POCKET NOTEBOOK

POCKET MEDICINE

SIXTH EDITION

Marc S. Sabatine

The Massachusetts General Hospital Handbook of Internal Medicine

Wolters Kluwer

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FOREWORD

To the 1st Edition

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

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

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

PREFACE

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

Written by residents, fellows, and attendings, the mandate for *Pocket Medicine* was to provide, in 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 sixth edition come several major improvements. We have updated every topic thoroughly. In particular, we have included the latest pharmacotherapy for acute coronary syndromes, heart failure, pulmonary hypertension, hepatitis C, HIV, and diabetes, as well as the latest device-based treatments for valvular heart disease, atrial fibrillation, and stroke. Recent paradigm shifts in the guidelines for hypertension and cholesterol have been distilled and incorporated. We have expanded coverage of the molecular classification of malignancies and the corresponding biologic therapies. We have added new sections on mechanical circulatory support, angioedema, non-invasive ventilation, toxicology, lung transplantation, GI motility disorders, and the cardiorenal syndrome, just to name a few. We have also updated the section on Consults in which non-internal medicine specialists provide expert guidance in terms of establishing a differential diagnosis for common presenting symptoms and initiating an evaluation in anticipation of calling a consult. As always, we have incorporated key references to the most recent high-tier reviews and important studies published right up to the time *Pocket Medicine* went to press. We welcome any suggestions for further improvement.

Of course medicine is far too vast a field to ever summarize in a textbook of any size. Long monographs have been devoted to many of the topics discussed herein. *Pocket Medicine* is meant only as a starting point to guide one during the initial phases of diagnosis and management until one has time to consult more definitive resources. Although the recommendations herein are as evidence-based as possible, medicine is both a science and an art. As always, sound clinical 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 the best experiences I have ever had. I am grateful to several outstanding clinical mentors, including Hasan Bazari, Larry Friedman, Nesli Basgoz, Eric Isselbacher, Bill Dec, 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, my academic coordinator. She shepherded every aspect of the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be.

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.

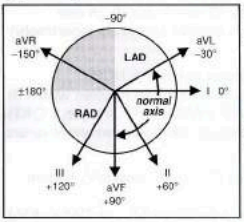
MARC S. SABATINE, MD, MPH

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



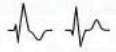
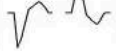
Left axis deviation (LAD)

- **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

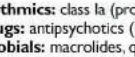
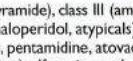
Bundle Branch Blocks (*Circ* 2009;119:e235)

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 = 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 = 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)

- QT measured from beginning of QRS complex to end of T wave (measure longest QT)
- 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 <440 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, atovaquone, 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)
		
	II >120 ms; or V_1 >40 ms; >1 mm	II >2.5 mm; or V_1 >1.5 mm

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)
  - **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)

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

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, 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 enlargement: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCM
- 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; Duchenne's; 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, $S_I S_{II} S_{III}$ w/ R/S ratio <1 in those leads)
  LBBB; WPW; clockwise rotation of the heart; lead misplacement; CMP; PTX

Pathologic Q waves

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

ST elevation (STE) (*NEJM* 2003;349:2128; *Circ* 2009;119:e241 & e242)

- **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 Ps)
- **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 (*JACC* 2015;66:470)
  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
- Posttachycardia or postpacing ("memory" T waves)
- Electrolyte, digoxin, PaO_2, $PaCO_2$, pH or core temperature disturbances
- Intracranial bleed ("cerebral T waves," usually w/ ↑ QT)
- Normal variant in children (V_1–V_4) and leads in which QRS complex predominantly ⊖

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

Disorder	Typical Characteristics & Diagnostic Studies
	Cardiac Causes
ACS (15–25% of chest pain in ED)	Substernal "pressure" (⊕ LR 1.3) → neck, jaw, arm (⊕ LR 1.3–2.6) 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*, 10th ed, 2014; *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; c/w priors & obtain serial ECGs; consider *posterior leads* (V_7–V_9) to ✓ for posterior STEMI if hx c/w ACS but stnd ECG unrevealing or ST ↓ V_1–V_3 (ant ischemia vs. post STEMI) and angina that is hard to relieve 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:** ✓ at baseline & 3–6 h after sx onset; repeat 6 h later if clinical or ECG Δs; level >99th %ile w/ rise & fall in appropriate setting is dx of MI; >95% Se, 90% Sp detectable 1–6 h after injury, peaks 24 h, may be elevated for 7–14 d in STEMI *high-sens.* assays (not yet available in U.S.) offer NPV >99% at 1 h (*Lancet* 2015;386:2481) 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, cardiac contusion) or (3) multifactorial (PE, sepsis, severe HF, renal failure, Takotsubo, infilt dis.) (*Circ* 2012;126:2020)
- CK-MB: less Se & Sp than Tn (other sources: skel. muscle, intestine, etc); CK-MB/CK ratio >2.5 → cardiac source. Useful for dx of post-PCI/CABG MI or (re)MI if Tn already high.

Early noninvasive imaging

- If low prob of ACS (eg, ⊖ ECG & Tn) & stable → outPt or inPt noninvasive fxnal or imaging test (qv). CCTA w/ high NPV but low PPV; ↓ LOS c/w fxnal testing (*NEJM* 2012;366:1393).
- "Triple r/o" CT angiogram sometimes performed to r/o CAD, PE, AoD if dx unclear

NONINVASIVE EVALUATION OF CAD

Stress testing (*Circ* 2007;115:1464; *JACC* 2012;60:1828)

- **Indications:** dx 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 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 as ECG not interpretable)

- Use if unable to exercise, low exercise tolerance, or recent MI. Se & Sp ≈ exercise.
- Preferred if LBBB or V-paced, as higher prob of false ⊕ imaging with exercise
- *Coronary vasodilator:* diffuse vasodilation → relative "coronary steal" from vessels w/ fixed epicardial disease. Reveals CAD, but *not* if Pt *ischemic w/ exercise*. Regadenoson, dipyridamole, adenosine. Side effects: flushing, ↓ HR & AVB, dyspnea & 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)

- In 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).
- In sx outPt, CCTA vs. fxnal testing → ↑ radiation, cath/PCI, = outcomes (*NEJM* 2015;372:1291)
- Unlike CCTA, MR does not require iodinated contrast, HR control or radiation. Can assess LV fxn, enhancement (early = microvasc obstr.; late = MI). Grossly = Se/Sp to CCTA.

Coronary artery calcium score (CACS; *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 (10–20% 10-y Framingham risk; ? value if 6–10% 10-y risk) (*Circ* 2010;122:e584).

CORONARY ANGIOGRAPHY AND REVASCULARIZATION

Indications for coronary angiography in stable CAD or asx Pts

- 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 or nonatherosclerotic cause of ischemia (eg, anomalous coronary)

Precath checklist & periprocedural pharmacotherapy

- Document peripheral arterial exam (radial, femoral, DP, PT pulses; bruits). Ensure can lie flat for several hrs. NPO >6 h. Ensure blood bank sample.
- ✓ CBC, PT, & Cr; IVF (? $NaHCO_3$), ± acetylcysteine (see "CIAKI"), hold ACEI/ARB
- ASA 325 mg × 1. Timing of $P2Y_{12}$ inhib debated. ASAP for STEMI. ? preRx NSTEACS if clopi (*JAMA* 2012;308:2507) or ticag (PLATO), not prasugrel. Cangrelor (IV $P2Y_{12}$ inhib) ↓ peri-PCI events vs. clopi w/o preload (*NEJM* 2013;368:1303). ? statin preRx (*Circ* 2011;123:1622).

