
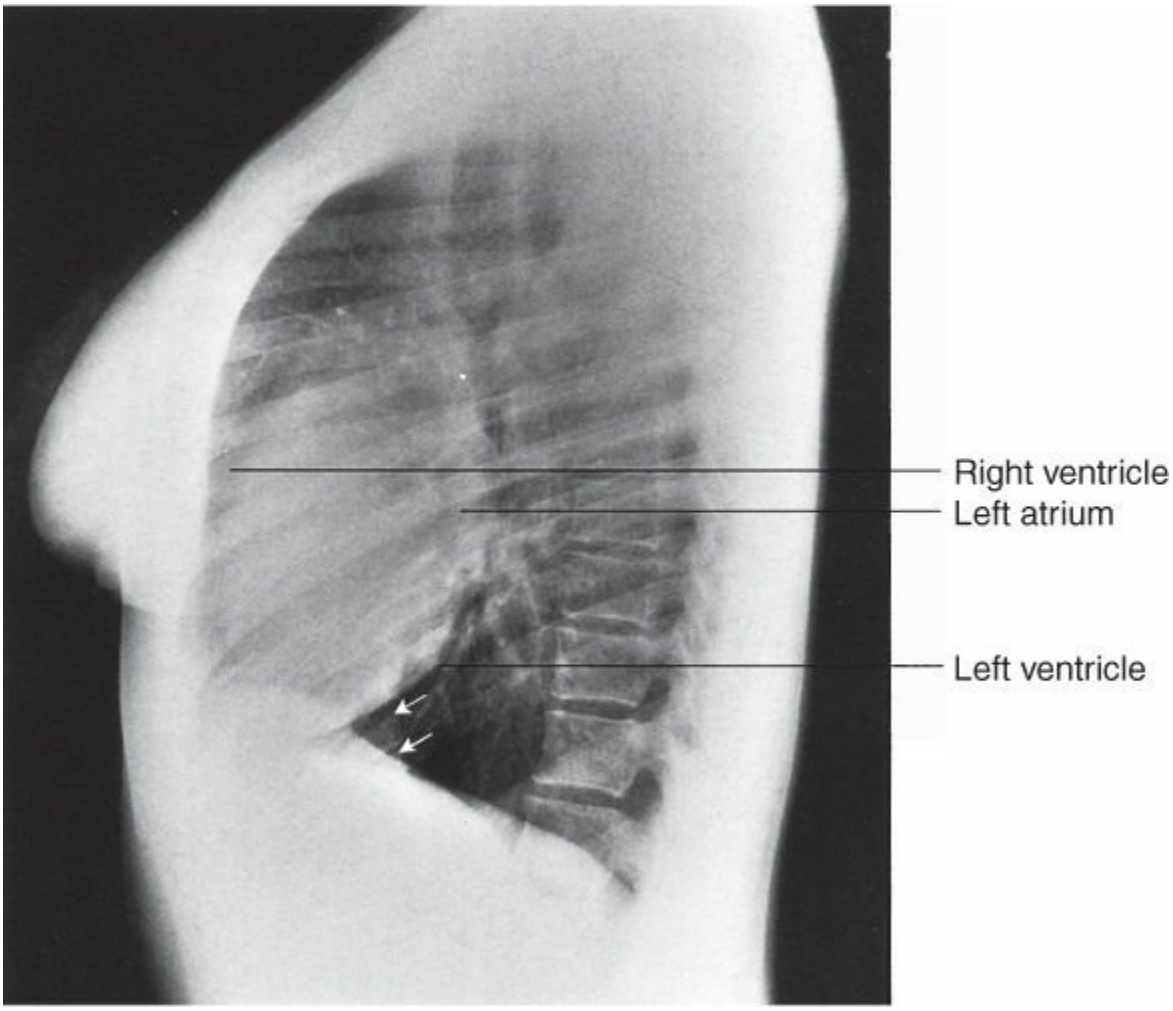
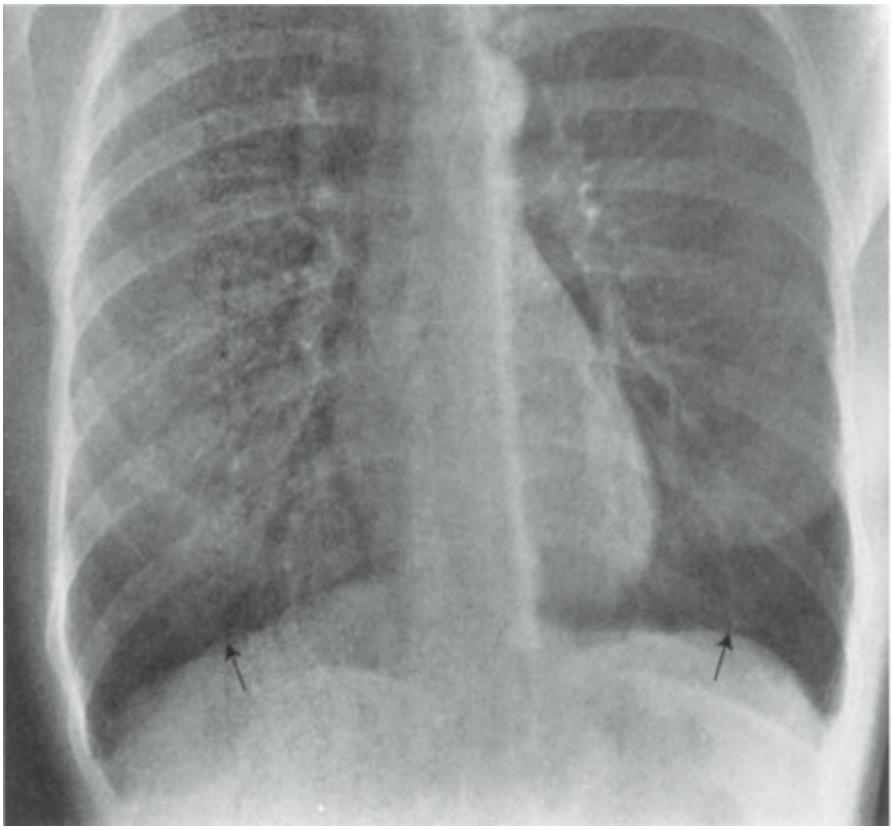
Radiology



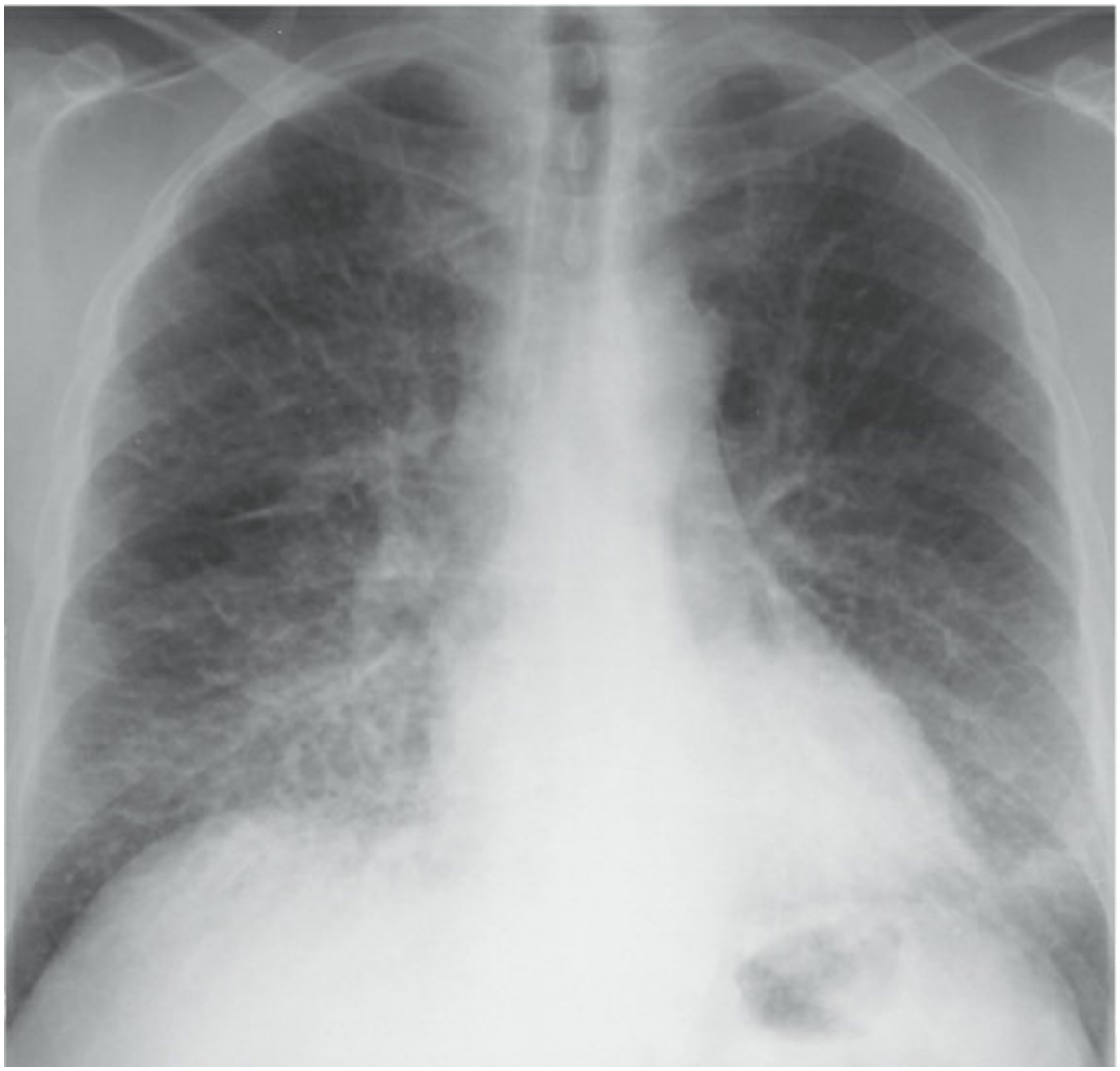
1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicate the location of the superior vena cava. The left cardiac and great vessels border what might be considered as 4 skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (*Radiology* 101, 3rd ed, 2009.)



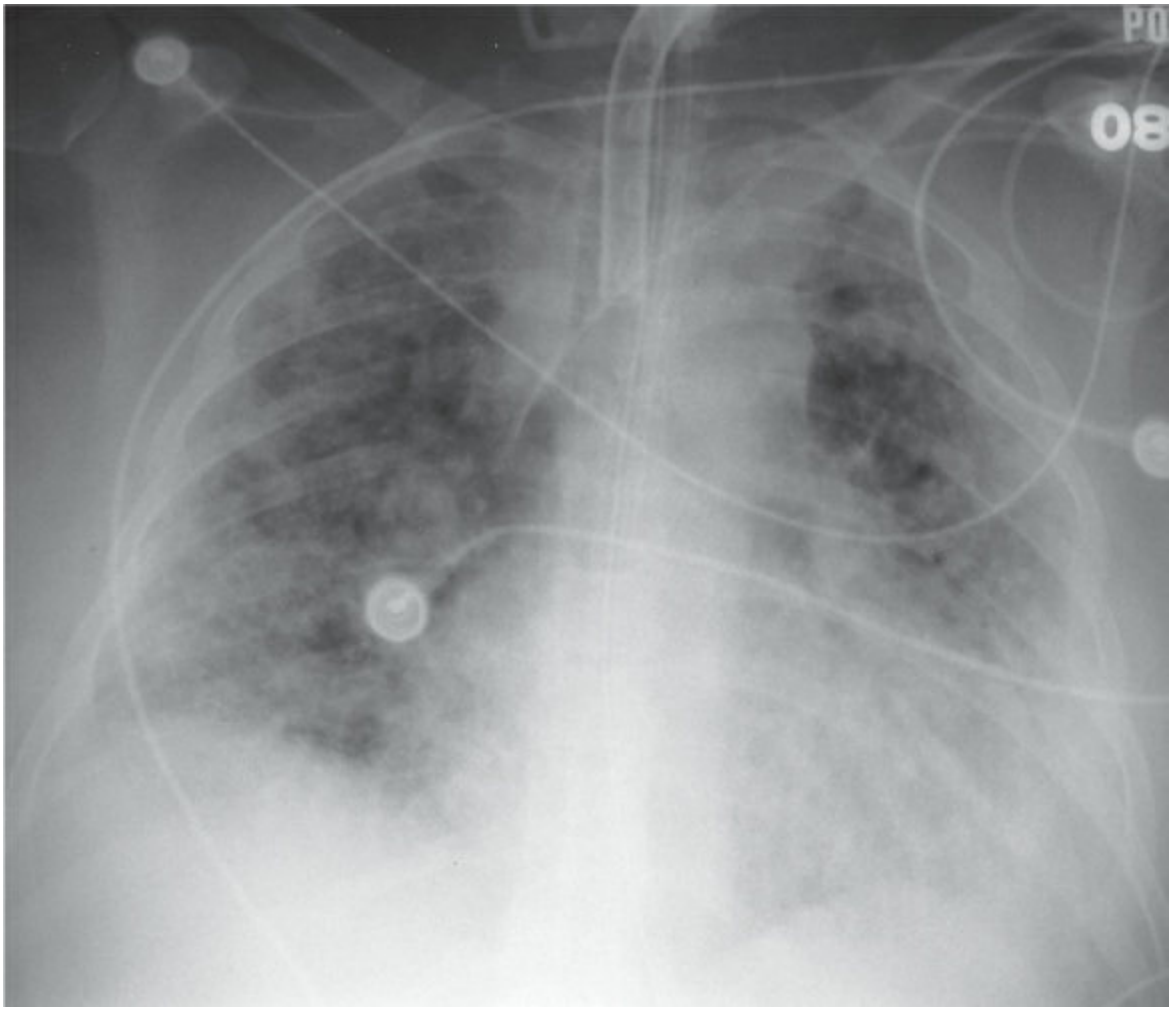
2 Normal lateral CXR. (*Radiology* 101, 3rd ed, 2009.)



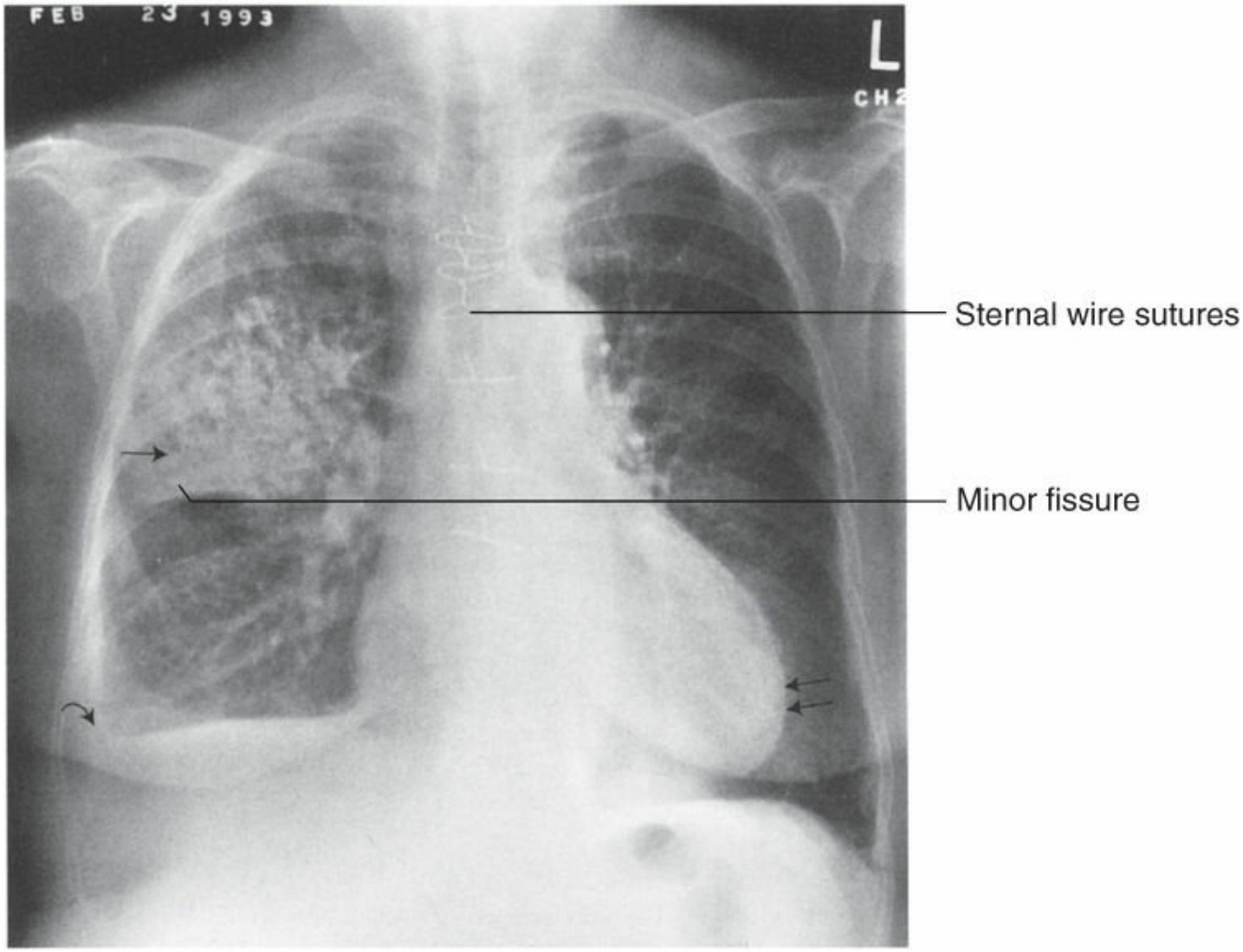
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology* 101, 3rd ed, 2009.)