Coronary revascularization in stable CAD (*Circ* 2011;124:e574; *NEJM* 2016;374:1167)

- Optimal med Rx (**OMT**) should be initial focus if stable, w/o critical anatomy, & w/o ↓ EF
- **PCI:** ↓ angina more quickly c/w OMT; does *not* ↓ D/MI (*NEJM* 2007;356:1503 & 2015;373:1204); if ≥1 stenosis w/ FFR (qv) ≤0.8, ↓ urg revasc & ? D/MI c/w OMT (*NEJM* 2014;371:1208); ? noninf to CABG in unprot LM dz. (*NEJM* 2011;364:1718)
- **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); in diabetics w/ ≥2VD, ↓ D/MI, but ↑ stroke c/w PCI (*NEJM* 2012;367:2375)
- 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; if 3VD/LM: CABG ↓ D/MI & revasc but trend toward ↑ stroke c/w PCI (*Lancet* 2013;381:629); SYNTAX score II helps identify Pts who benefit most from CABG (*Lancet* 2013;381:639)

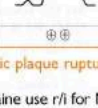
PCI and peri-PCI interventions

- **Access:** radial vs femoral, w/ former → ↓ bleeding and MACE (*JACC Intv* 2016;9:1419)
- **Fractional flow reserve** (FFR): ratio of max flow (induced by IV or IC adenosine) distal vs. prox to stenosis; help ID lesions that are truly hemodyn. significant
- 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):** ↓ neointimal hyperplasia → ~75% ↓ restenosis, ~50% ↓ repeat revasc (<5% by 1 y), ? ↑ late stent thrombosis, no Δ D/MI c/w BMS (*NEJM* 2013;368:254); latest gen. DES w/ very low rates of restenosis, repeat revasc & stent thrombosis
- **Bioresorbable stent:** resorbs over yrs, but ? ↑ MACE & stent thromb. (*NEJM* 2015;373:1905)
- Duration of DAPT: ASA (81 mg) lifelong. *If SIHD,* $P2Y_{12}$ inhib × 4 wk (BMS) or ≥6 mo (DES). *If ACS,* $P2Y_{12}$ >12 mo → ~20% ↓ MACE, ↑ bleeding and ~15% ↓ CV death (*NEJM* 2014;371:2155 & 2015;372:1791). If need oral anticoag, consider clopi + NOAC ± ASA.

Post-PCI complications

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr
- **Bleeding**
  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
  if bleeding uncontrolled, consult performing interventionalist or surgery
- **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 acute kidney injury:** manifests w/in 48 h, peaks 3–5 d (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 to 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**
  - 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

- **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 if 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	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 (preferred over CK-MB) at presentation & 3–6 h after sx onset; repeat 6 h later if clinical or ECG Δs; rise to >99th %ile in appropriate clinical setting dx of MI (see "Chest Pain"); rise in Tn in CKD 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 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 and initial ECG & Tn non-dx, repeat ECG q15–30min × 1 h & Tn 3–6 h after sx onset
- If remain nl and low likelihood of ACS, search for alternative causes of chest pain
- If remain nl, have ruled out MI, *but* if 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 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). IV βB prior to 1° PCI ↓ infarct size and ↑ EF (*Circ* 2013;128:1495). *Contraindic.* PR >0.24 sec, HR <60, 2°/3° AVB, severe bronchospasm, s/s HF or low output, risk factors for shock (eg, >70 y, HR >110, SBP <120, late presentation STEMI)
CCB (nondihydropyridines)	If cannot tolerate βB b/c bronchospasm
Morphine	Relieves pain/anxiety; venodilation ↓ preload. Do not mask refractory sx. May delay antiplt effects of $P2Y_{12}$ inhib.
Oxygen	Use prn for resp distress or to keep S_vO_2 >90% ? ↑ infarct size in STEMI w/o hypoxia (*Circ* 2015;131:2143)

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 (*JACC* 2014;63:71)
- **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
- Ezetimibe, aldosterone blockade, and ranolazine discussed later (long-term Rx)
- 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
$P2Y_{12}$ ($P2Y_{12}$ receptor) inhibitor (choose one of the following in addition to ASA). Timing remains controversial. European guidelines recommend $P2Y_{12}$ inhibitor as soon as possible (except prasugrel; *EHJ* 2011;32:2999). See below for specific recommendations.	
• **Ticagrelor** (preferred over clopi) 180 mg × 1 → 90 mg bid Reversible, but wait 3–5 d prior to surg 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_vO_2 & PFTs nl) & ventricular pauses

• **Prasugrel** (preferred over clopi) 60 mg × 1 at PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery	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 Not sup to clopi if med mgmt w/o PCI (*NEJM* 2012;367:1297) 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; $t^{1}/_{2}$ 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) Unclear benefit if upstream clopi administered (*NEJM* 2009;361:2318) and no data vs. prasugrel or ticagrelor
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 PCI	24% ↓ D/MI (*JAMA* 1996;276:811) Titrate to aPTT 1.5–2× control (~50–70 sec) Hold until INR <2 if already on warfarin
Enoxaparin (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IVB) (qd if CrCl <30) × 2–8 d or until PCI	–10% ↓ D/MI vs. UFH (*JAMA* 2004;292:45,89). Can perform PCI on enox (*Circ* 2001;103:658), but ↑ bleeding if switch b/w enox and UFH.
Bivalirudin (direct thrombin inhibitor) 0.75 mg/kg IVB at PCI → 1.75 mg/kg/h	↓ bleeding (espec vs. UFH + GPI), ± ↑ early MI (*Lancet* 2014;384:599). Use instead of UFH if HIT.
Fondaparinux (Xa inhibitor) 2.5 mg SC qd × 2–8 d	C/w enox, 17% ↓ death & 38% ↓ bleeding (*NEJM* 2006;354:1464). However, ↑ risk of catheter thrombosis; ∴ must supplement w/ UFH if PCI.

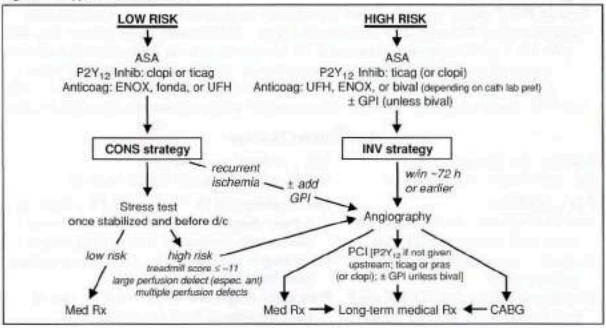
Coronary angiography (*Circ* 2014;130:e344)

- **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-umassmed.org/grace) >140 (*NEJM* 2009;360:2165)
  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;41:895)	
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")

- Immediate reperfusion (ie, opening occluded culprit coronary artery) is critical
- 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 (*NEJM* 2007;356:47; *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)
- Complete revasc: ↓ MACE vs. culprit artery alone (*NEJM* 2013;369:1115; *JACC* 2015;65:963); alternatively, assess ischemia due to residual lesions w/ imaging stress (*Circ* 2011;124:e574)

Fibrinolysis vs. Hospital Transfer for Primary PCI: Assess Time and Risk

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

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

Fibrinolysis

- Indic: STE/LBBB + sx <12 h (& >120 min before PCI can be done); benefit if sx >12 h less clear; reasonable if persist. sx & STE or 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	• H/o severe HTN, SBP >180 or DBP >110 on presentation (? absolute if low-risk MI)
• Intracranial neoplasm, aneurysm, AVM	• Ischemic stroke >3 mo prior
• Ischemic stroke or closed head trauma w/in 3 mo; head/spinal surg. w/in 2 mo	• CPR >10 min; trauma/major surg. w/in 3 wk
• Active internal bleeding or known bleeding diathesis	• Internal bleed w/in 2–4 wk; active PUD
• Suspected aortic dissection	• Noncompressible vascular punctures
• Severe uncontrollable HTN	• Pregnancy
• For SK, SK Rx w/in 6 mo	• 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 abciximab, eptifibatide, tirofiban	*Lysis:* no indication (*Lancet* 2001;357:1905) *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:* ↓ bleeding (espec vs. UFH + GP IIb/IIIa inhib), ± ↑ MI, ↑ stent thromb, ? ↓ mortality (*Lancet* 2014;384:599; *JAMA* 2015;313:1336; *NEJM* 2015;373:997)

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

Intraaortic Balloon Pump (IABP) Counterpulsation

- *Routine* use in high-risk STEMI → ↑ stroke/bleeds w/o Δ in survival (*JAMA* 2011;306:1329)
- In cardiogenic shock, no survival benefit w/ IABP if early revasc (*NEJM* 2012;367:1287); 18% ↓ death in Pts w/ cardiogenic shock treated with lytic (*EHJ* 2009;30:459)

LV failure (~25%)

- Diurese to achieve PCWP ~18 → ↓ pulmonary edema, ↓ myocardial O_2 demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O_2 demand
  can use IV NTG or nitroprusside (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 L/min/m², PCWP >18 mmHg; inotropes, mech circulatory support to keep CI >2; pressors to keep MAP >60; if not done already, coronary revasc (*NEJM* 1999;341:625)

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 → compromised flow to RV marginal branch) Angiographically present in 30–50%, but only ⅓ of those clinically signif.
  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; *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 a lone) 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; monomorphic VT <48 h post-MI does *not* worsen prognosis; >48 h, consider ICD (? wearable; see below)
- Accelerated idioventricular rhythm (AIVR): slow VT (<100 bpm), often seen after successful reperfusion; typically asx, self-terminates, and does not require treatment
- May consider ***backup* transcutaneous pacing** (TP) if: 2° AVB type I, BBB
- **Backup TP *or* initiate transvenous pacing** if: 2° AVB type II; BBB + AVB
- **Transvenous pacing** (TV) if: 3° AVB; new BBB + 2° AVB type II; alternating LBBB/RBBB (can bridge w/ TP until TV, which is best accomplished with fluoroscopic guidance)

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, as 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
- **Statin:** high-intensity lipid-lowering (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)
- **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 or LV thrombus), warfarin w/ target INR 2–2.5 or NOAC.
  Clopi (not ticag or pras) and ? stop ASA if at high bleeding risk (*Lancet* 2013;381:1107).
  Not FDA approved: low-dose rivaroxaban (2.5 mg bid) in addition to ASA & clopi in patients *without* an indication for anticoag → 16% ↓ D/MI/stroke and 32% ↓ all-cause death, but ↑ major bleeding and ICH (*NEJM* 2012;366:9).