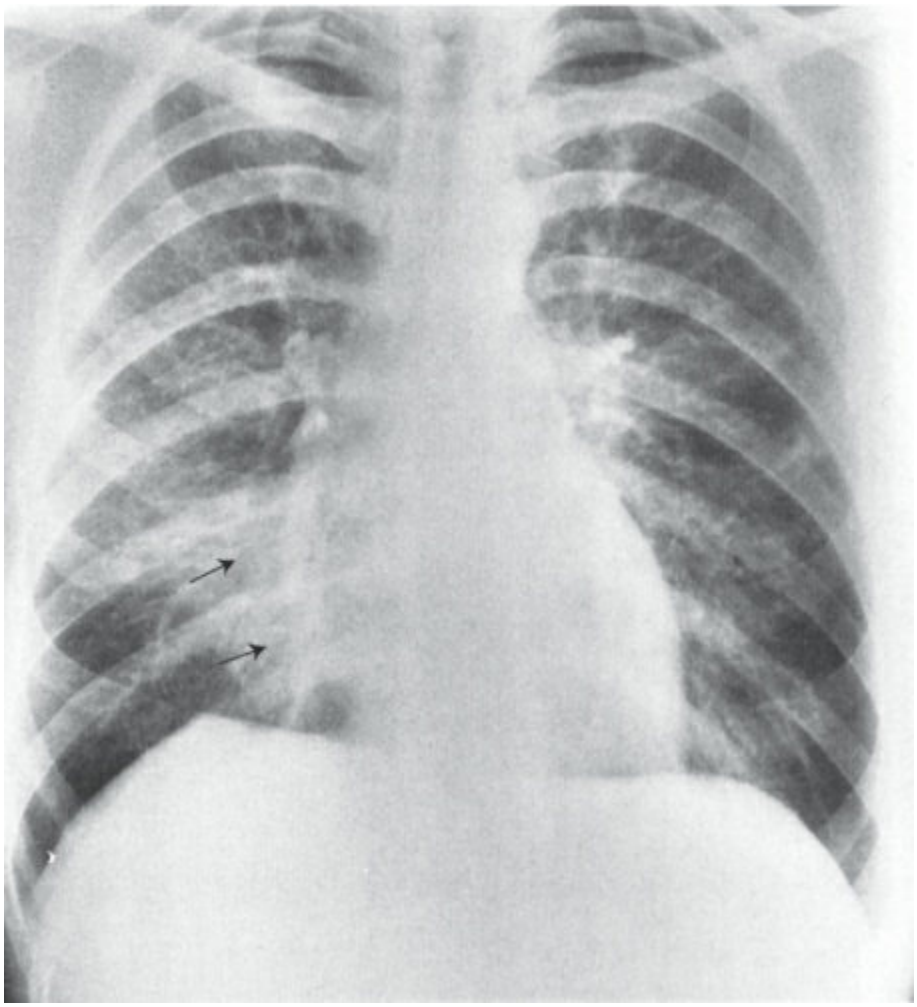
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology* 3rd ed, 2006.)



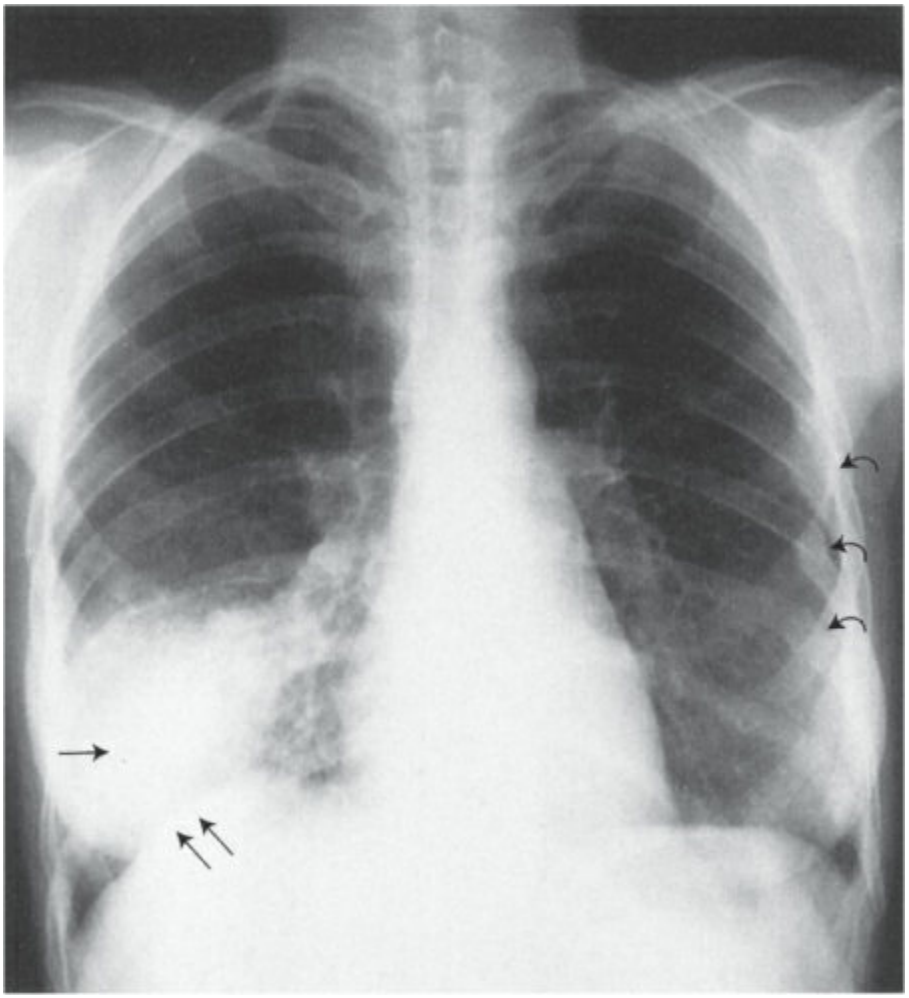
5 Alveolar pulmonary edema. (*Fund. Diag. Radiology* 3rd ed, 2006.)



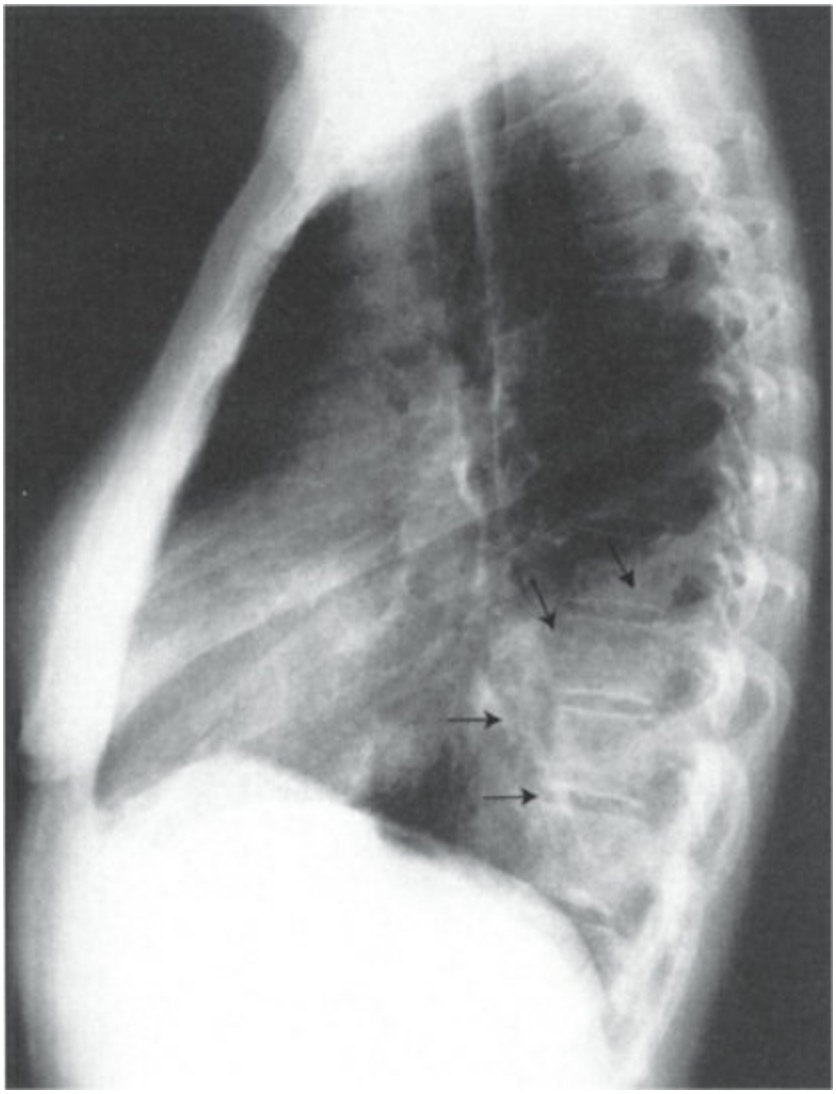
6 Right upper lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



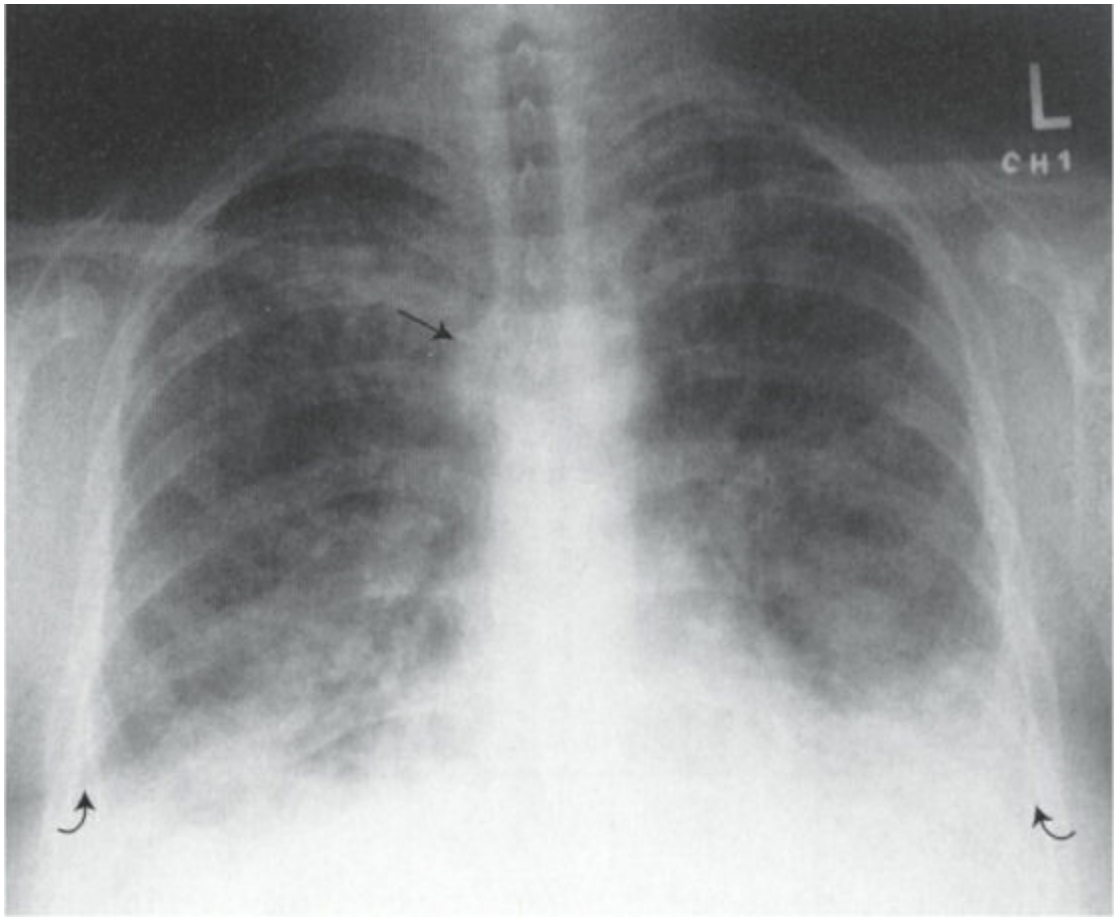
7 Right middle lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



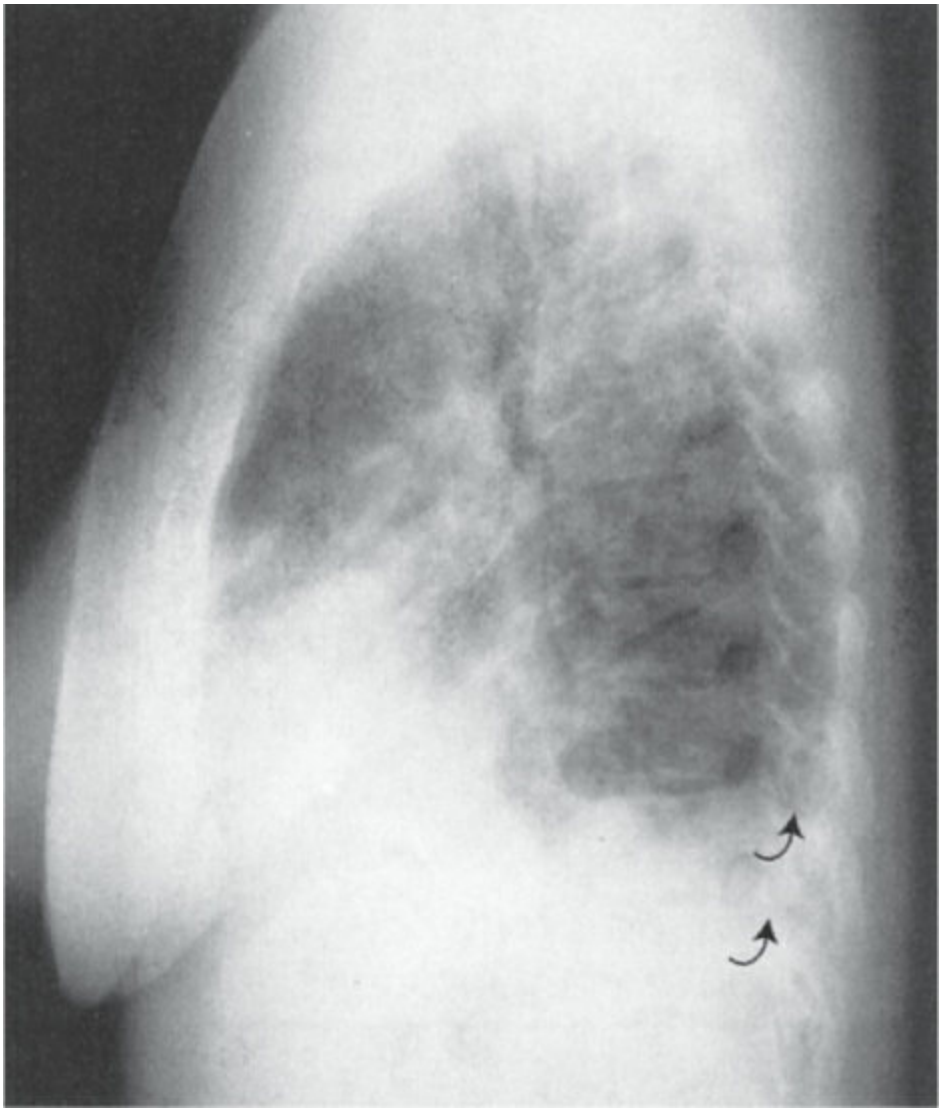
8 Right lower lobe pneumonia (PA). (*Radiology* 101, 3rd ed, 2009.)



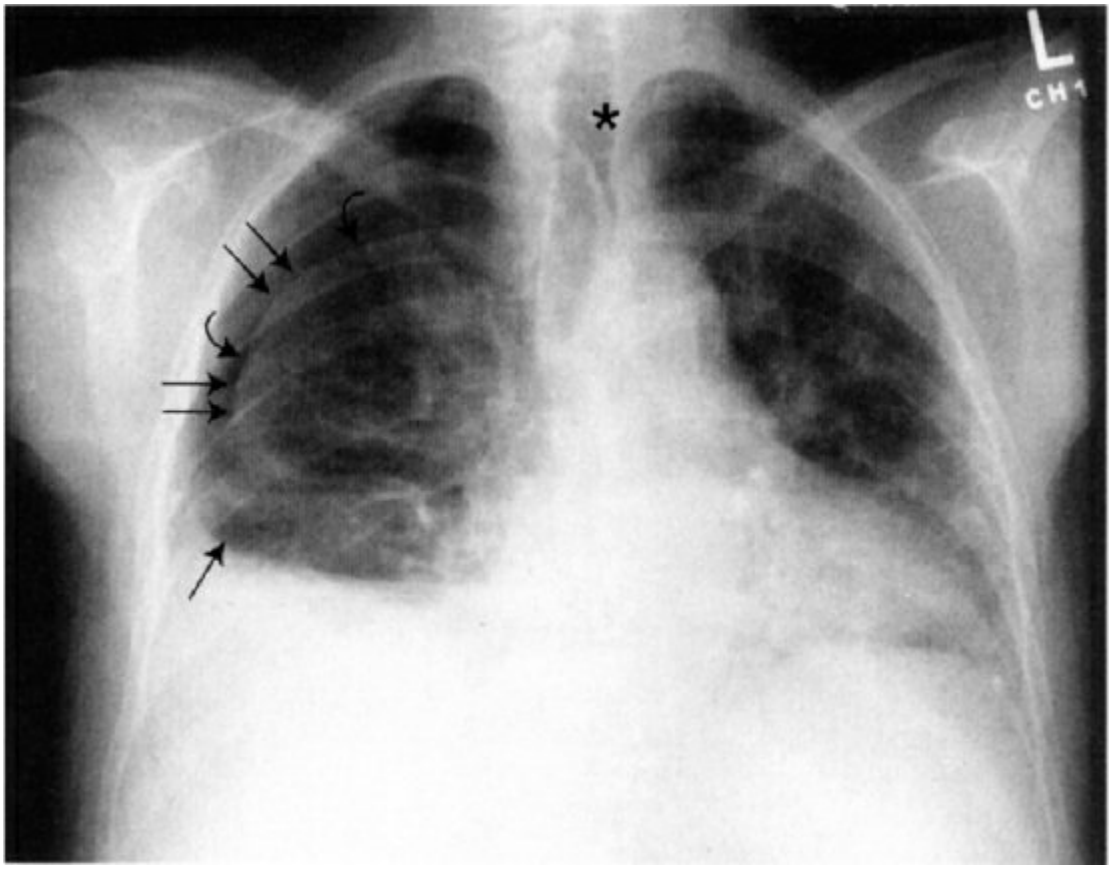
9 Right lower lobe pneumonia (lateral). (*Radiology* 101, 3rd ed, 2009.)



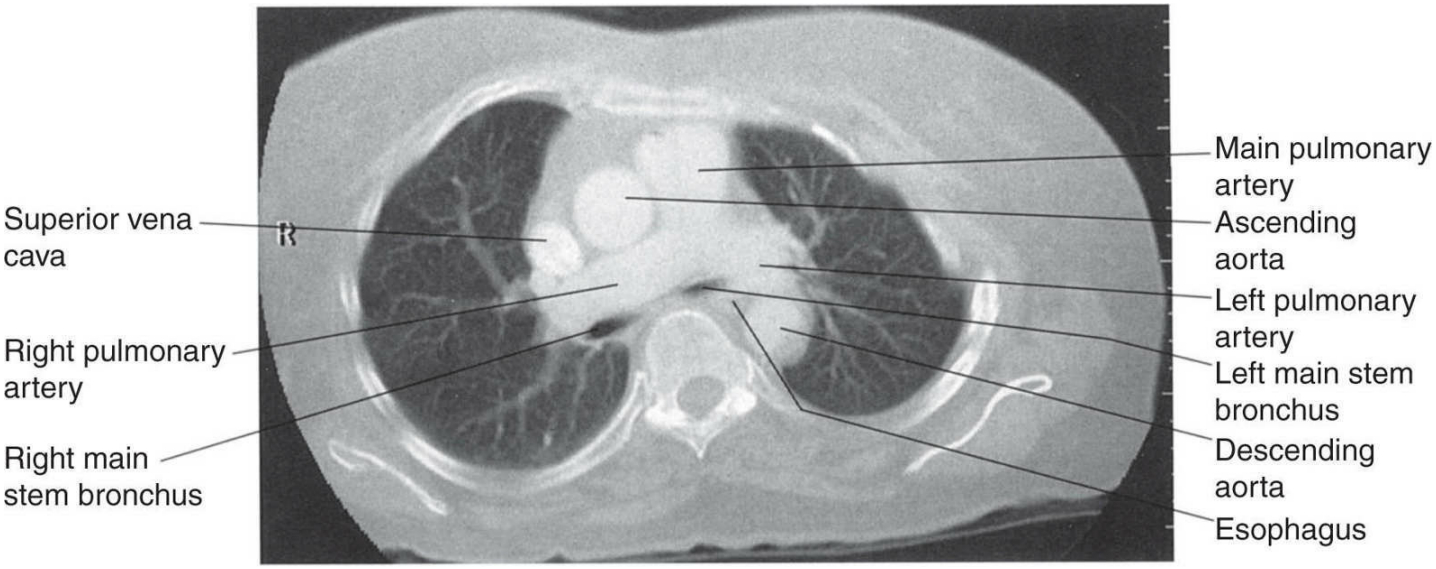
10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow) (PA). (*Radiology* 101, 3rd ed, 2009.)



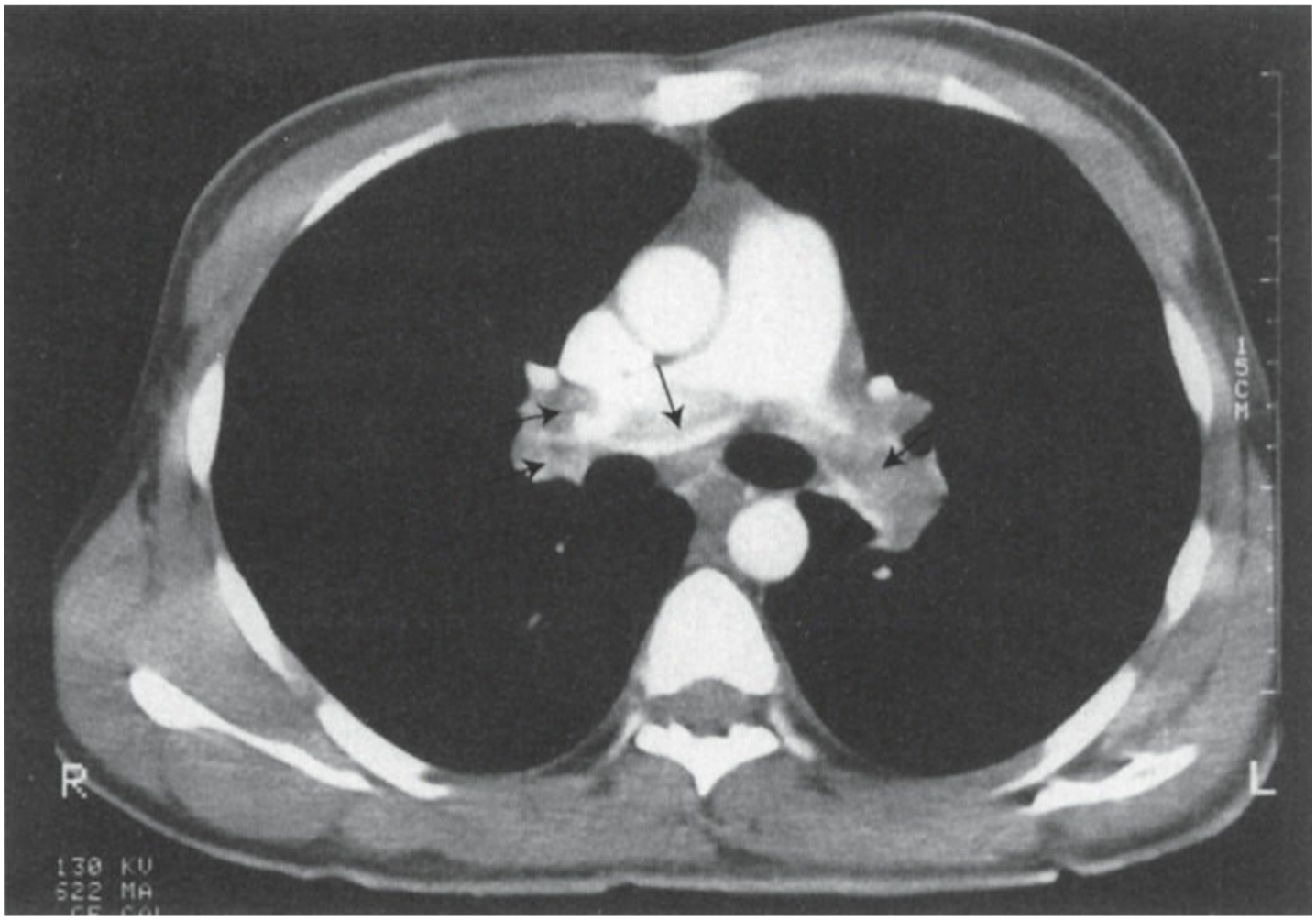
11 Bilateral pleural effusions (curved arrows) (lateral). (*Radiology* 101, 3rd ed, 2009.)



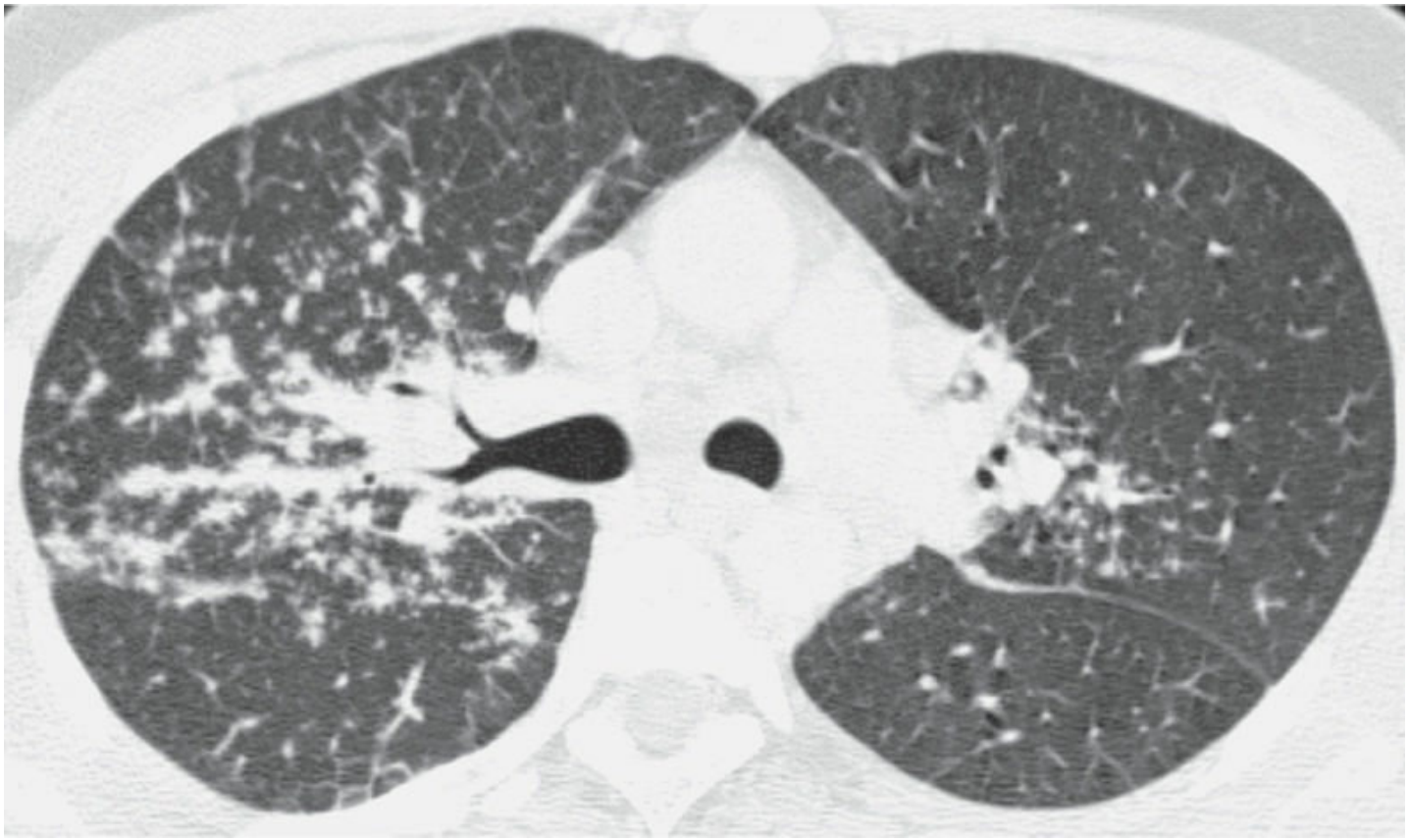
12 Pneumothorax. (*Radiology* 101, 3rd ed, 2009.)



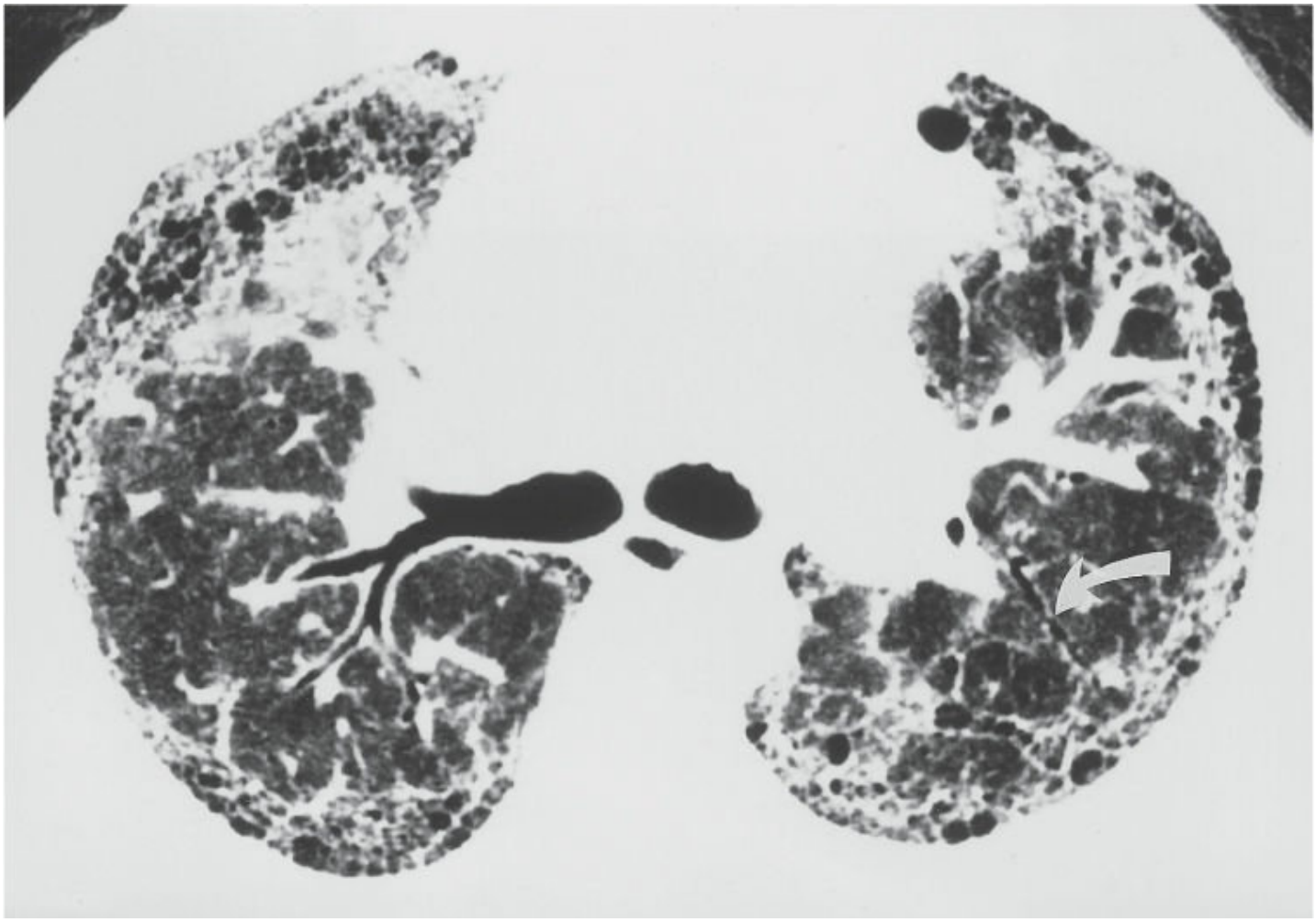
13 Normal chest CT at level of pulmonary arteries (parenchymal windows). (*Radiology* 101, 3rd ed, 2009.)



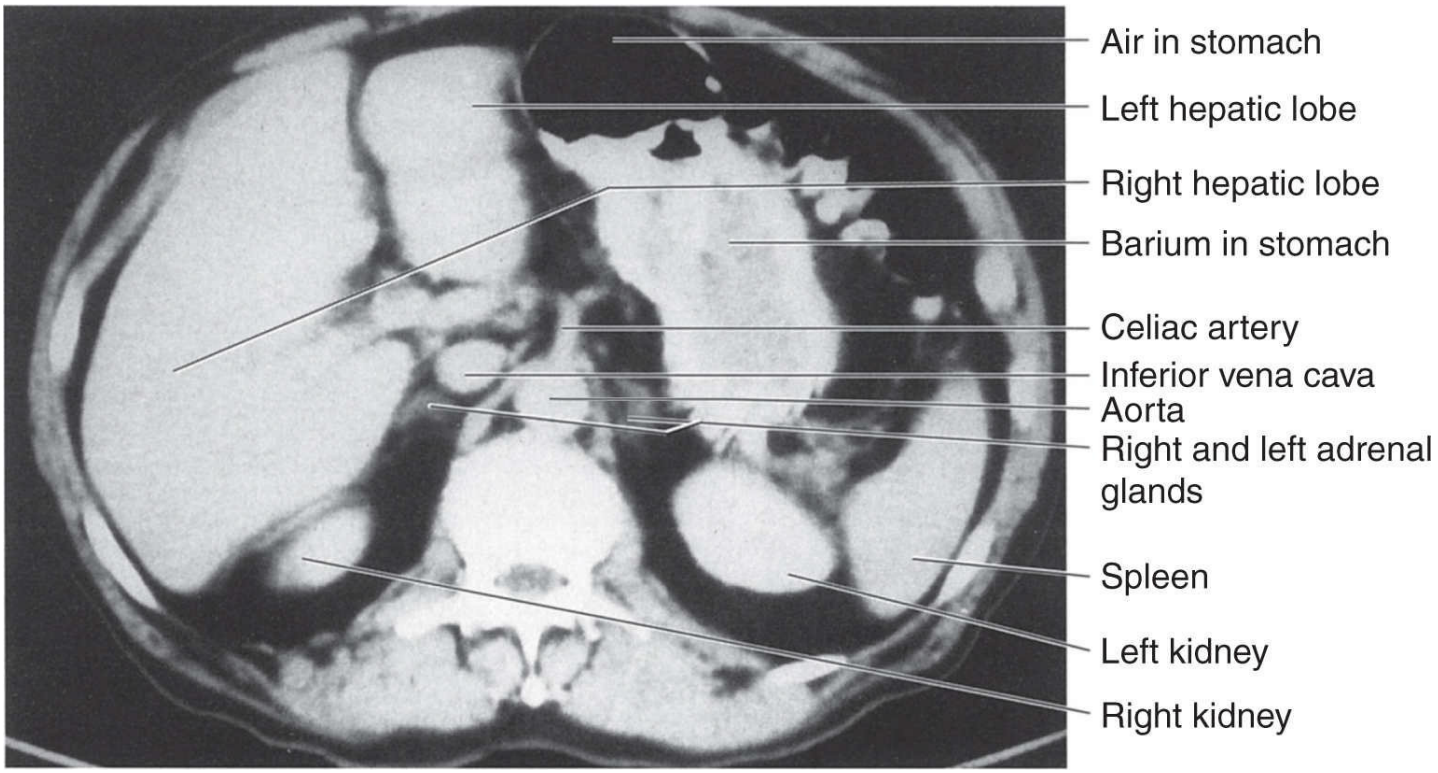
14 Bilateral PE (mediastinal windows). (*Radiology* 101, 3rd ed, 2009.)