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

- If sust. VT/VF >2 d post-MI not due to reversible ischemia; consider wearable defib
- Indicated in 1° prevention of SCD if post-MI w/ EF ≤30–40% (NYHA II–III) or ≤30–35% (NYHA I); need to 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
- Traditional LDL-C goal <70 mg/dL; current recs w/o target; given IMPROVE-IT, ? mid 50s
- BP <140/90 & ? 120–130/80 mmHg (*HTN* 2015;65:1372; *NEJM* 2015;373:2103); quit smoking
- If diabetic, tailor HbA1c goal based on Pt (avoid TZDs if HF); in Pts w/ CAD, empagliflozin (*NEJM* 2015; 373:2117) and liraglutide (*NEJM* 2016;375:311) ↓ cardiovascular events
- Exercise (30–60 min 5–7×/wk); cardiac rehab; BMI goal 18.5–24.9 kg/m^2
- Influenza & *S. pneumo* vaccines (*Circ* 2006;114:1549; *JAMA* 2013;310:1711); ✓ 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) ΔLVEDP-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: ~½ of *clinical* CO & PCWP estimates incorrect; CVP & PCWP not well correl.; ∴ use PAC to (a) answer hemodynamic *?* and then remove, or (b) manage cardiogenic shock

Placement (*NEJM* 2013;369:e35)

- Insertion site: **R 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

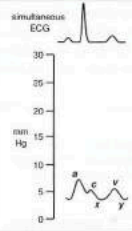
Intracardiac pressures

- 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 ~½ 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
  ∴ $\mathbf{CO = \dot{V}O_2 \,/\, C(a\text{-}v)O_2}$
  $\dot{V}O_2$ ideally measured (esp. if ↑ metab demands), but freq estimated (125 mL/min/m²)
  $C(a\text{-}v)O_2 = [10 \times 1.36\ \text{mL}\ O_2/\text{g of Hb} \times \text{Hb g/dL} \times (S_aO_2 - S_{MV}O_2)]$. *$S_{MV}O_2$ is key variable 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)

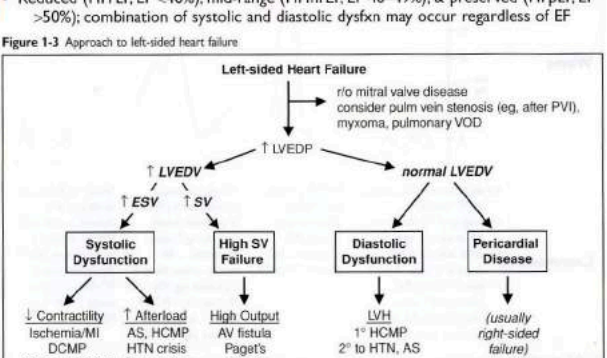
- **Goals:** optimize both MAP and CO while ↓ risk of pulmonary edema
  MAP = CO × SVR; CO = HR × SV (which depends on preload, afterload and contractility)
  pulmonary edema when PCWP >20–25 (↑ levels may be tolerated in chronic HF)
  hepatic and renal congestion when CVP/RAP >15 mmHg
- **Optimize preload** = 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, 10th ed., 2014)

- 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.

Treatment of acute decompensated heart failure

- Assess degree of congestion & adequacy of perfusion
- For **congestion: "LMNOP"**
  - **L**asix 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)*
  - **M**orphine (↓ sx, venodilator, ↓ afterload)
  - **N**itrates (venodilator)
  - **O**xygen ± noninvasive vent (↓ sx, ↑ P_aO_2; no Δ mortality; see "Mechanical Ventilation")
  - **P**osition (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 ½ if mod HF, d/c if severe HF and/or need inotropes

Low perfusion?	Congestion? No	Congestion? Yes
No	**Warm & Dry** *OutPt Rx*	**Warm & Wet** *Diuresis*
Yes	**Cold & Dry** *inotropes (CCU)*	**Cold & Wet** *Diuresis, inotropes and/or vasodil (CCU)*

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; prolonged use → cyanide/thiocyanate toxicity); nesiritide (rBNP) not rec for routine use *(NEJM 2011;365:32)*
- **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
- **Ultrafiltration:** similar wt loss to aggressive diuresis, but ↑ renal failure *(NEJM 2012;367:2296)*
- **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 *(Circ 2015;131:676)*
  - *Durable:* surgically placed LVAD ± RVAD as bridge to recovery *(NEJM 2006;355:1873)* or transplant (HeartMate II or HeartWare LVAD or Total Artificial Heart if BiV failure), or as destination Rx (>50% ↓ 1-y mort. vs. med Rx; *NEJM 2001;345:1435 & 2009;361:2241).*
- 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 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 Heart Failure with Reduced Ejection Fraction	
Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
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;374:1840) 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)*	*Alternative to ACEI/ARB, espec if sx despite ACEI/ARB.* Neutral endopeptidase (NEP, aka neprilysin) degrades natriuretic peptides, bradykinin & angiotensins. Valsartan + sacubitril (NEPi) ↓ CV mort & HF hosp c/w ACEi; ↑ HoTN, AKI, ? angioedema (*NEJM* 2014;371:993).
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 & non-isch CMP; no Δ mort. early post-MI (*NEJM* 2004;351:2481 & 2009;361:1427), ∴ wait ≥40 d
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	*? if NYHA III/III, EF ≤40%, Fe-defic* (ferritin <100 or ferritin 100–200 & TSAT <20%). ↓ Sx, ↑ 6MWD, independent of Hct (*NEJM* 2009;361:2436).
Anticoagulation	*If AF, VTE, LV thrombus, ± if large akinetic LV segments* In SR w/ EF <35%, ↓ isch stroke, but ↑ bleed (*NEJM* 2012;366:1859)
Heart rhythm	Catheter ablation of AF → ↑ in EF, ↓ sx (*NEJM* 2004;351:2373) No mortality benefit to AF rhythm vs. rate cntl (*NEJM* 2008;358:2667) Pulm vein isolation ↓ sx c/w AVN ablation & CRT (*NEJM* 2008;359:1778)
Meds to avoid	NSAIDs, nondihydropyridine CCB, TZDs
Experimental	Serelaxin ± ↓ dyspnea & ? ↓ mortality (*Lancet* 2013;381:29) Empagliflozin (SGLT2i) ↓ death/HF hosp in DM (*NEJM* 2015;373:2117) Interatrial shunting ↓ PCWP & sx (*Lancet* 2016;387:1290)

(*Circ* 2013;128:e240 & 2016 ACC/AHA/HFSA Update: *EHJ* 2016;37:2129)

Heart failure with preserved EF (HFpEF; "Diastolic HF") (*Circ* 2011;124:e540)

- Epidemiology: ~½ 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 (*Lancet* 2012;380:1387) and serelaxin (*Lancet* 2013;381:29) under study

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 (*NEJM* 2015;373:456)
- **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, Wegener's; *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 (*Lancet* 2009;373:1289)
- **Tachycardia:** likelihood ∝ rate/duration; often resolves w/ rate cntl (*Circ* 2005;112:1092)
- **LV noncompaction** (*JACC* 2015;66:578): 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)
- 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 of 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
- Morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical

Pathophysiology
- Subaortic outflow obstruction: 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)
- ? Genotyping for family screening, but pathogenic mutation ID'd in <½ (*Circ* 2011;124:2761)