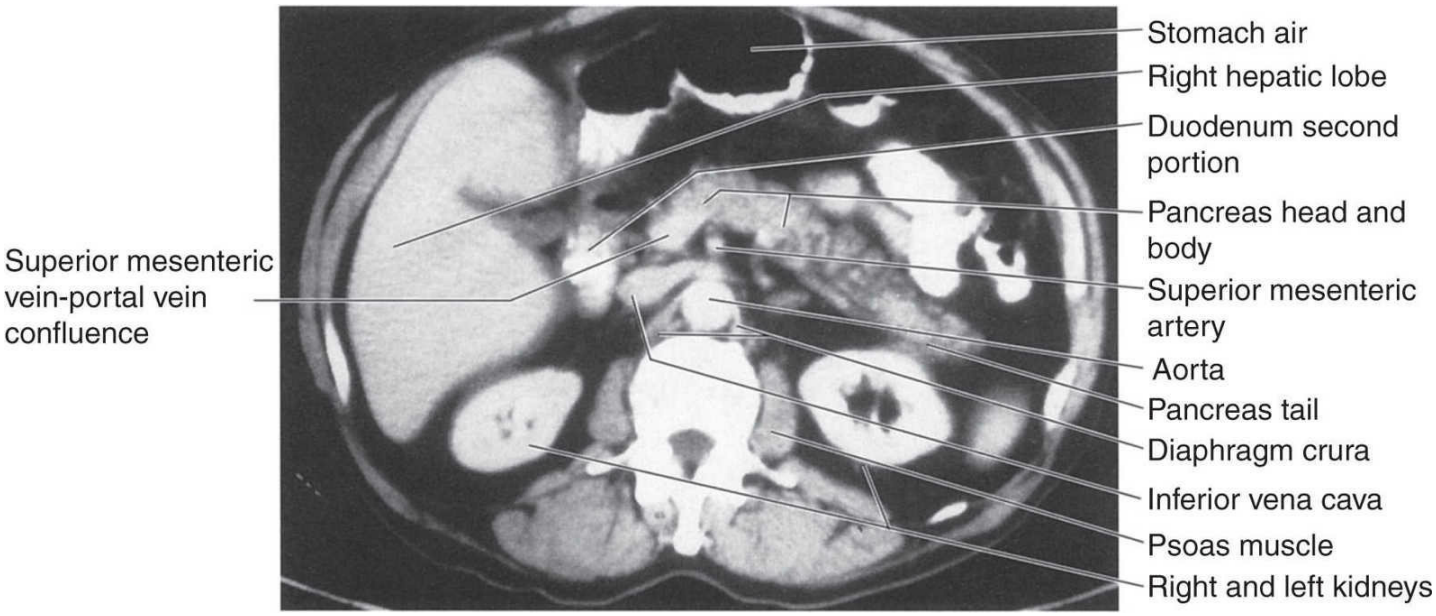
15 Sarcoidosis with perilymphatic nodules. (*Fund. Diag. Radiology* 3rd ed, 2006.)



16 Idiopathic pulmonary fibrosis. (*Fund. Diag. Radiology* 3rd ed, 2006.)

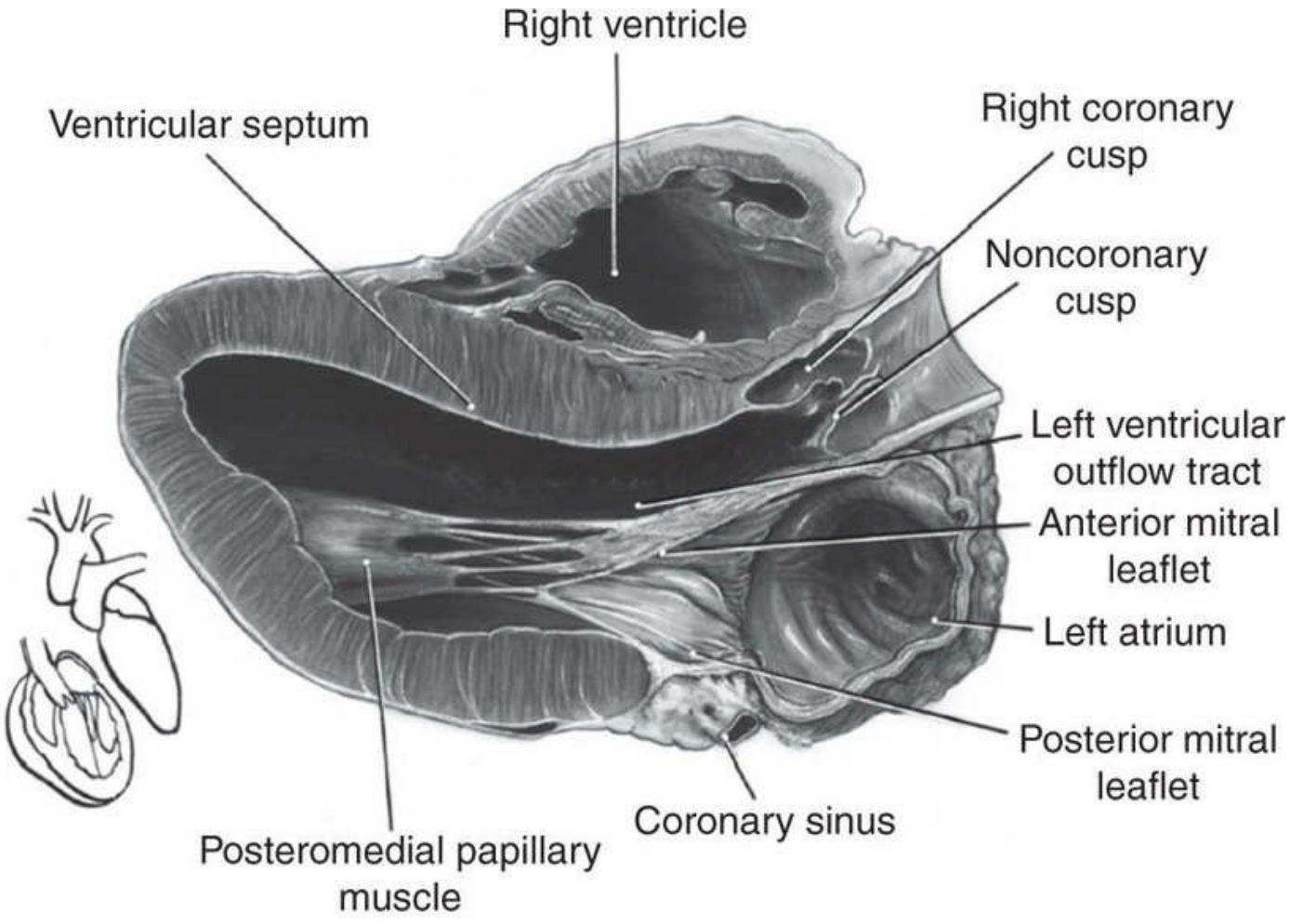


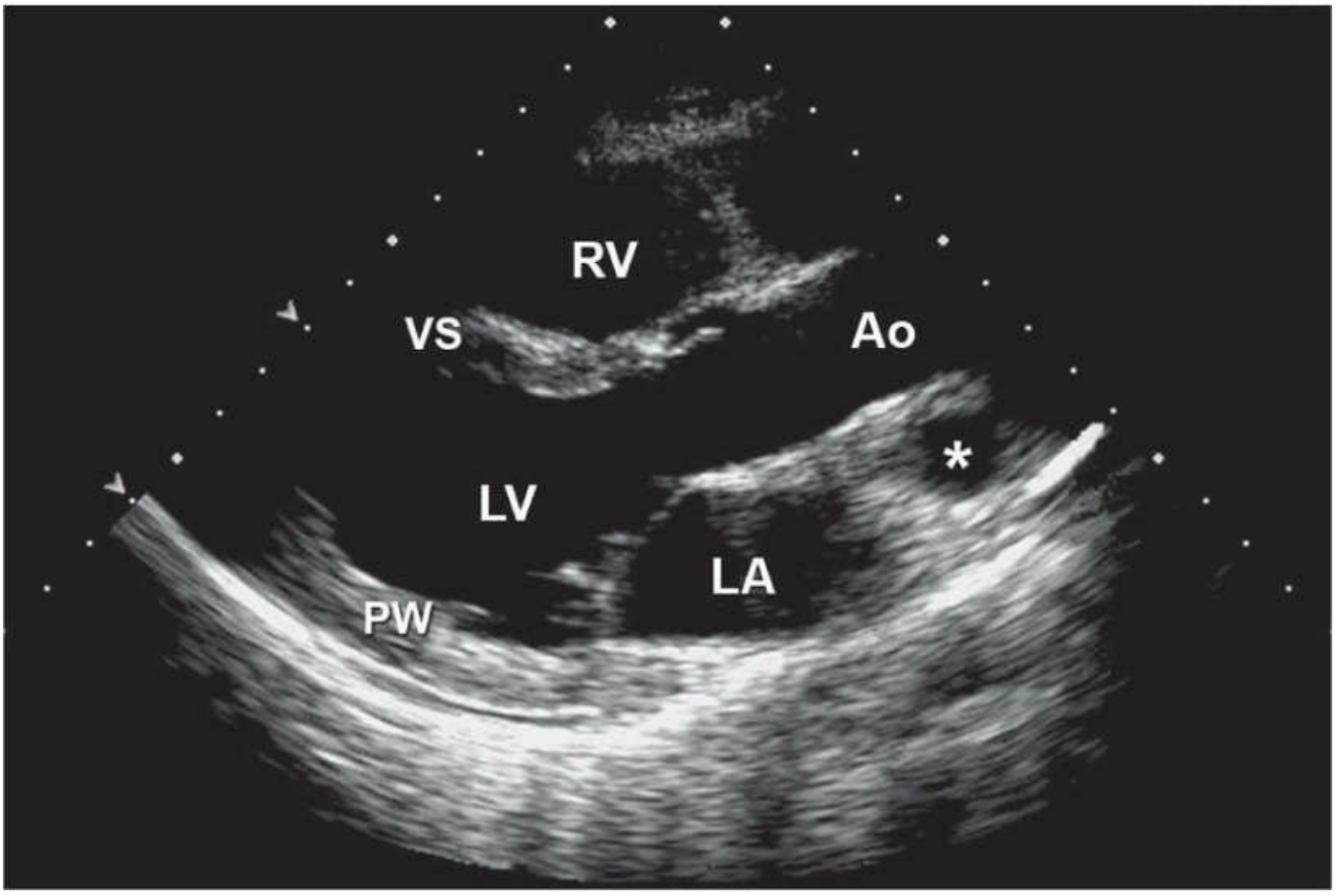
17 Normal abdomen CT at level of liver & spleen. (*Radiology* 101, 3rd ed, 2009.)



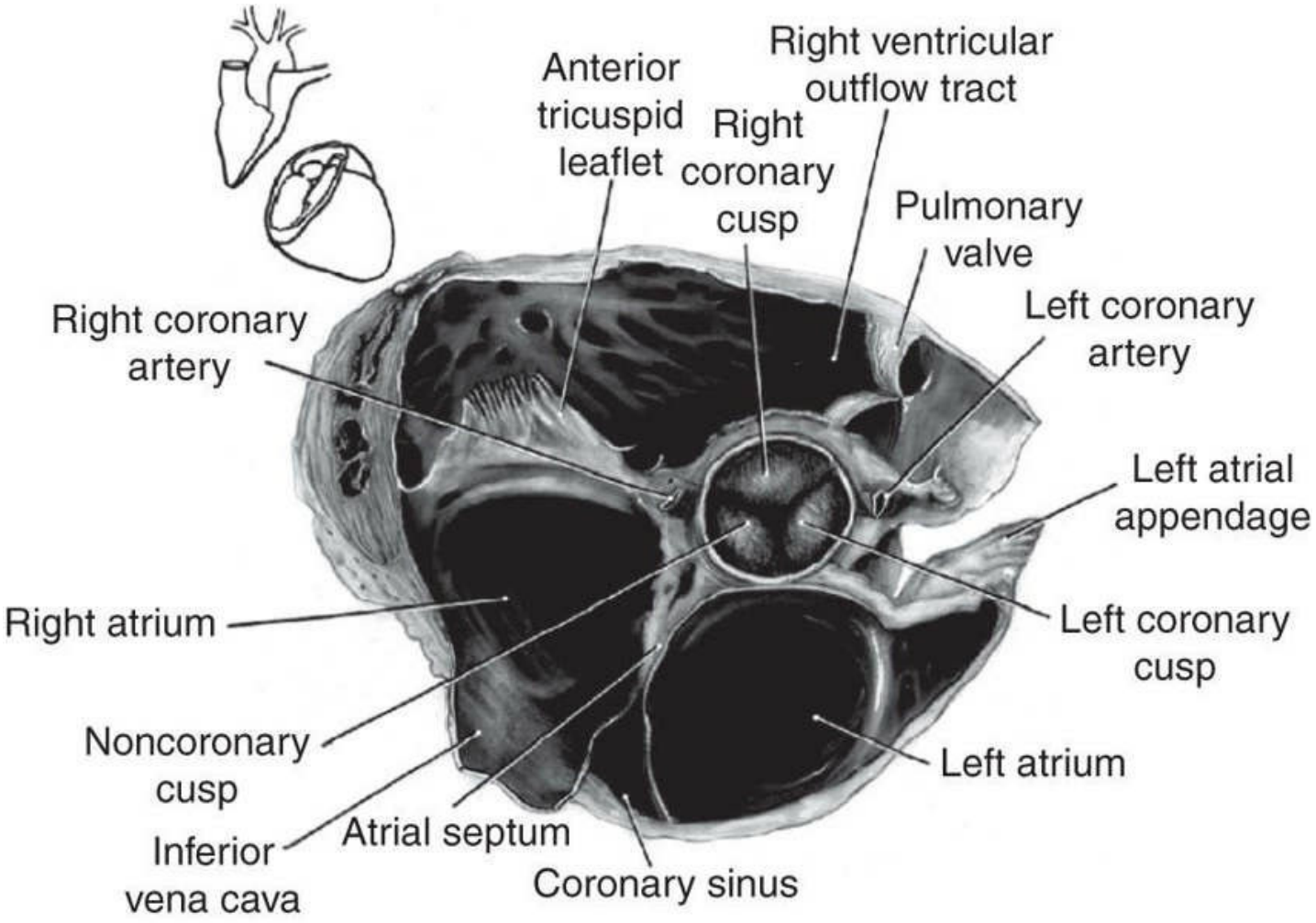
18 Normal abdomen CT at level of pancreas. (*Radiology* 101, 3rd ed, 2009.)

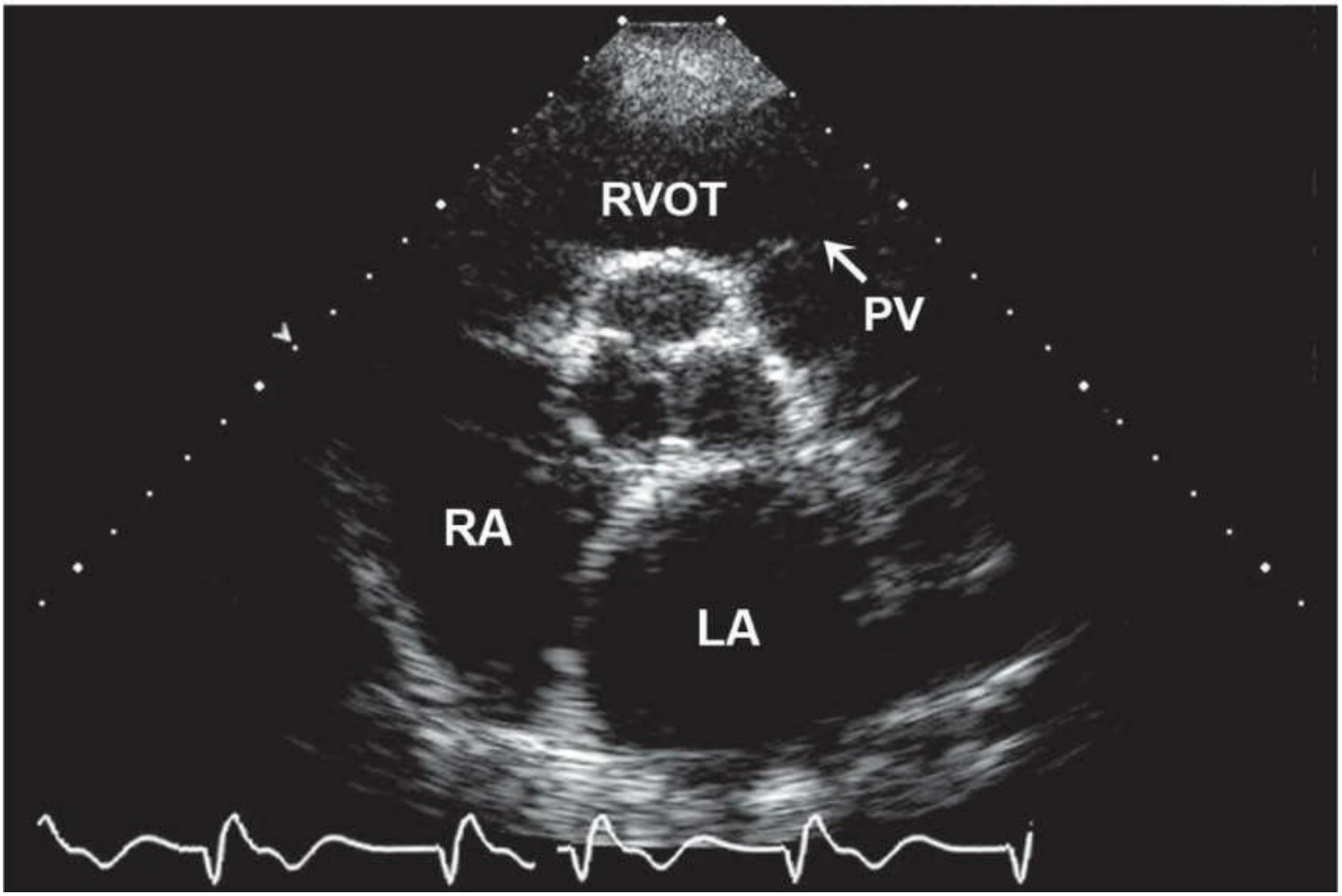
Echocardiography


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

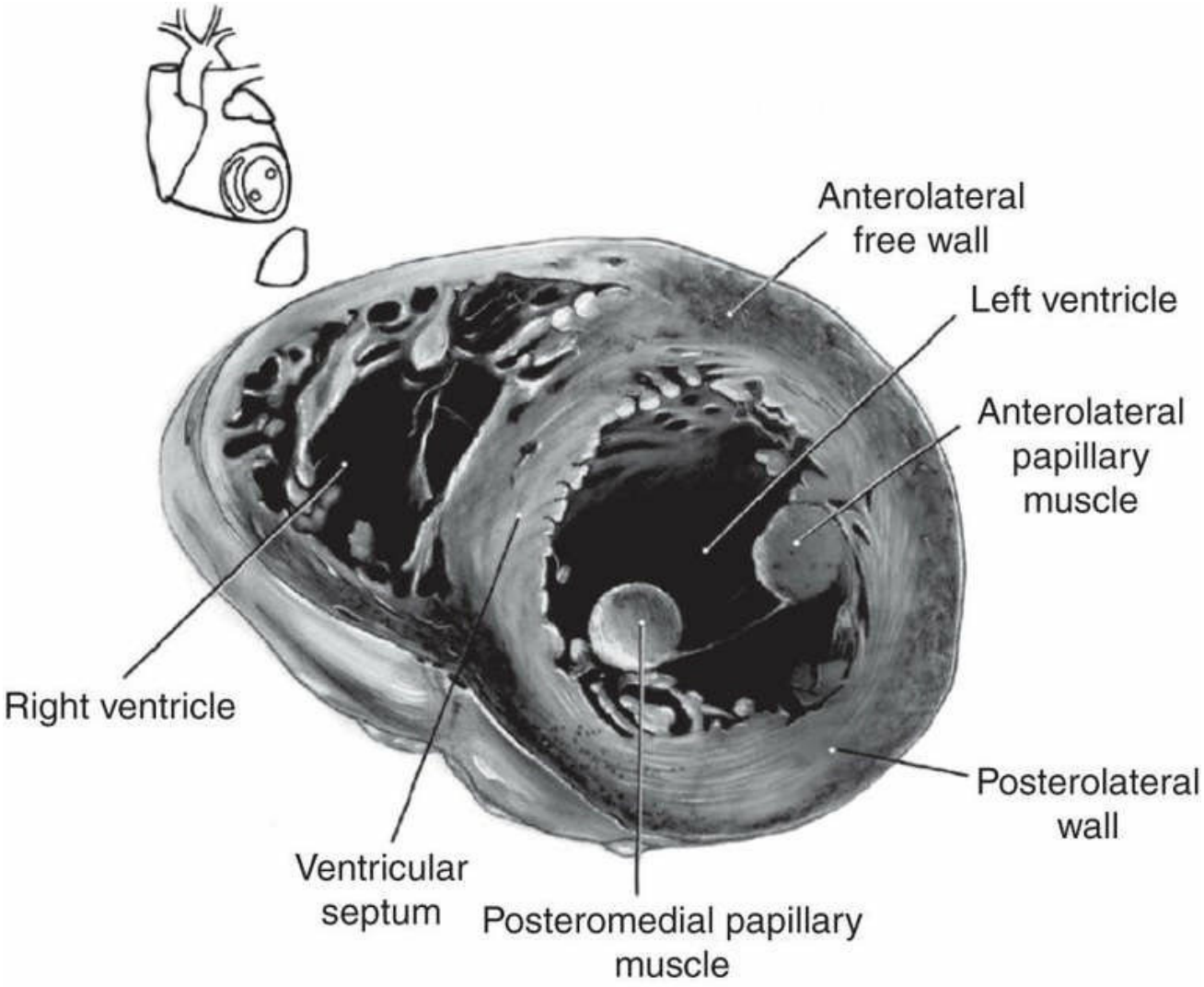

RV
VS
Ao
*
LV
LA
PW

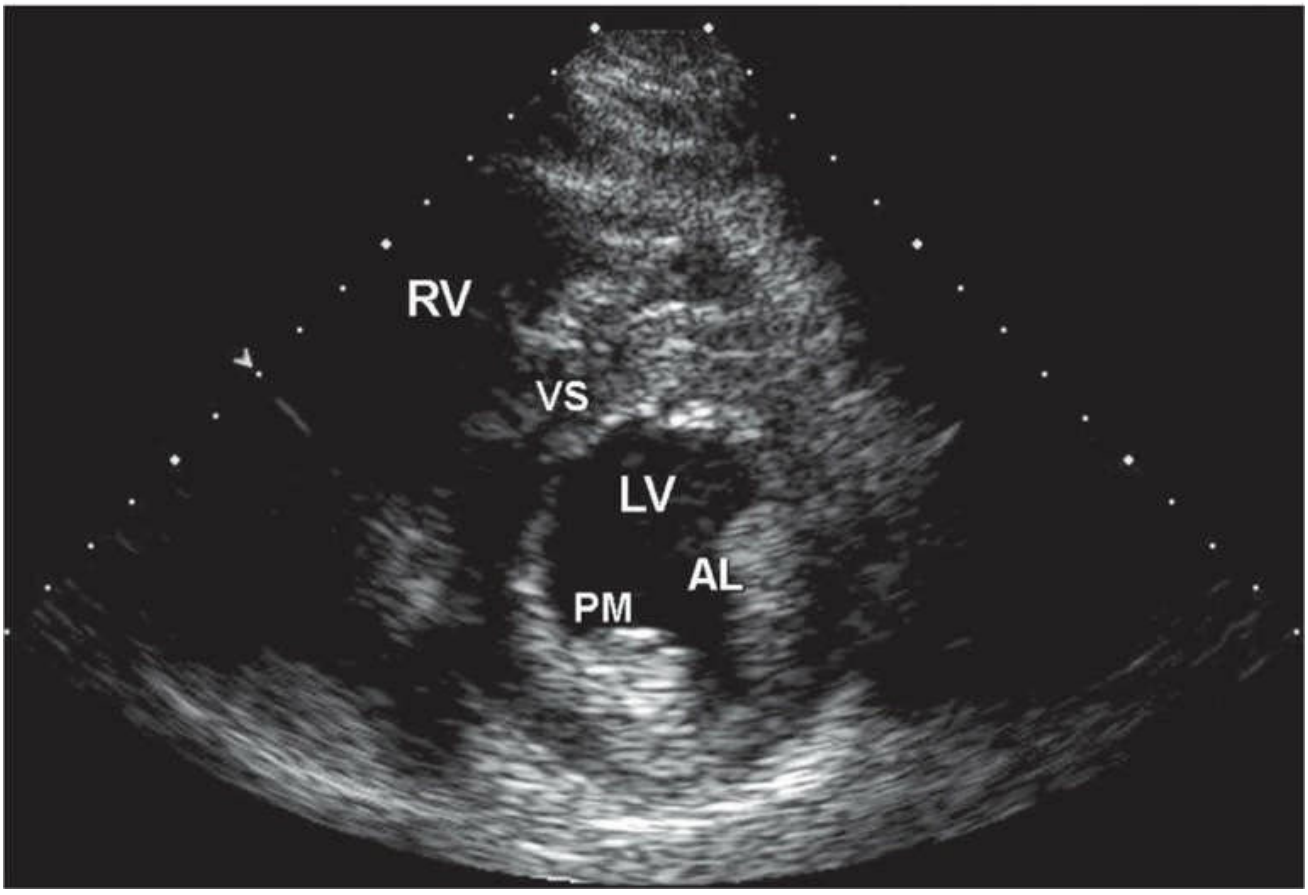
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ven- tricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: From Mayo Clinic Proceedings [Tajik AJ, Seward 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. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


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

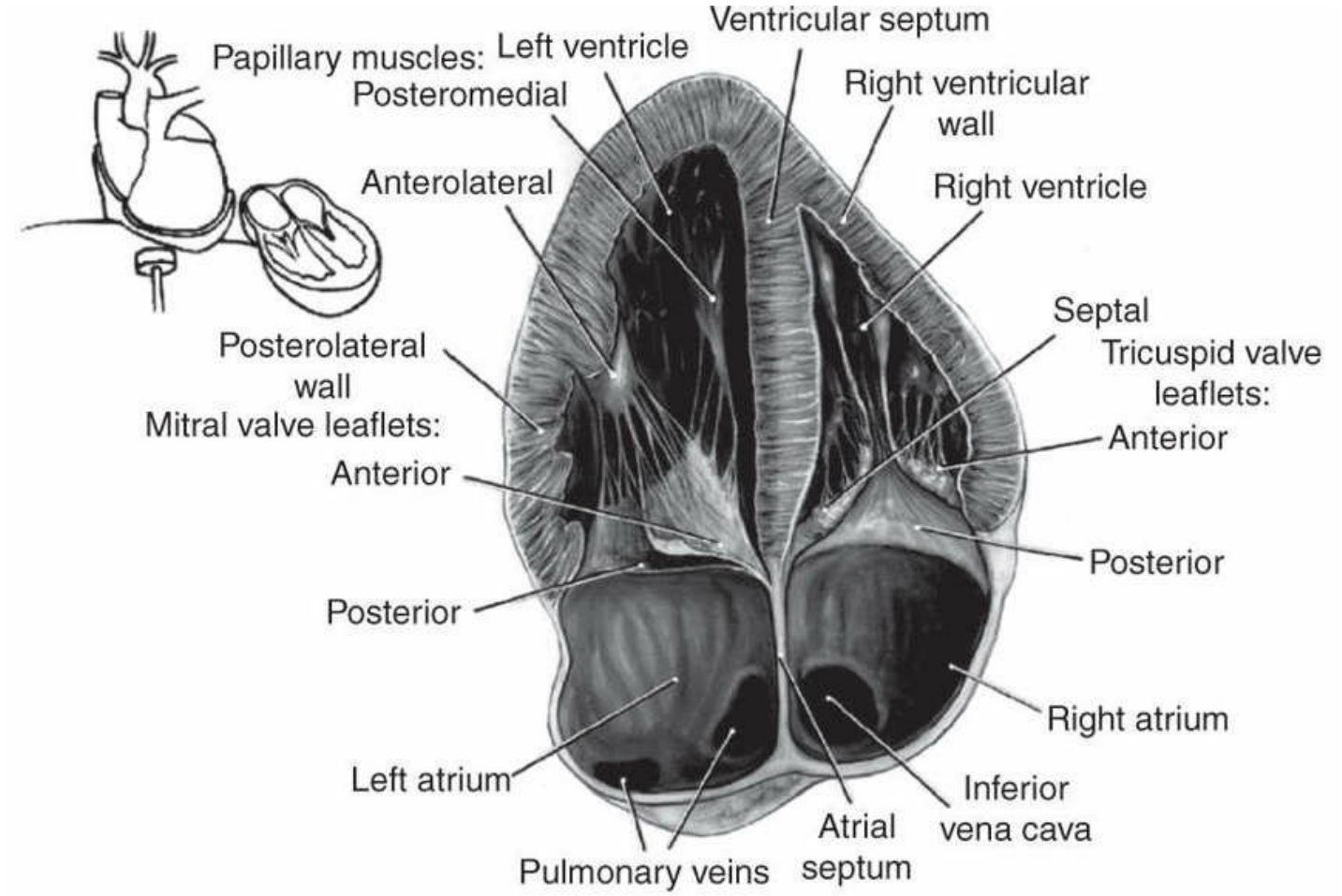

RVOT
PV
RA
LA

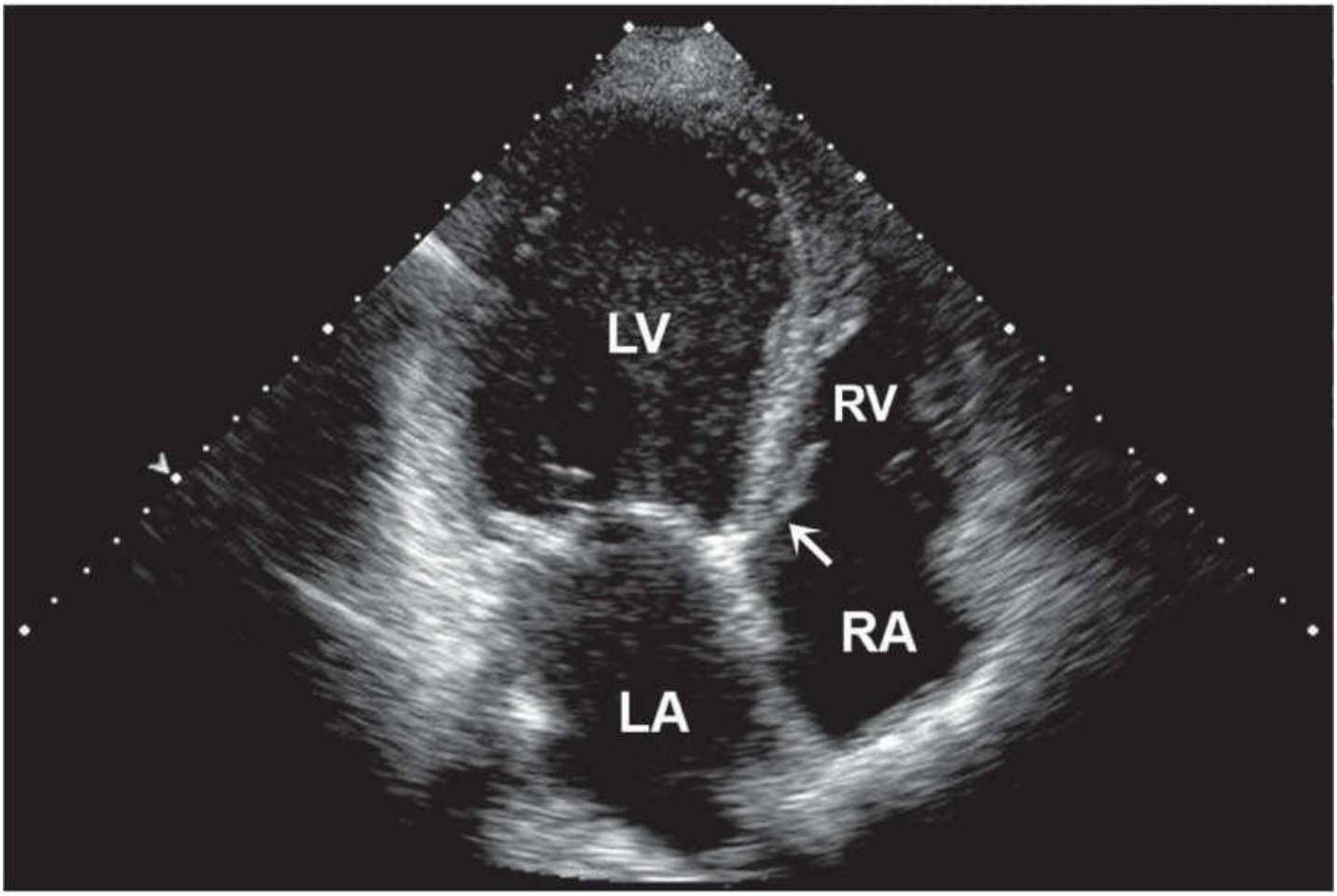
2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: From Mayo Clinic Proceedings [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: 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. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


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; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum; LV, left 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.)

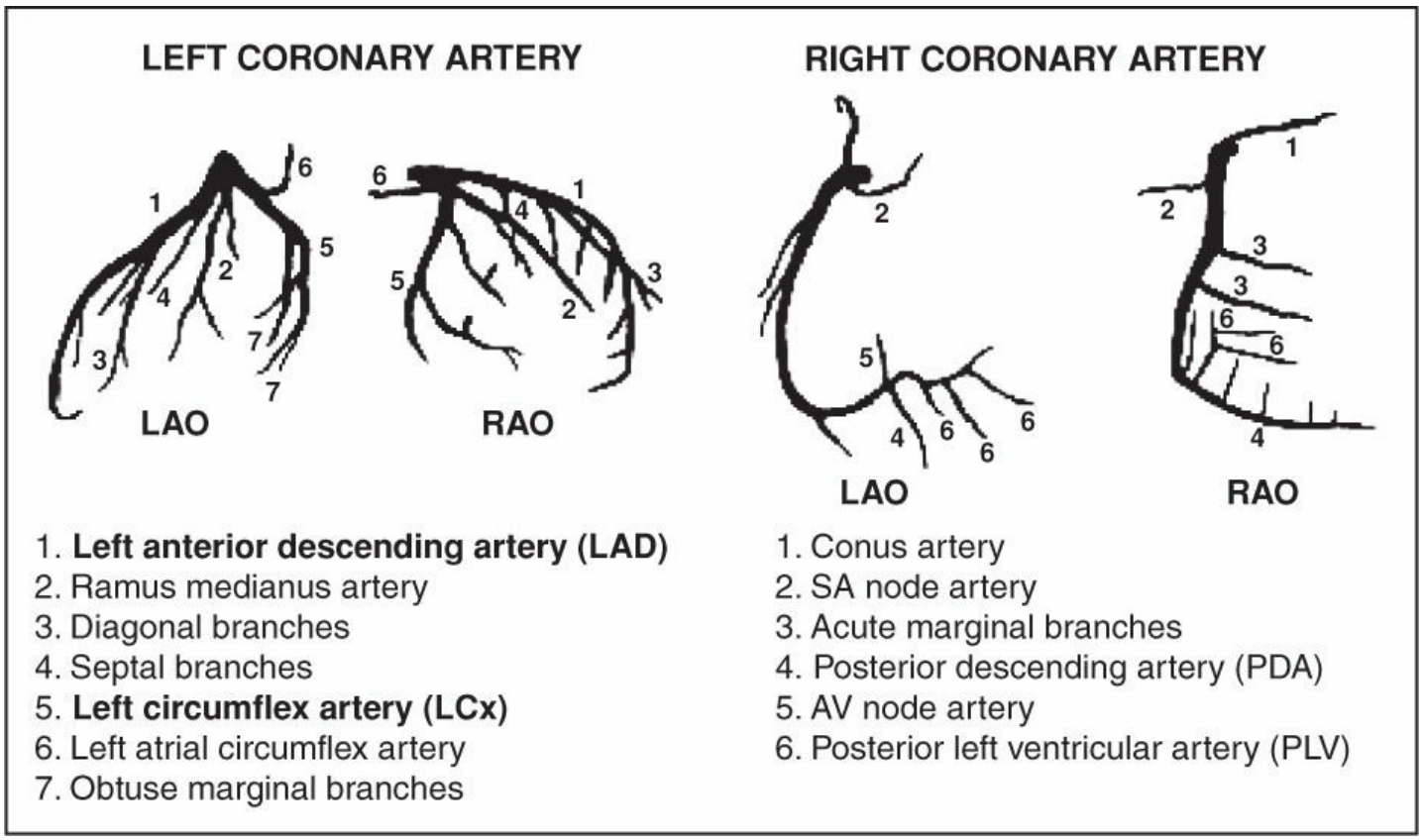




4 Apical four-chamber view: Note that at some institutions the image is reversed so that the left side of the heart appears on

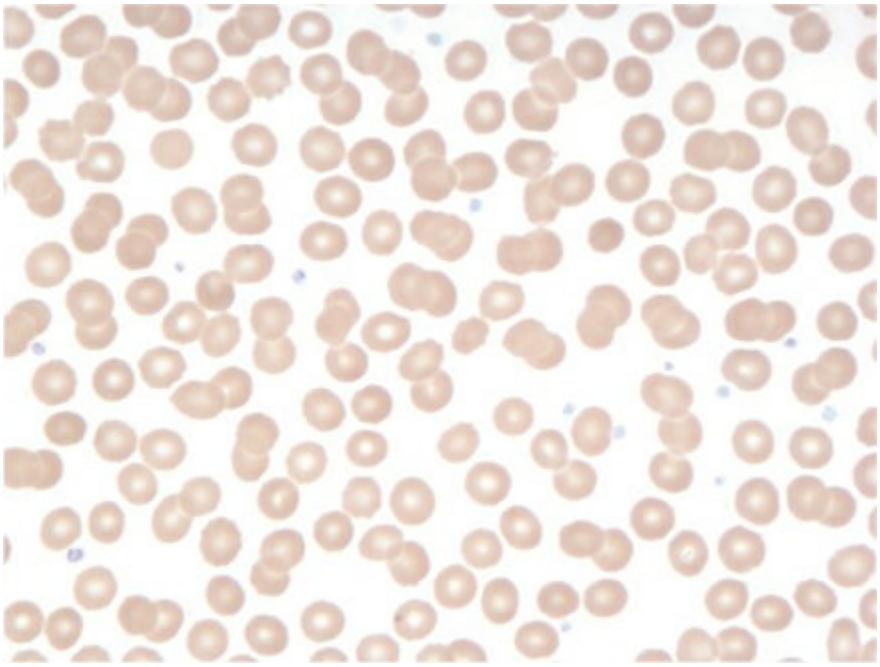
the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: From *Mayo Clinic Proceedings* [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, 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