Treatment (*Circ* 2011;124:e783 & 2012;125:1432; *Lancet* 2013;381:242)
- Heart failure
  - ⊖ **inotropes/chronotropes:** β-blockers, CCB (verapamil), disopyramide
  - Careful use of diuretics, as may further ↓ preload. Vasodilators only if systolic dysfxn. Avoid digoxin.
  - 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 (*JCHF* 2015;3:896): gradient ↓ 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
- SCD: ICD (*JACC* 2003;42:1687). Risk factors: h/o VT/VF, ⊕ FHx SCD, unexplained syncope, NSVT, ↓ SBP or rel HoTN (↑ SBP <20 mmHg) w/ exercise, LV wall ≥30 mm, ? extensive MRI delayed enhancement. EPS *not* useful. Risk 4%/y if high-risk (*JAMA* 2007;298:405).
- Counsel to avoid dehydration, extreme exertion
- Endocarditis prophylaxis not recommended (*Circ* 2007;16:1736)
- 1st-degree relatives: periodic screening w/ echo, ECG (as 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)

- **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 texture (30%), biatrial enlargement (40%), thickened atrial septum, valve thickening (65%), diastolic dysfxn, small effusions
      - NI 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

AORTIC STENOSIS (AS)

Etiology

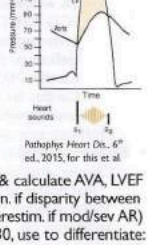
- **Calcific:** predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- **Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- **Rheumatic heart disease** (AS usually accompanied by AR and MV disease)
- AS mimickers: subvalvular (HCMP, subAo membrane)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

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

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

Physical exam

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



Pathophys Heart Dis., 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 ∇ <30, 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; *NEJM* 2014;371:744; *Lancet* 2016;387:1312)

- Based on *symptoms:* once they develop, AVR needed. If asx, HTN can be cautiously Rx'd.
- **AVR:** indicated in **sx** (stage D1); **asx severe + EF <50%** (stage C2); or asx 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) indicated if surgical risk prohibitive or as reasonable alternative to surgery if medium (STS predicted 30-d mortality ~4–8%) or high (mortality 8–15%) operative risk

- 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 in HF w/ sev. AS, EF <35%, CI <2.2, & MAP >60 (*NEJM* 2003;348:1756) or if low flow w/ ↓ EF and HTN (*Circ* 2013;128:1349)
- IABP: stabilization, bridge to surgery
- Balloon AoV valvotomy (BAV): 50% ↑ AVA & ↓ peak ∇, *but* 50% restenosis by 6–12 mo & ↑ risk of peri-PAV stroke/AR (*NEJM* 1988;319:125), ∴ bridge to AVR or palliation

TAVR (transcatheter AoV replacement)

- Valves: balloon-expandable (Edwards SAPIEN) or self-expanding (Medtronic CoreValve)
- Approaches: most commonly retrograde via perc. transfemoral access; also retrograde via axillary art. or ascend. Ao (via small sternotomy & aortotomy). Alternatively antegrade transapical via small thoracotomy & LV puncture (if narrow iliofem art. or calcified Ao).
- Peri- & postprocedural complic.: low CO; annular rupture or coronary occlusion (both rare); local vascular; paravalvular leaks; CHB.
- Lifelong ASA + ? clopidogrel (or OAC) × 6 mo; ? subclinical valve thrombus in ~20%, ↓ w/ anticoag (*NEJM* 2015;373:2015)
- 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).
  In *high-risk Pts* vs. surg AVR (*NEJM* 2012;366:1686 & 2014;370:1790): mortality = (balloon-expand) or 26% ↓ (self-expand); ↑ vasc complic; ↑ early risk of stroke/TIA w/ balloon-expand; PPM required for CHB in ~20% w/ self-expand; paravalvular leaks in ~7%.
  In *medium-risk Pts* (*NEJM* 2016;374:1609): death/stroke ≈, ↑ vasc complic but ↓ bleeding, AKI, AF. If transfemoral 21%, ↓ death/stroke, whereas tended to be 21% ↑ if transapical.

AORTIC REGURGITATION (AR)

Etiology (*Circ* 2006;114:422)

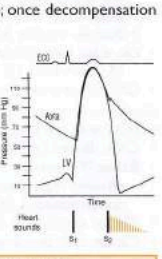
- **Valve disease** (43%): **rheumatic heart disease** (usually mixed AS/AR + MV disease); **bicuspid AoV** (natural hx: $^1/_3$→ normal, $^1/_3$ → AS, $^1/_6$ → AR, $^1/_6$ → endocarditis → AR); **infective endocarditis;** valvulitis (RA, SLE, certain anorectics & serotonergics, XRT)
- **Root disease** (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, hyperdynamic 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%, regurg orifice ≥0.3 cm^2, 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 undergoing cardiac surg
- Transcatheter AoV replacement (TAVR) being explored (*JACC* 2013;61:1577 & 2015;66:169)
- 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)

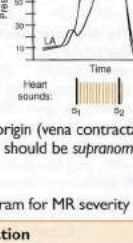
- **Primary** (degeneration of valve apparatus)
  leaflet abnl: myxomatous (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs (phen-fen), XRT
  chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma
  papillary muscle dysfxn b/c of 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 (*Circ* 2014;129:e521; *Lancet* 2016;387:1324)

- **Acute severe MR:** consider ischemia & endocarditis as precipitants; IV afterload reduction (nitroprusside), relieve congestion (diuresis & NTG), ± inotropes (dobuta), IABP, avoid vasoconstrictors; surgery usually needed as prognosis poor w/o (*JAMA* 2013;310:609)

- **Chronic severe primary MR: surgery** (repair [preferred if feasible] vs. replacement) indicated if **sx & EF >30%** or if **asx & either EF 30–60% or LV sys. diam. ≥40 mm** 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)
- Severe *secondary MR*: consider surgery if NYHA III-IV; replacement results in more durable correction & ↓ HF & ↓ CV admissions than repair (*NEJM* 2016;374:344)
- In Pts undergoing CABG w/ moderate fxnal MR, annuloplasty ↓ MR but longer surgery, ↑ neurologic events, & no impact on fxnal status or mortality (*NEJM* 2016;374:1932)
- Percut. MV repair (*Circ* 2014;130:1712): edge-to-edge clip less effective than surgery but consider for sev. sx nonoperative Pt (*NEJM* 2011;364:1395); perc valve under study (*JACC* 2014;64:1814)
- 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 (MVP most common cause), endocarditis, embolic events, arrhythmias (rarely SCD)
- High-pitched, midsystolic click (earlier w/ ↓ preload) ± mid-to-late systolic murmur
- No Rx per se [endocarditis Ppx no longer rec. (*Circ* 2007;116:1736)]; Rx MR as above

Mitral Stenosis (MS)

Etiology (*Lancet* 2012;379:953)

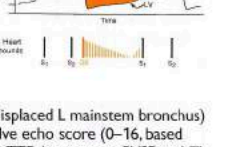
- **Rheumatic heart disease** (RHD): *fusion of commissures* → "fish-mouth" valve from autoimmune rxn to β strep infxn; seen largely in developing world today
- **Mitral annular calcification:** encroachment upon leaflets → fxnal MS; espec in ESRD
- Congenital, infectious endocarditis w/ large lesion, 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 ½ 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* valve 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

- 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, annuloplasty or replacement for sx and severe TR (eg, ERO ≥0.40 cm^2); transcatheter system (provides surface for coaptation) under study (*JACC* 2015;66:2475)

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 <~60 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 ½ bleeding or stroke vs. mech (*JAMA* 2014;312:1323 & 2015;313:1435)

Physical exam

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

Anticoagulation & antiplatelet therapy (*Circ* 2014;129:e521)

- *High-risk features:* prior thromboembolism, AF, EF <30–35%, hypercoagulable
- **Warfarin (∅ NOACs):** mech MVR or high-risk mech AVR: INR 2.5–3.5. Low-risk mech AVR or high-risk bio MVR/AVR: INR 2–3. Consider in low-risk bio MVR/AVR for 1st 3 mo.
- + **ASA** (≤100 mg): all prosth. valves unless h/o 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)

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

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 (*JAMA* 2014;312:162)
- 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 lg (? ≥0.8 cm) thrombus; lytic successful in ~70% of L-sided thrombosis, but w/ 14% risk of stroke; consider UFH ± lytic (? low-dose tPA via slow infusion; *JACC CV Imaging* 2013;6:206) if mild sx & small clot burden or poor surg candidate; 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