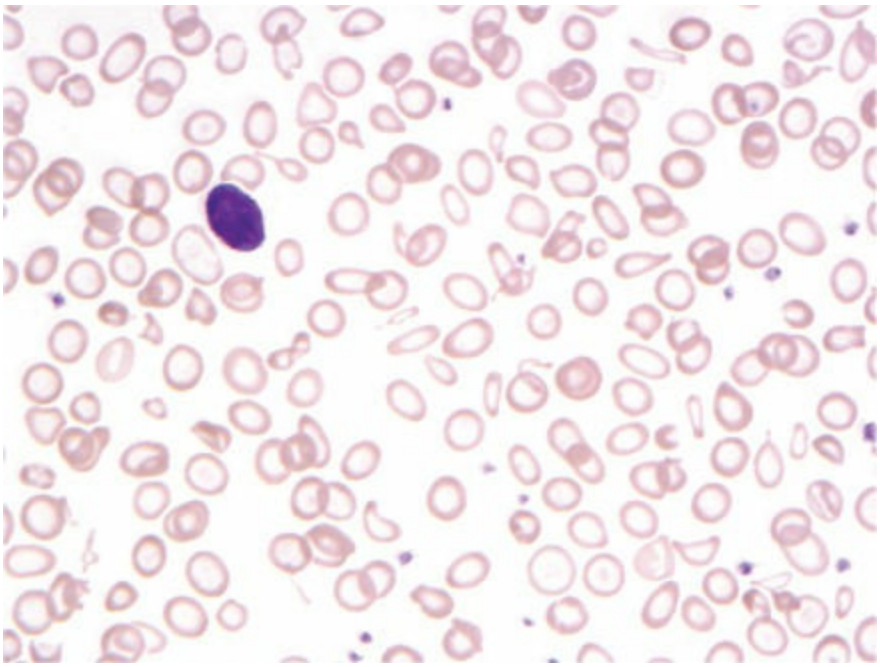


Coronary arteries. (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

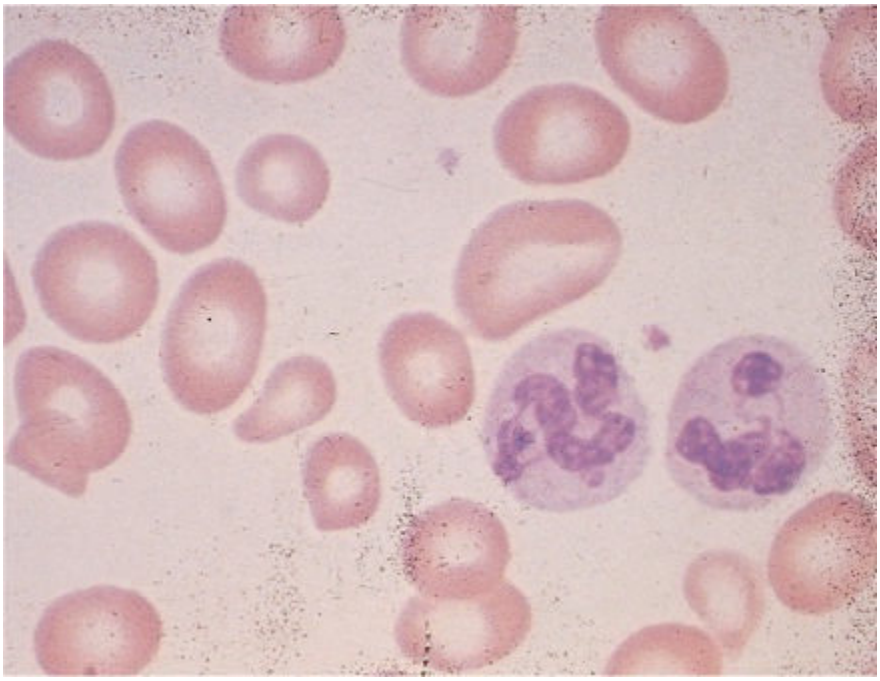
Peripheral Blood Smears



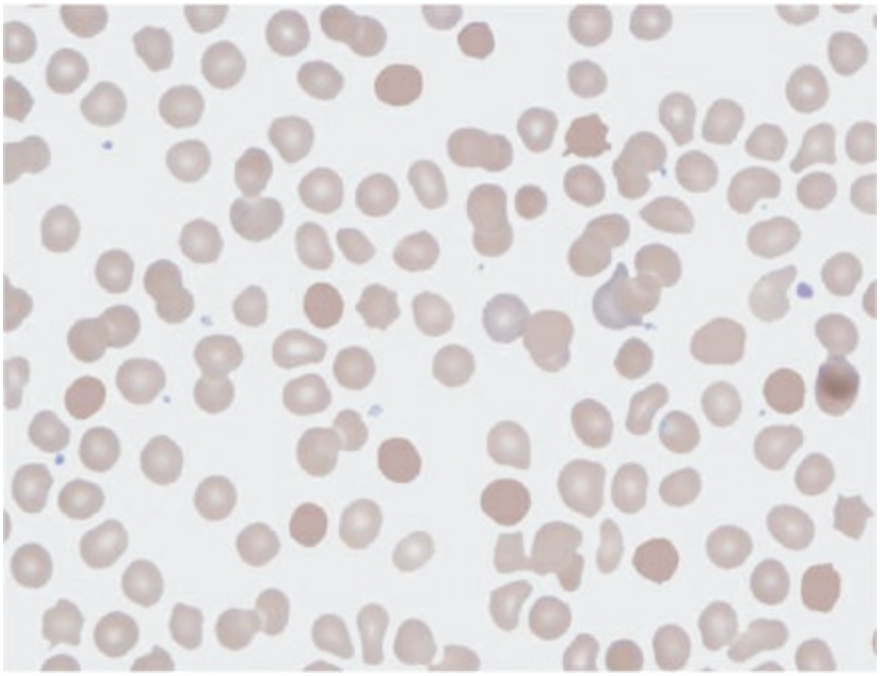
1 Normal smear.



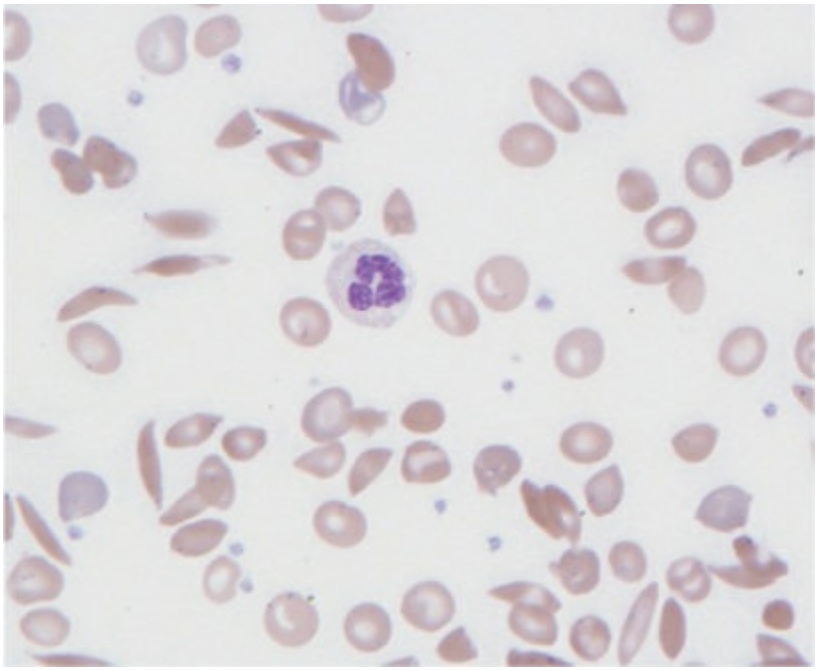
2 Hypochromic, microcytic anemia due to iron-deficiency.



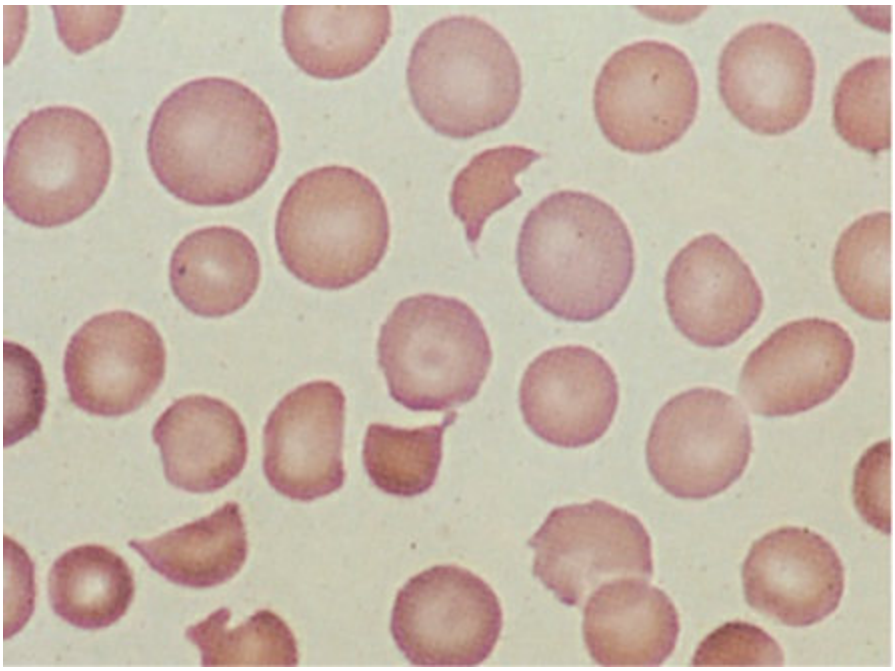
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



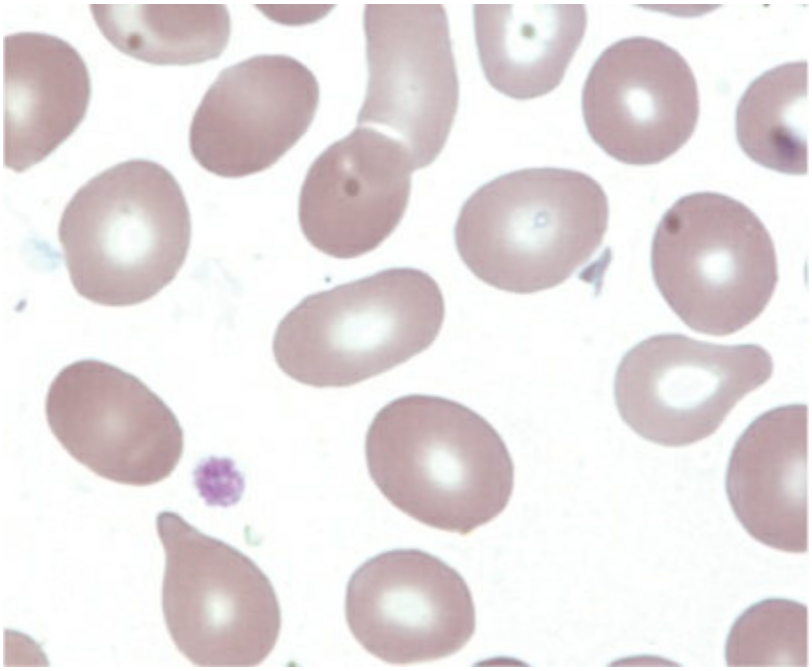
4 Spherocytes due to autoimmune hemolytic anemia.



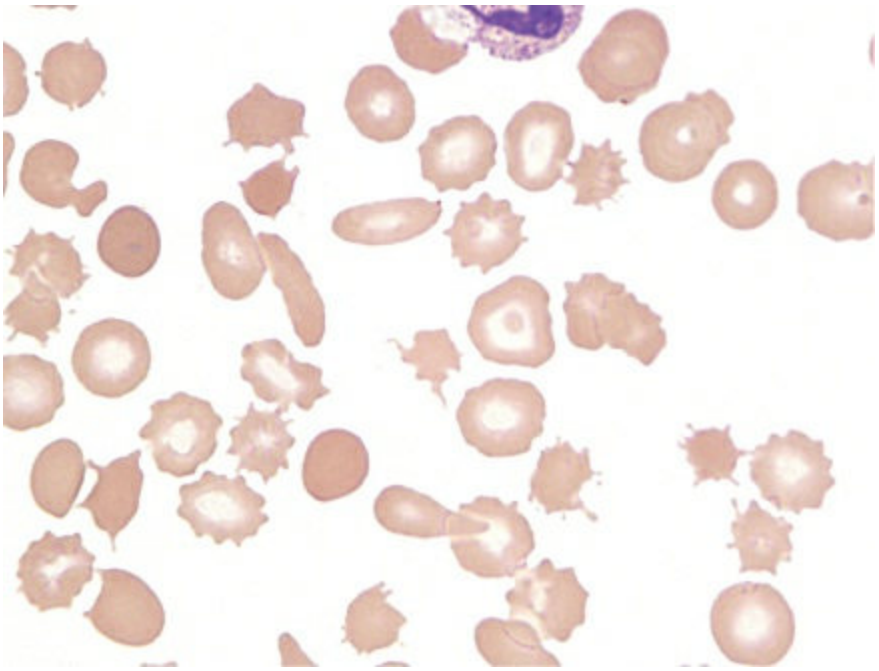
5 Sickle cell anemia.



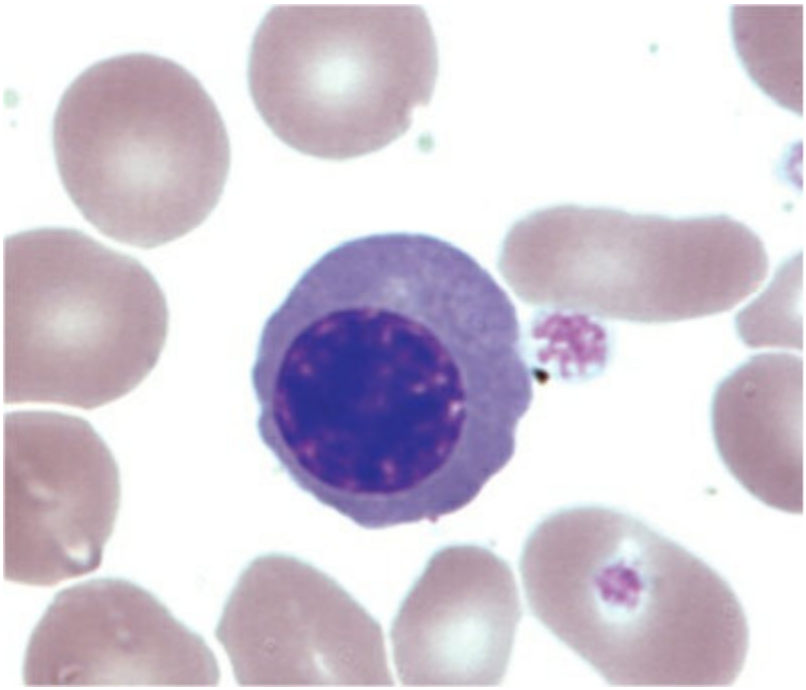
6 Schistocytes.



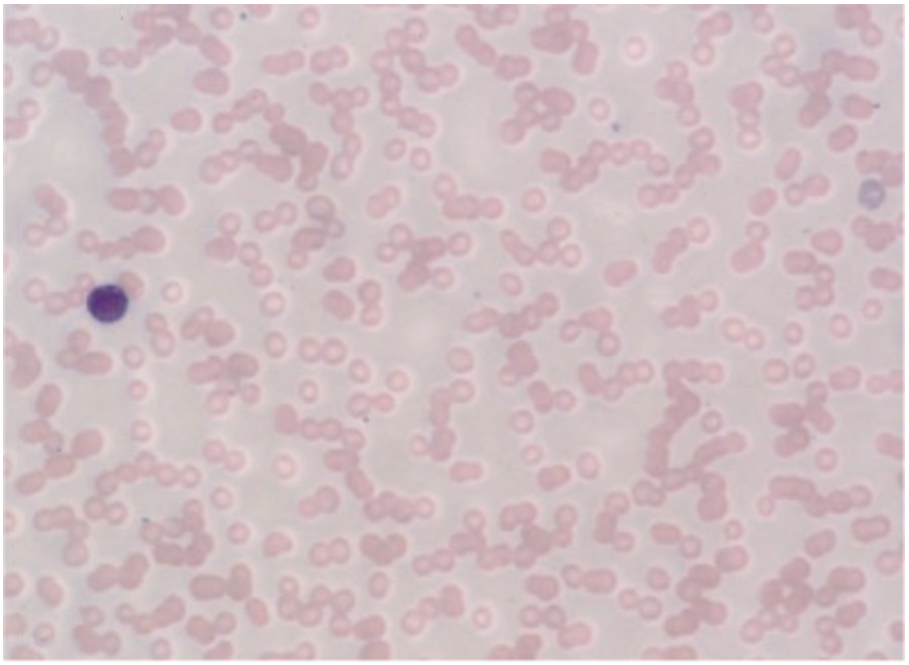
7 Teardrop shaped RBC (dacrocyte).