General Principles

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)

Idiopathic (>80%)	Most presumed to be undiagnosed viral etiologies
Infectious (<5% can be confirmed infectious)	Viral: Coxsackie, echo, adeno, EBV, VZV, HIV, influenza Bacterial (from endocarditis, pneumonia or s/p cardiac surgery): *S. pneumococcus, N. meningitidis, S. aureus, Borrelia* (Lyme); TB Fungal: *Histo, Coccidio, Candida*; Parasitic: *Entamoeba, Echino*
Neoplastic (<10%)	*Common:* metastatic (lung, breast, lymphoma, leukemia, RCC) *Rare:* primary cardiac & serosal tumors (mesothelioma)
Autoimmune	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, eosin GPA (Churg-Strauss), GPA (Wegener's) 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: will reveal pericardial effusions, but they often appear larger by CT than by echo.
- **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, 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 remains for malignancy or TB

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** 0.5 mg bid (qd if ≤70 kg) × 3 mo; ↓ risk of refractory or recurrent pericarditis by 50% (NEJM 2013;369:1522)
- Avoid steroids except for systemic autoimmune disorder, uremic, preg., NSAIDs contra-indicated, or refractory idiopathic dis. 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
- Acute idiopathic pericarditis self-limited in 70–90% of cases
- Recurrent pericarditis (Circ 2007;115:2739)
  risk factors: subacute, lg effusion/tamponade, T >38°C, lack of NSAID response after 7 d treatment: colchicine 0.5 mg bid × 6 mo (Annals 2011;155:409 & Lancet 2014;383:2232)
- 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 as 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, constriction (~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 elevated after drainage, may have effusive-constrictive disease (constriction from visceral pericardium; NEJM 2004;350:469) or myocardial dysfxn (eg, from concomitant myocarditis)

Treatment (EHJ 2014;35:2279)

- Volume (but be careful as overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- Avoid vasoconstrictors as will ↓ stroke volume & potentially ↓ HR
- Avoid positive pressure ventilation as 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

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,** as 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 >1/3 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 <1/3 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

Ambulatory Thresholds		
Setting	**Systolic**	**Diastolic**
24-hr avg	135	85
Day (awake)	140	90
Night (asleep)	125	75

(*Circ* 2005;111:697)

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)

Epidemiology (*JAMA* 2014;311:1424; *Circ* 2015;131:e29)

- 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

- **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) seek 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, resistant, or white coat HTN

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 (*JAMA* 2014;311:507; *J Clin HTN* 2014;16:14; *HTN* 2015;65:1372; *JACC* 2015;65:1998)

- Every ↓ 10 mmHg → 20% ↓ MACE, 28% ↓ HF, 13% ↓ mort. (*Lancet* 2016;387:957)
- Traditional goal: <140/90; *if prior MI/stroke:* reasonable to consider <130/80
  - *If high-risk* (CV dis., 10-y risk of CV dis. ≥15%, CKD, or ≥75 y; non-DM and no h/o stroke) SBP ~120 vs. ~135 (via unattended automated cuff) → ↓ MACE 25%, ↓ death 27%, ↓ HF 38%, but ↑ HoTN, AKI, syncope, electrolyte abnl (*NEJM* 2015;373:2103)
  - *If DM:* optimal goal disputed b/c lack of clear benefit in one study (*NEJM* 2010;362: 1575); may consider <130/80 for renal protection if CKD & albuminuria (ASH/ISH)
  - *If intermed risk* (RF for but w/o CV dis.), benefit only if SBP >~140 (*NEJM* 2016;374:2009)
  - *In elderly:* ? more lenient targets, but benefit to Rx'ing stage 2 HTN in low-risk (*NEJM* 2008; 358:1887) and targeting SBP ~120 in high-risk (↓ MACE & mortality; *JAMA* 2016;315:2673)

- **Lifestyle modifications** (each may ↓ SBP ~5 mmHg)
  weight loss: goal BMI 18.5–24.9; aerobic exercise: ≥30 min exercise/d, ≥5 d/wk
  diet: rich in fruits & vegetables, low in saturated & total fat (DASH, *NEJM* 2001;344:3)
  limit Na: ≤2.4 g/d (ideally ≤1.5 g/d); maintain K intake (*NEJM* 2007;356:1966 & 2010;362:2102)
  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 (*NEJM* 2009;361:2153). βB not 1st line (*Lancet* 2005;366:1545).
  For non-black Pts <60 y: reasonable to start w/ ARB or ACEI, then add CCB or thiazide if needed, and then add remaining class if still needed
  For black, elderly, and ? obese Pts (all of whom more likely to be salt sensitive): reasonable to start with CCB or thiazide, then add either the other 1st choice class or ARB or ACEI if needed, and then all 3 classes if still needed
  +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")
  +2° stroke prevention: 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 ½ max dose; after 2–3 wk, uptitrate or add drug
- **Pregnancy:** methyldopa, labetalol, & nifed pref. Hydral OK; avoid diuretics; Ø ACEI/ARB. Targeting DBP 85 vs. 105 safe and ↓ severe HTN (*NEJM* 2015;372:407).

Resistant HTN (BP > goal on ≥3 drugs incl diuretic; *JAMA* 2014;311:2216)
- 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 dosing (chlorthalidone > HCTZ, loop > thiazide if eGFR <30)
- Can add aldosterone antagonist (*Lancet* 2015;386:2059), β-blocker (particularly vasodilators like labetalol, carvedilol, or nebivolol), α-blocker, or direct vasodilator

Hypertensive Crises

- **Hypertensive emergency:** ↑ BP → acute target-organ ischemia and damage
  neurologic damage: encephalopathy, hemorrhagic or ischemic stroke, papilledema
  cardiac damage: ACS, HF/pulmonary edema, aortic dissection
  renal damage: proteinuria, hematuria, acute renal failure; scleroderma renal crisis
  microangiopathic hemolytic anemia; preeclampsia-eclampsia
- **Hypertensive urgency:** SBP >180 or DBP >120 (?110) w/ min. or Ø 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 (*Chest* 2007;131:1949)
- Tailor goals to clinical context. Treat Ao dissection aggressively. Do *not* treat HTN in acute ischemic stroke unless lysis planned or extreme BP (>220/120).
- Emergency: ↓ MAP by ~25% in *mins to 2 h* w/ IV agents (may need arterial line for monitoring); goal DBP <110 w/in 2–6 h, as tolerated
- Urgency: ↓ BP to ≤160/100 in *hrs* using PO agents; goal normal BP in ~1–2 d
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

Drugs for Hypertensive Crises

IV	Nitroprusside* 0.25–10 μg/kg/min	Nitroglycerin 5–1000 μg/min
	Labetalol 20–80 mg IVB q10min or 0.5–2 mg/min. *Preferred in pregnancy.*	Esmolol 0.5 mg/kg load → 0.05–0.2 mg/kg/min
	Fenoldopam 0.1–1.6 μg/kg/min	Hydralazine 10–20 mg q20–30min
	Nicardipine 5–15 mg/h	Clevidipine 1–16 mg/h
	Phentolamine 5–15 mg bolus q5–15min	Enalaprilat 1.25 mg
PO	Captopril 12.5–100 mg q8h	Labetalol 200–800 mg, repeat after 2–3 h
	Clonidine 0.2 mg load → 0.1 mg qh	Hydralazine 10–75 mg qid

*Metabolized to cyanide →Δ MS, lactic acidosis, death. Limit use of very high doses (8–10 μg/kg/min) to <10 min. Monitor thiocyanate levels. Hydroxocobalamin or sodium thiosulfate infusion for treatment of cyanide toxicity.

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 >60y; 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 2006;113:e463; 2008;117:1883; 2010;121:e266; 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 mg/dL
- **BP control:** βB (↓ 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, bi-AoV, L-D, vascular EDS); size may not predict repair benefit; descending Ao >6 cm; ≥4.5 cm and planned AoV surgery
  - **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 proven Δ in overall mortality in trials, except ? in those <70 y (*NEJM 2010;362:1863, 1881 & 2012;367:1988*)
  In observ. data, EVAR a/w ↑ early survival but ↑ long-term rupture (*NEJM 2015;373:328*)
  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 q2–3 y; 4–5.4 cm q6–12 mos; 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, TB); *pregnancy* (typically 3rd trimester)
- **Trauma:** blunt, decel. injury (eg, MVA); IABP, cardiac or aortic surgery, 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 propogates 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:** Se/NPV ~97%, Sp ~47%; ? <500 ng/mL to r/o dissec (Circ 2009;119:2702) but not in Pts at high clinical risk (Annals EM 2015;66:368); does not r/o IMH

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 βB** (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy in response to vasodilators; verap/dilt if βB 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, since dissection often along outer Ao curvature); *innominate/carotid* → CVA, Horner; *intercostal/lumbar* → spinal cord ischemia/paraplegia; *innominate/subclavian* → upper extremity ischemia; iliac → lower extremity ischemia; celiac/mesenteric → bowel ischemia; *renal* → AKI or gradually ↑ Cr, refractory HTN
- **AI:** due to annular dilatation or disruption or displacement of leaflet by false lumen
- Mortality: historically ~1%/h × 48 h for acute prox AoD w/ 10–35% at 30 d
- **Long-term serial imaging** (CT or MRI; latter may be preferred due to lower cumulative radiation exposure) at 1, 3, and 6 mo, and then annually (18 mo, 30 mo, etc.)

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, etc.
- 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)

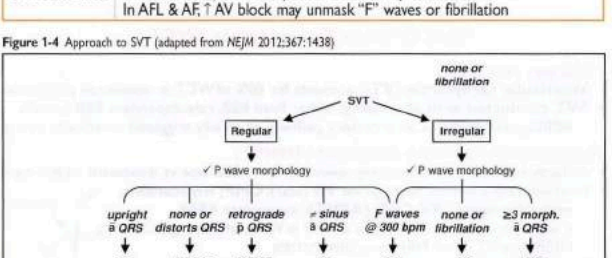
*Arise above the ventricles, ∴ **narrow QRS** unless aberrant conduction or pre-excitation.*

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 preexcitation (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 as 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 → ST, AT (P different from sinus), MAT (≥3 morphologies) After QRS & inverted in inf. leads → *retrograde* atrial activation via AVN 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 re-entrant 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 antiarrhythmics
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 antiarrhythmics (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, digoxin, AAD**	RFA; βB or CCB ± class III antiarrhyth.
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 ~80%) 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
- **Preexcitation (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, as can ↓ refractoriness of pathway → ↑ vent. rate → VF (*Circ* 2016;133:e506).
- **Long term:** RFA if sx; if not candidate for RFA, then antiarrhythmics (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, ≤250ms) and if SVT inducible

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 w/ inferior axis; typically ablate
  idiopathic LV VT: RBBB-type VT 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): ♂ > ♀; 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* 1991;83:1649)
  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
  concordance (QRS in all precordial leads w/ same pattern/direction)

Long-term management (*JACC* 2006;48:1064; *EHJ* 2015;36:2793; *Circ* 2016;133:1715)

- 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 etiology or waiting for ICD? 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)

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**

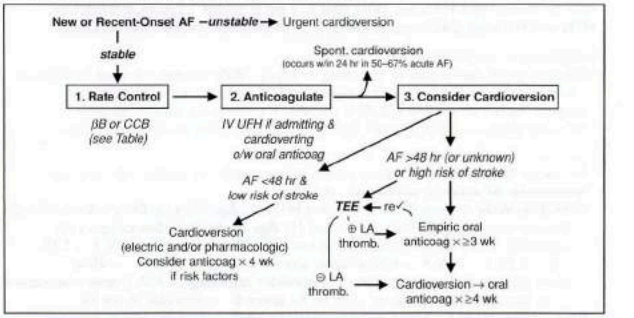
Epidemiology and etiologies (*Circ* 2011;124:1982)

- 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 ("holiday heart"), cocaine, amphetamines, theophylline, caffeine, smoking
  - **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

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; *Lancet* 2016;388:818)

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
CCB	**Diltiazem**	0.25 mg/kg over 2′ may repeat after 15′ 5–15 mg/h infusion	120–360 mg/d in divided doses	Preferred if severe COPD Can ↑ dig levels
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 & bronchospas.
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		

Circ 2014;130:e199. IV βB, CCB & dig ***contraindicated*** if evidence of WPW (ie, pre-excitation or WCT) since may facilitate conduction down accessory pathway leading to VF; ∴ use procainamide, ibutilide or amio.
*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 for ≥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 cardivert, consider pre-Rx w/ AAD (eg, ibutilide), esp. if 1st cardivert 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; ∅ if perm AF or ↓ EF; liver tox
	Ibutilide	1 mg IV over 10′ may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT (3–8% risk of TdP): give w/ IV Mg
	Dofetilide	500 mcg PO bid	500 mcg bid	↑ QT, ↑ risk of TdP; renal adj
	Sotalol	n/a	80–160 mg bid	✓ for ↓ HR, ↑ QT: renal adj
IC	Flecainide	300 mg PO × 1	100–150 mg bid	PreRx w/ AVN blocker. ø *if structural/ischemic heart dis.*
	Propafenone	600 mg PO × 1	150–300 mg tid	
IA	Procainamide	10–15 mg/kg IV over 1 h	n/a	↓ BP; ↑ QT ± PreRx w/ 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

Nonpharmacologic therapy

- Ablation (pulm vein isolation; radiofreq or cryo): ~80% success; no need to interrupt anticoag. If w/o ↑↑ LA or ↓ EF, superior to AAD. (*NEJM* 2016;374:2235; *JAMA* 2014;311:692)
- Surgical "maze" procedure (70–95% success) if undergoing cardiac surgery
- AV node ablation + PPM if other Rx inadequate (*NEJM* 2001;344:1043; 2002;346:2062)

Oral anticoagulation (*Circ* 2014;130:e199; *JAMA* 2015;313:1950; EHRA Practical Guide *EHJ* 2016:epub)

- *All valvular AF* (ie, rheum MS, valve prosthesis or repair), as stroke risk very high
- Nonvalvular AF (NVAF): stroke risk ~4.5%/y
- **CHA_2DS_2-VASc** to guide Rx **C**HF (1 point); **H**TN (1); **A**ge ≥75 y (2); **D**M (1), **S**troke/TIA (2); **V**ascular disease (eg, MI, PAD, Ao plaque) (1); **A**ge 65-74 (1); ♀ **S**ex **c**ategory (1)
  annual risk of stroke (*Lancet* 2012;379:648): at low end, ~1% per point: 0 → ~0%, 1 → 1.3%, 2 → 2.2%, 3 → 3.2%, 4 → 4.0%; at higher scores, risk ↑↑ (5 → 6.7%, ≥6 → ≥10%)
  score ≥2 → 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: NOAC** (NVAF only) or warfarin (INR 2–3): if Pt refuses anticoag, ASA + clopi or, even less effective, ASA alone (*NEJM* 2009;360:2066)
- AF w/ CAD/ PCI: can consider anticoag + clopi, omit ASA (*Lancet* 2013;381:1107)
- Periop rate of arterial embolization in NVAF <0.5%; no benefit to bridging anticoag w/ LMWH & ↑ bleeding c/w stopping warfarin 5 d preop (*NEJM* 2015;373:823)

Non-vit K antag Oral Anticoag (NOACs) 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.

No monitoring required. Onset w/in hrs; 1 missed dose may ↓ protection. Specific reversal agents: idarucizumab for dabigatran; andexanet for FXa (*NEJM* 2015;373:511 & 373:2413).