8 Acanthocytes.

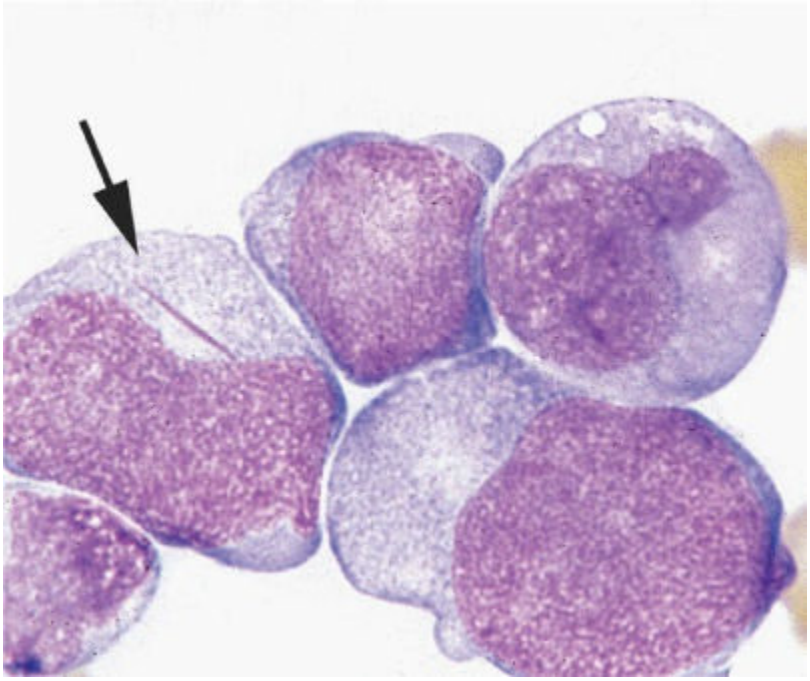


9 Nucleated RBC.

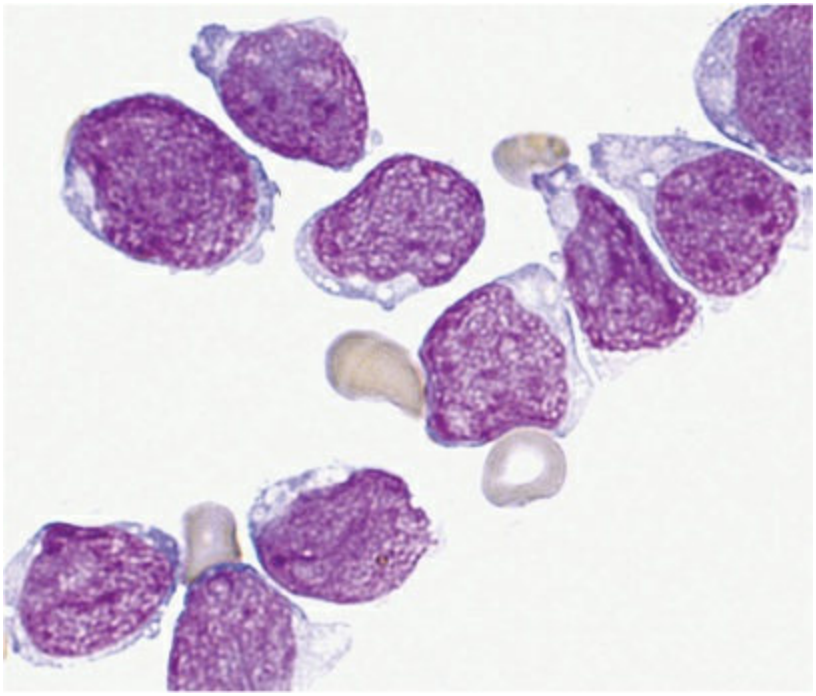


10 Rouleaux.

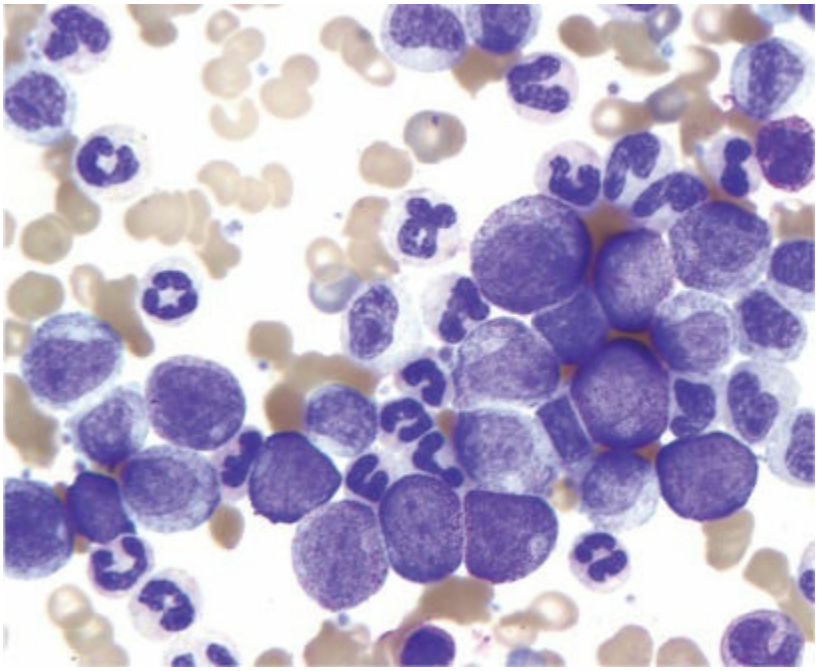
Leukemias



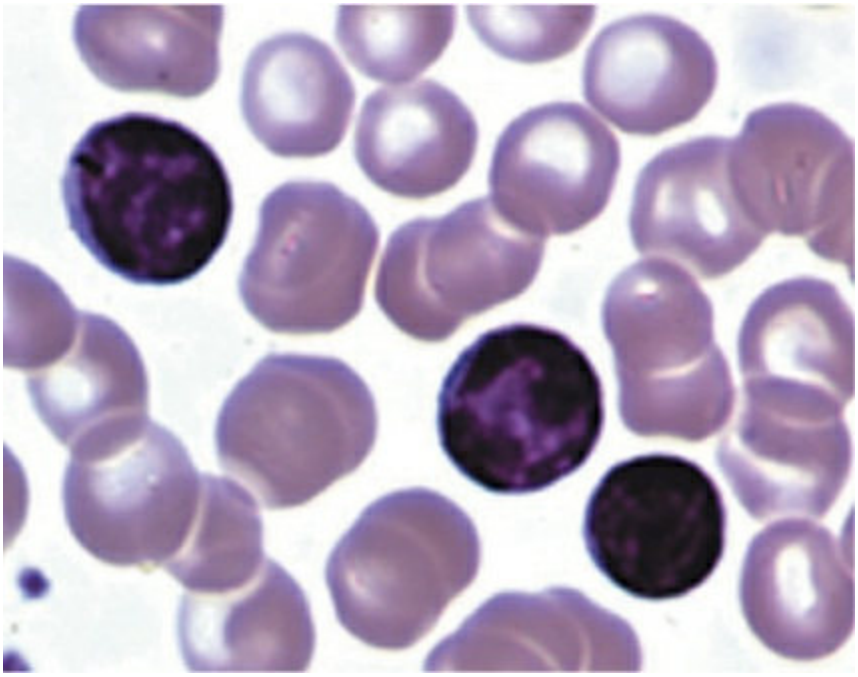
1 AML with Auer rod.



2 ALL.



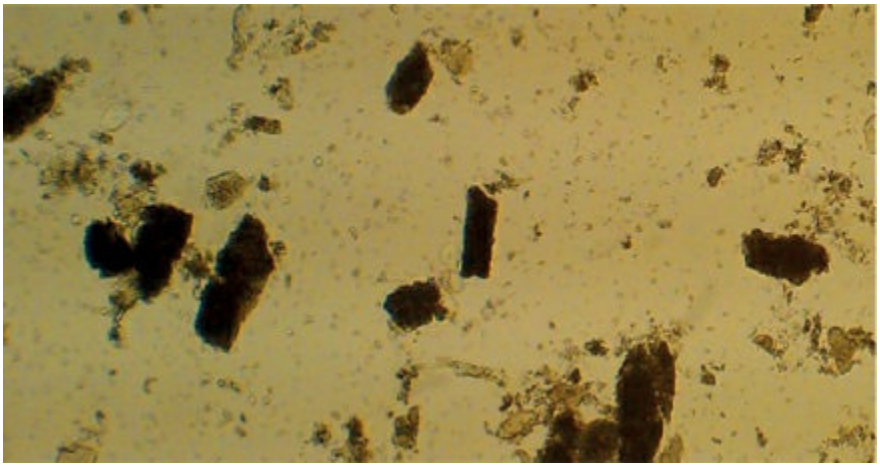
3 CML.



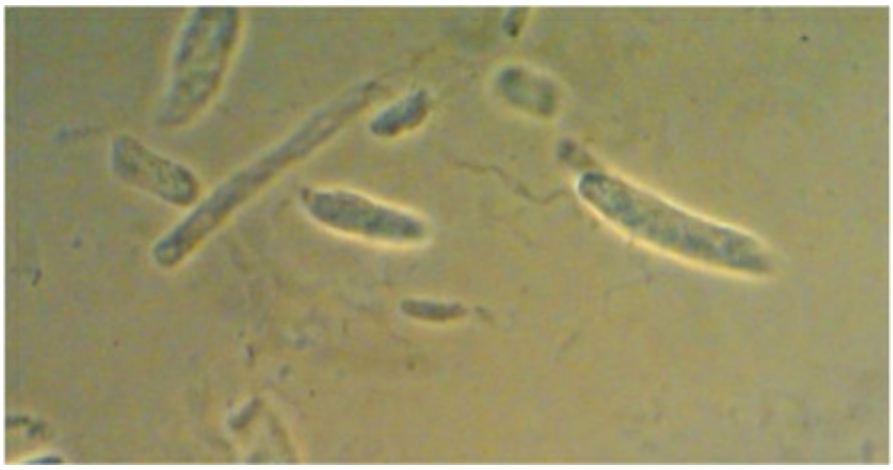
4 CLL.

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.

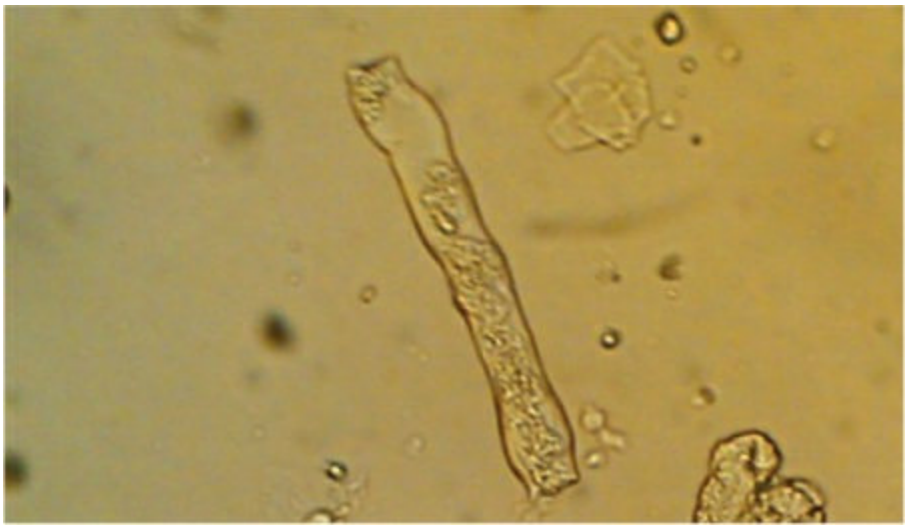
Urinalysis



1 “Muddy brown” or granular cast (courtesy Nicholas Zwang, MD)

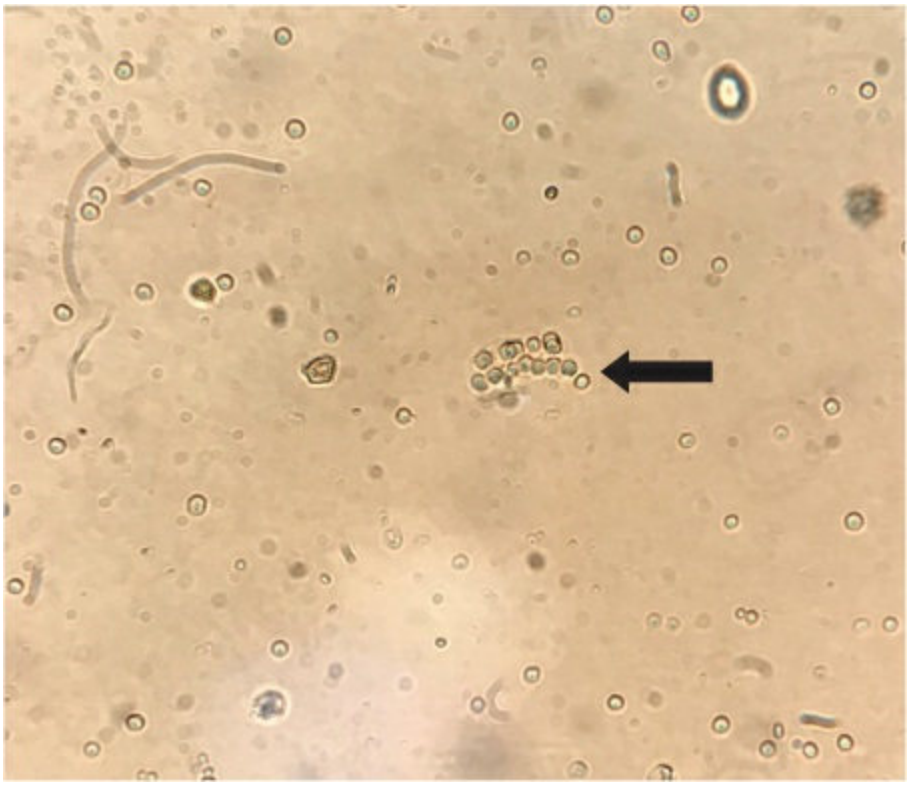


2 Hyaline cast (courtesy Nicholas Zwang, MD)

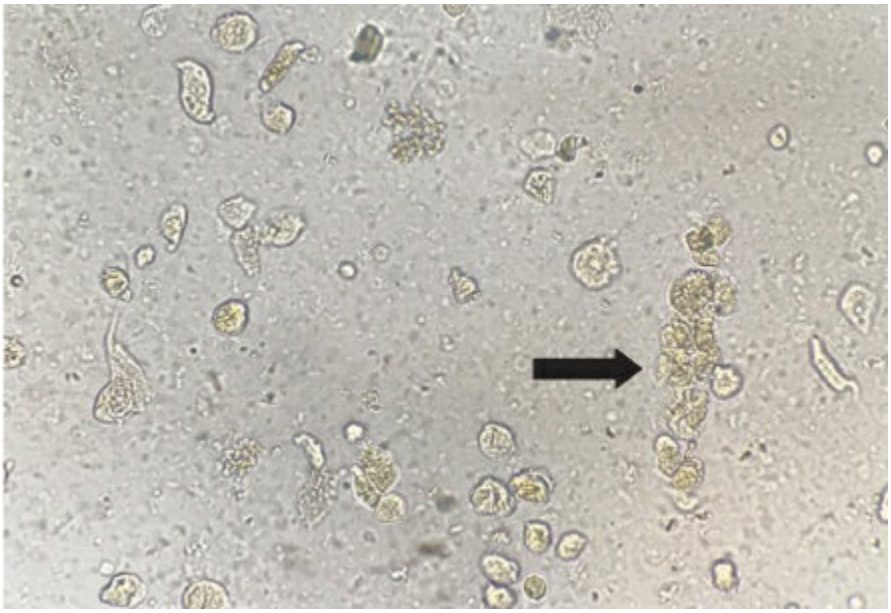


3 “Waxy broad” cast (courtesy Nicholas Zwang, MD)

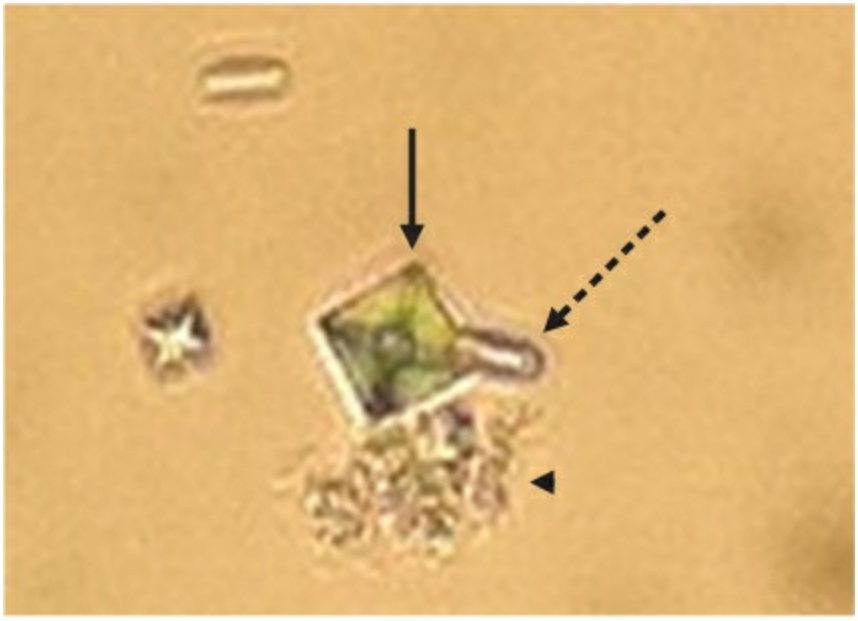
4 Renal tubular epithelial cell (courtesy Nicholas Zwang, MD)



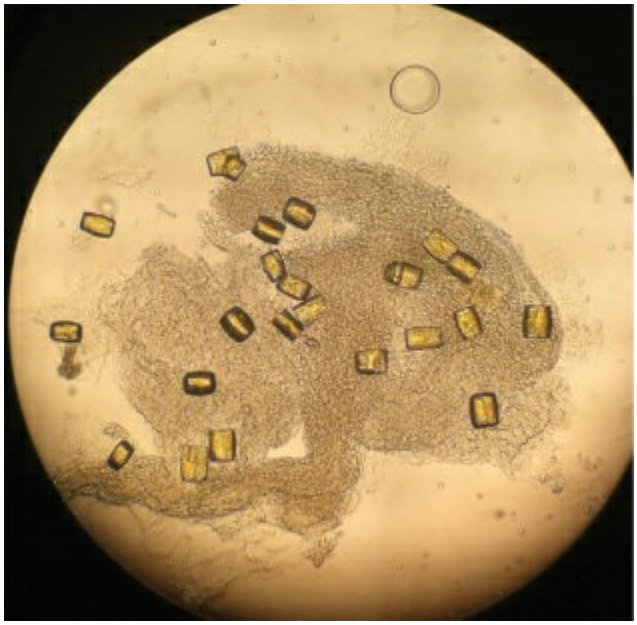
5 RBC cast (courtesy Harish Seethapathy, MBBS)