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

- Perc left atrial appendage (LAA) occlusion (Watchman) noninf to anticoag (*JACC* 2015;65:2614)
- Epicardial snare to ligate LAA. High rate of initial tech success (*JACC* 2013;62:108).
- Surgical LAA resection reasonable if another indication for cardiac surgery

Atrial flutter

- Macroreentrant atrial loop (typical: counterclockwise w/ flutter waves ⊖ in inf leads)
- Risk of stroke similar to that of AF, ∴ anticoagulate same as would for AF
- Ablation of cavotricuspid isthmus has 95% success rate for typical AFL

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 (*NEJM* 2002;347:878; *JACC* 2006;47:473; *Eur Heart J* 2009;30:2631)

- **Neurocardiogenic** (a.k.a. vasovagal, ~25%; *NEJM* 2005;352:1004): ↑ sympathetic tone → vigorous contraction of LV → mechanoreceptors in LV trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ HR (cardioinhibitory) 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 as often transient
  Bradyarrhythmias: SSS, high-grade AV block, ⊖ chronotropes, PPM malfunction
  Tachyarrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)
  Mechanical (5%)
  Endocardial/Valvular: AS, MS, PS, prosthetic valve thrombosis, myxoma
  Myocardial: pump dysfxn from MI or outflow obstruction from HCMP (but usually VT)
  Pericardial: tamponade; Vascular: PE, PHT, AoD, ruptured AAA, subclavian steal
- **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)

- *H&P incl. orthostatic VS have highest yield and most cost effective* (*Archives* 2009;169:1299)
- **History** (from Pt and *witnesses* if available)
  activity and posture before the incident
  precipitating factors: exertion (AS, HCMP, PHT), positional Δ (orthostatic hypotension), stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/micturition/defecation/swallowing (neurocardiogenic), head turning or shaving (carotid sinus hypersens.); arm exercise (subclavian steal)
  prodrome (eg, diaphoresis, nausea, blurry vision): cardiac <~5 sec, vasovagal >~5 sec
  associated sx: chest pain, palp., neurologic, postictal, bowel or 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 including *orthostatics* (⊕ if supine → standing results in >20 mmHg ↓ SBP, >10 mmHg ↓ DBP, or >10–20 bpm ↑ HR), 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, preg test (child-bearing age ♀), ? D-dimer, ? troponin (low yield w/o other s/s)

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

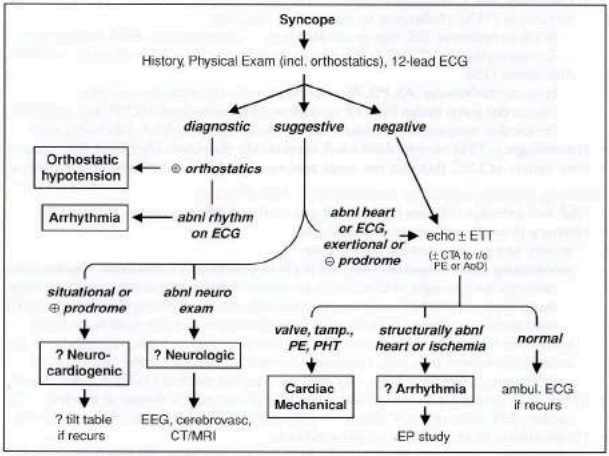
- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope
  Holter monitoring (continuous ECG 24–48 h): useful if *frequent* events
  arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)
  Event recorder (activated by Pt to record rhythm strip): limited role in syncope as 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 (inserted SC; can record >1 y): useful if episodes <1/mo; dx in 55% of cases (*Circ* 2001;104:46); recommended for recurrent syncope w/o prodrome

- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ARVC], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT/CCTA/Cath: esp. w/ exertional syncope; r/o ischemia or catechol-induced arrhythmia
- Electrophysiologic studies (EPS): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected, but cannot be confirmed;
  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 (*Annals* 1997;127:76)
- ? Tilt table testing: debated utility due to poor Se/Sp/reproducibility; consider only if vasovagal dx suspected but cannot be confirmed by hx
- Cardiac MRI: helpful to dx ARVC if suggestive ECG, echo (RV dysfxn) or ⊕ FHx of SCD
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield

Figure 1-6 Approach to syncope



(Adapted from *JACC* 2006;47:473)

High-risk features (usually admit w/ telemetry & testing; *J Emerg Med* 2012;42:345)

- 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
- ECG suggesting conduction abnormality, arrhythmia, or ischemia; Pt w/ PPM/ICD

Treatment

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder
- Vasovagal syncope: ? benefit of fludrocortisone, midodrine or SSRI (*Int J Cardiol* 2013;167:1906; *JACC* 2016;68:1); no proven benefit for disopyramide or βB (*Circ* 2006;113:1164)
  ? 16 oz of H_2O before at-risk situations (*Circ* 2003;108:2660)
  ? benefit w/ PPM if ≥3 episodes/2y & loop recorder w/ asystole >3 sec (*Circ* 2012;125:2566); PPM likely ineffective if positive tilt-test and no arrhythmia (*EHJ* 2014;35:2211)
- If orthostatic: vol replete (eg, 500 mL PO q a.m.); if chronic → rise from supine to standing *slowly*, stockings, midodrine, ? atomoxetine (*HTN* 2014;64:1235), fludrocort, ↑ Na diet

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

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope: 2-fold ↑ in mort., 20–40% 1-y SCD rate, median survival ~6 y
- 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
- Vasovagal syncope: Pts not at increased risk for death, MI, or stroke
- ✓ state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

Pacemaker Code				
A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive	1st letter Chamber paced	2nd letter Chamber sensed	3rd letter Response to sensed beat	4th letter 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 with emerging indications *(NEJM 2015;373:1125 & 2016;374:53)*	

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
- Synchronize & enhance LV fxn (↑ CO, ↓ adverse remodeling)
- **Indications:** LVEF ≤35% + NYHA II–IV despite med Rx + SR + LBBB ≥150 (? ≥120) ms; 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)*
  consider in AF: need rate control or AVN ablation; more pacing → greater CRT effect
- **Benefits:** ↓ HF sx, ↓ HF hosp., ↑ survival *(NEJM 2005;352:1539 & 2010;363:2385)*

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. Wearable defib & subcut-ICD, but ∅ pace/ATP.
- **Pt selection** *(NEJM 2004;350:2151 & 351:2481; 2005;352:225; 2009;361:1427; Circ 2012;126:1784)*
  2° prevention: survivors of VF arrest, unstable VT w/o reversible cause; structural heart disease & spontaneous sustained VT (even if asx)
  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*; consider if unexplained syncope + DCM, or if HCM, ARVC, Brugada, sarcoid, LQTS, Chagas or congenital heart disease if at risk for SCD; ? wearable vest as bridge to ICD
- **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); if recurrent VT, ? drug Rx (eg, amio + βB; *JAMA 2006;295:165*) or VT ablation *(NEJM 2007;357:2657)*; ablation at time of ICD ↓ risk of VT by 40% *(Lancet 2010;375:31)*

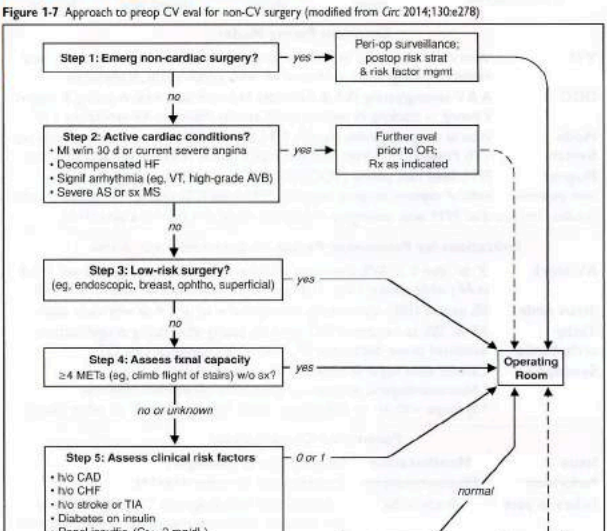
Device infection *(Circ 2010;121:458; JAMA 2012;307:1727; NEJM 2012;367:842)*

- Presents as *pocket infection* (warmth, erythema, tenderness) and/or *sepsis w/ bacteremia*
- Incidence ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%
- 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.

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

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, since at ↑ risk even if sx not severe; be careful to maintain preload, avoid hypotension, and watch for atrial fibrillation)

- If severe symptomatic AS and surg AVR not an option, balloon aortic valvuloplasty (BAV) or transcatheter aortic valve replacement (TAVR) can be considered (*JACC* 2014;64:e77)

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 mos (min 3 mos) after DES implantation (2016 ACC/AHA Update) unless risk of bleeding > risk of stent thrombosis or ACS. If must discontinue $P2Y_{12}$ inhibitor, continue ASA and restart $P2Y_{12}$ inhibitor ASAP.
- **β-blockers** (*Circ* 2009;120:2123; *JAMA* 2010;303:551; *Am J Med* 2012;125:953)
  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.
  In terms of initiating, conflicting evidence; may depend on how done. Some studies show ↓ death/MI, another ↓ MI, but ↑ death & stroke and ↑ brady/HoTN (*Lancet* 2008;371:1839).
  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: may cause HoTN perioperatively. If held before surgery, 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* 2012;307:2295) 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** (dull ache, often in calves) precip by walking and relieved by stopping (vs. spinal stenosis, qv); Leriche synd = claudication, ↓ or ∅ femoral 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