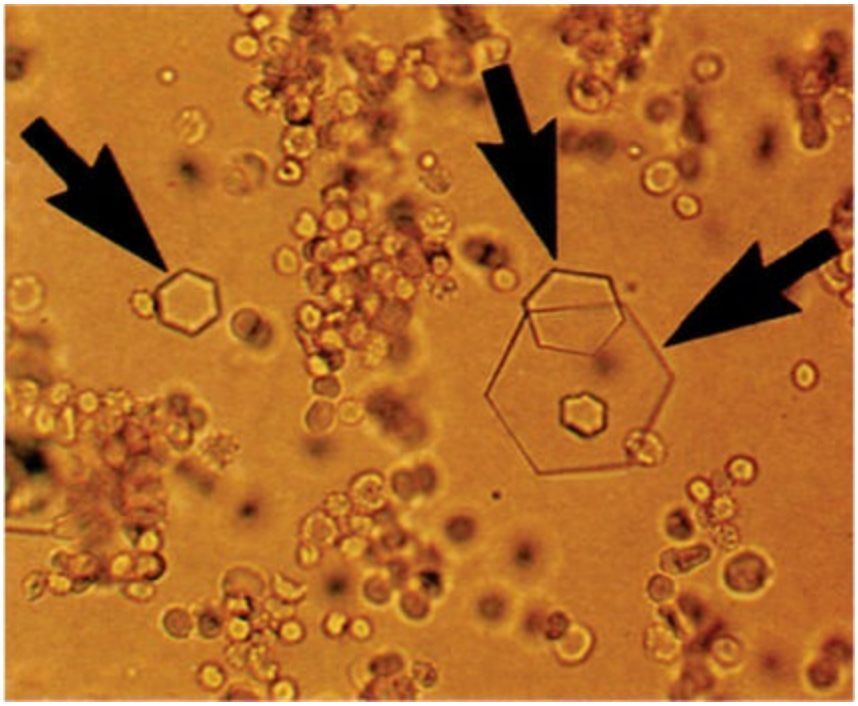
6 WBC cast (courtesy Harish Seethapathy, MBBS)



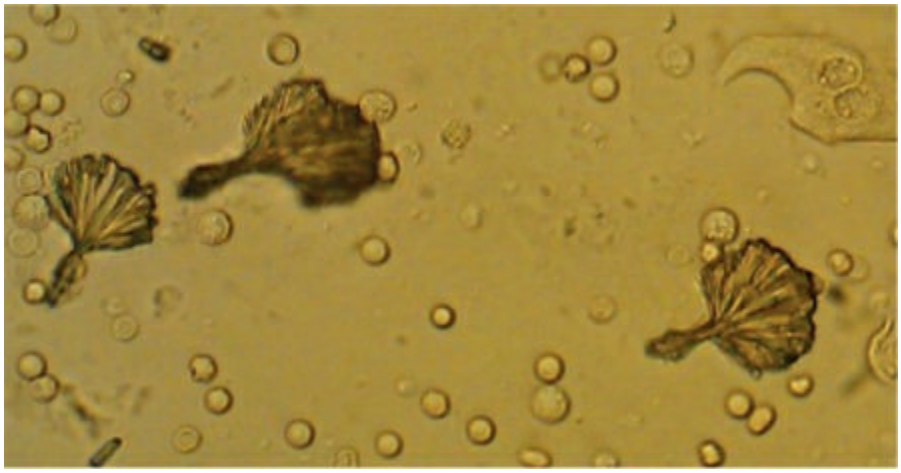
7 Calcium oxalate crystals (courtesy Mallika Mendu, MD). Calcium dihydrate (arrow), calcium monohydrate (dashed arrow), and amorphous calcium crystals (arrow-head)



8 “Struvite” magnesium ammonia phosphate crystals (courtesy Brett Carroll, MD)

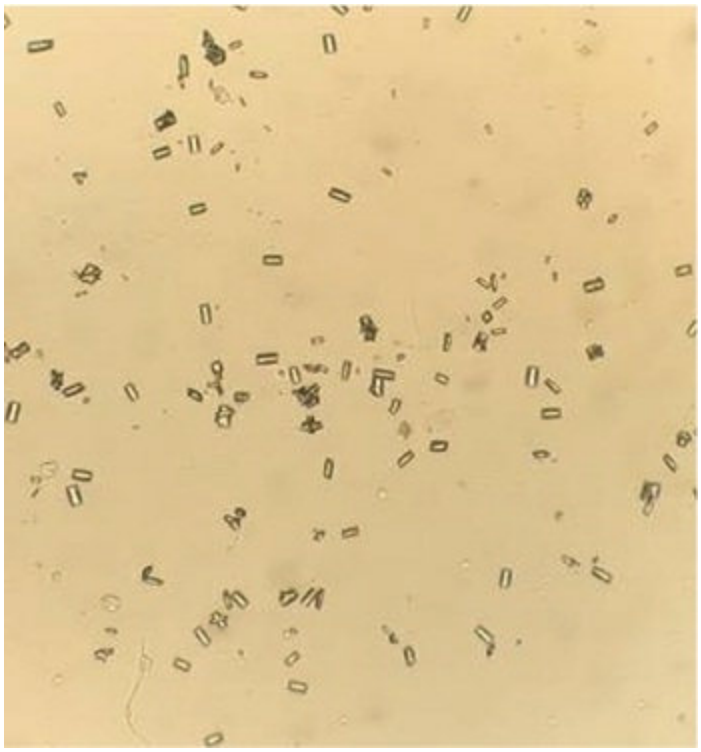


9 Cystine crystals (*Clin. Lab. Medicine*, 1994.)

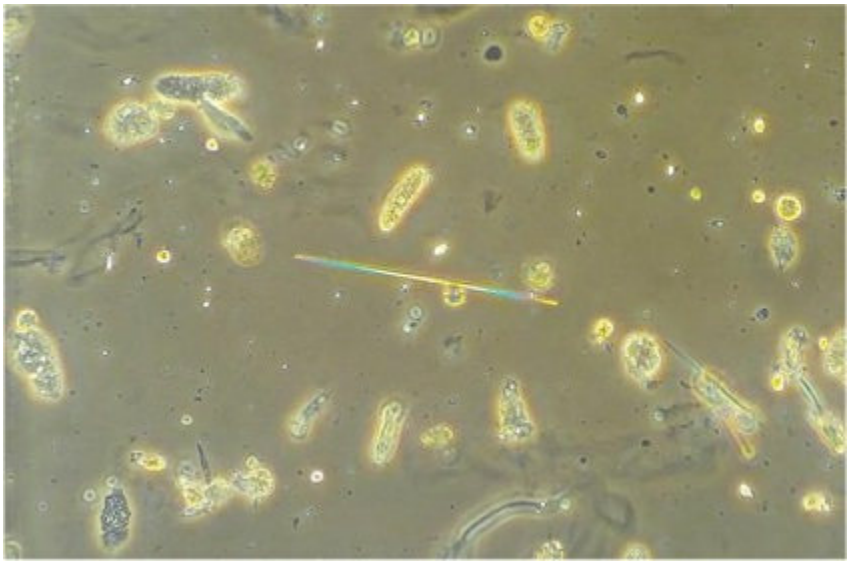


10 Sulfadiazine “shock of wheat” crystals (courtesy Nicholas Zwang, MD)

11a Uric acid crystals under polarized light (courtesy Harish Seethapathy, MBBS)

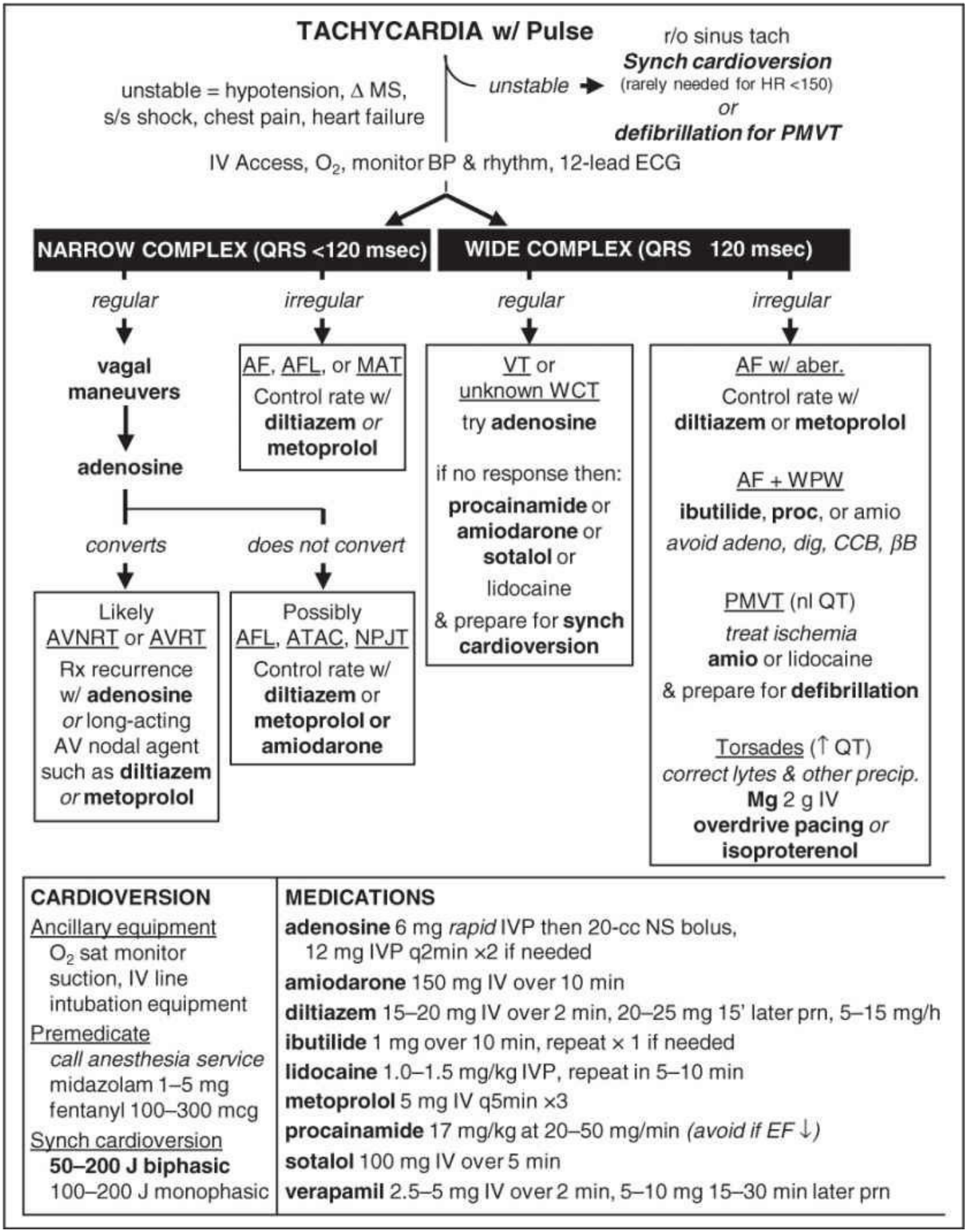


11b Uric acid crystals under normal light (courtesy Harish Seethapathy, MBBS)



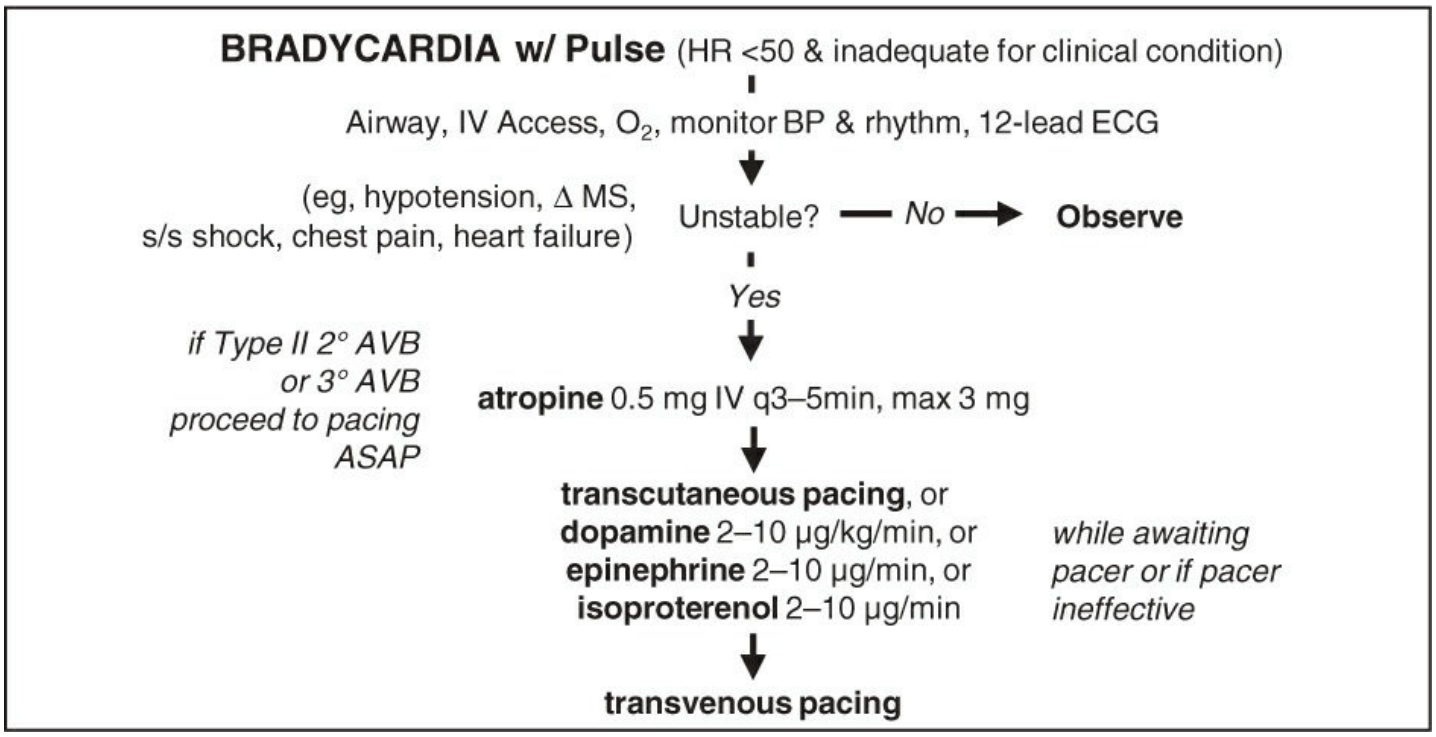
12 Acyclovir needle crystals (courtesy Yuvaram Reddy, MBBS)

Figure ACLS-1 ACLS Tachycardia Algorithm



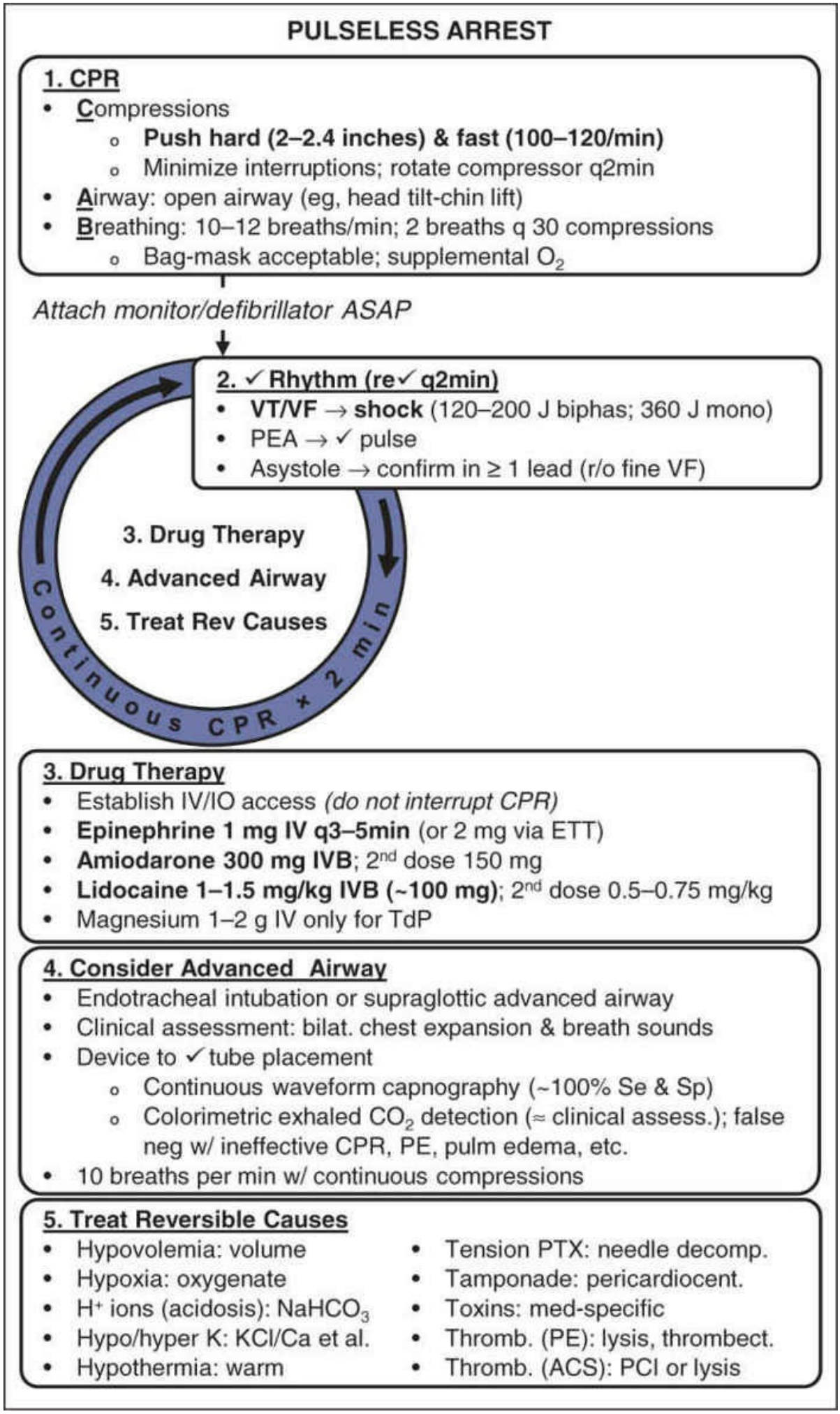
(Adapted from ACLS 2015 *Guidelines & Circ* 2016;133:e506)

Figure ACLS-2 ACLS Bradycardia Algorithm



(Adapted from ACLS 2015 Guidelines)

Figure ACLS-3 VF/Pulseless VT, Asystole & PEA Algorithms



(Adapted from ACLS 2018 *Guidelines & Circ* 2018;138:e740)