- ↓ peripheral pulses; other 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. If ABI abnl → segmental ABI w/ PVR to localize disease. If ⊕ sx but nl ABI, ✓ for ↓ lower extrem BP after exercise.
- 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 modification. Screen for CAD. Structured exercise program (*JAMA* 2013;310:57).
- If sx, ASA or clopi to ↓ D/MI/stroke. More intensive Rx (eg, adding ticagrelor or vorapaxar) ↓ both MACE and limb ischemic events (*Circ* 2013;112:679 & *JACC* 2016;67:2719).
- Cilostazol (if no HF) & ? ACEI & statins to ↓ sx (*Circ* 2003;108:1481)
- Endovascular (angioplasty vs. stent) or surgical revasc if limiting/refractory sx or CLI

Acute limb ischemia (ALI)

- Sudden decrement in limb perfusion that threatens viability;
  viable (no immed threat of tissue loss): audible art. Doppler signals, sensory, & motor OK
  threatened (salvage requires prompt Rx): loss of arterial Doppler signal, sensory, or motor
- 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: thorough pulse & neuro exam; arterial Doppler; angiography, either CT w/ bilateral run-off through feet or arteriography
- Urgent consultation w/ vascular medicine and/or vascular surgery
- Treatment: immediate anticoagulation ± intra-arterial lytic; angioplasty or surgery

DYSPNEA

Pathophysiology	Etiologies
Airway obstruction (↑ resistance to airflow)	**Asthma, COPD,** bronchiectasis, cystic fibrosis, tumor, foreign body, **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

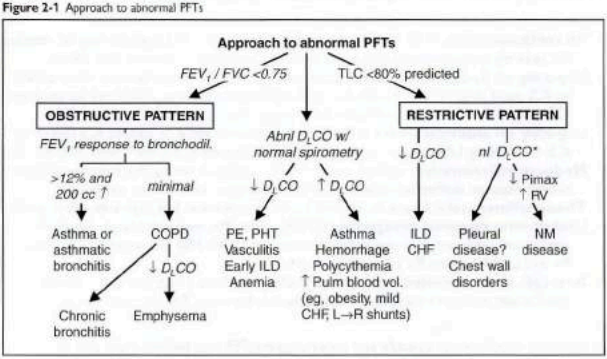
Evaluation

- 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



*D_LCO can be diminished due to secondary atelectasis

ASTHMA

Definition and epidemiology (Lancet 2013;382:1360)

- 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 and 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

- **Peak exp flow (PEF):** ≥60 L/min ↑ after bronchodil or ≥20% diurnal variation c/w asthma. <80% personal best c/w poor control, <50% c/w severe exacerbation.
- **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% (AJRCCM 2000;161:309)
- Allergy suspected → consider ✓ 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 (Lancet 2002;360:1313)

- Atopy = asthma + allergic rhinitis + atopic dermatitis
- ASA-sensitive asthma (Samter's syndrome) = asthma + ASA sensitivity + nasal polyps
- ABPA = asthma + pulmonary infiltrates + allergic rxn to *Aspergillus*
  Dx: ↑ IgE to *Asperg.* & total (>1000), ↑ *Asperg.* IgG levels, ↑ eos, central bronchiect.
  Rx: steroids ± itra-/voriconazole for refractory cases (NEJM 2000;342:756)
- 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) (NEJM 2009;360:1002)

- Inh **corticosteroids** (ICS): Rx of choice (JAMA 2001;285:2583). PO steroids may be needed for severely uncontrolled asthma, but avoid if possible b/c systemic side effects.
- *Long-acting* inh **β_2-agonists** (LABA; eg, salmeterol): safe & ↓ exacerbations when added to ICS (NEJM 2016;374:1822). Except for exercise-induced asthma, should *not* be used w/o ICS (may ↑ mortality, esp. in African-Americans) (Chest 2006;129:15; Annals 2006;144:904).
- *Long-acting* inh **antimuscarinics** (LAMA; eg, tiotropium): add if sx despite ICS (super. to ↑ ICS, ≈ to adding LABA; NEJM 2010;363:1715) or if sx despite ICS+LABA (NEJM 2012;367:1198)
- **Nedocromil/cromolyn:** limited use in adults. Useful in young Pts, exercise-induced bronchospasm; ineffective unless used before trigger or exercise exposure.
- **Theophylline:** useful if hard to control sx; PO convenient, but high side-effect profile
- **Leukotriene receptor antagonists** (LTRA): some Pts very responsive, esp. ASA-sens (AJRCCM 2002;165:9) and exercise-induced (Annals 2000;132:97). May be noninf to ICS initial Rx and LABA add-on Rx (NEJM 2011;364:1695).
- **Anti-IgE:** for uncontrolled mod-to-severe allergic asthma (↑ IgE) on ICS ± LABA (NEJM 2006;354:2689; Annals 2011;154:573); not cost-effective for most Pts (JACI 2007;120:1146)

Other (Lancet 2015;386:1086)

- Behavior modification: identify and avoid triggers; PPI w/o benefit (NEJM 2009;360:1487)
- ImmunoRx may be useful if significant allergic component (JAMA 2016;315:1715)
- TNF antagonists may be helpful in refractory asthma (NEJM 2006;354:697)
- Anti-IL5 (mepolizumab, reslizumab) ↓ exac. in sev asthma (NEJM 2014;371:1189 & 1198)
- Anti-IL13 (lebrikizumab) ↑ FEV_1 (NEJM 2011;365:1088), not yet FDA approved
- Anti-IL4 (dupilumab): ↓ exac. in sev asthma (NEJM 2013;368:2455; Lancet 2016;388:31)

- Bronchial thermoplasty (exp'tal): radiofrequency destruction of airway smooth muscle no Δ in FEV_1, but ↓ in sx and # of exacerbations (*NEJM* 2007;356:1327)

Principles of treatment

- Education and avoidance of environmental triggers (*Lancet* 2015;386:1075); yearly flu shot
- Use quick-relief rescue medication as needed for all Pts
- Goal to achieve **complete control** = daily sx ≤2/wk, Ø nocturnal sx or limitation of activity, reliever med ≤2/wk, nl PEF 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
- If PEF ↓ 15% × 2 d or ↓ 30%, 4× ICS dose ↓ need for PO steroids (*AJRCCM* 2009;180:598)

Asthma Stepwise Therapy (Adapted from Global Initiative for Asthma [GINA] 2015 update)

	Step 1	Step 2	Step 3	Step 4	Step 5
	Rapid-acting β_2-agonists prn				
Controller options		*Select one*	*Select one*	*Do one or more*	*Add one or both*
		Low-dose ICS	**Low-dose ICS + LABA**	**↑ ICS dose (w/ LABA)**	Oral steroids (lowest dose)
		LTRA	Low-dose ICS + LAMA	**Add LAMA**	Anti-IgE Rx
			Med-dose ICS	Add LTRA	
			Low-dose ICS + LTRA	Add Theo	
			Low-dose ICS + Theo		

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: **PEF** (used to follow clinical course); **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

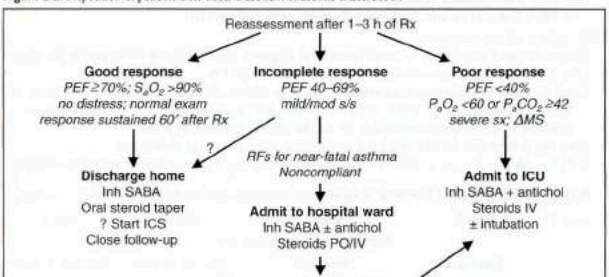
Feature	Mild	Moderate	Severe
Breathless w/. . .	Walking	Talking	At rest
Talking in . . .	Sentences	Phrases	Words
Mental status	± Agitated	Agitated	Agitated
RR	↑	↑	>30
Accessory muscles	Ø	⊕	⊕
Wheeze	Moderate, end-expir	Loud	Usually loud
HR	<100	100–120	>120
Pulsus paradoxus	Normal (<10)	10–25	>25
PEF	>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 Ø air movement), bradycardia, loss of abdominal paradox (respiratory muscle fatigue). Presence of several parameters (not necessarily all) indicates classification (adapted from *Chest* 2003;123:1018; GINA 2015 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 0.5–1 mg/kg PO; IV if impending resp arrest
- **Ipratropium** MDI (4–6 puffs) or nebulizer (0.5 mg) q20min if severe (*Chest* 2002;121:1977)
- Epinephrine (0.3–0.5 mL SC of 1:1000 dilution) no advantage over inh SABA
- Montelukast IV ↑ FEV_1 but did not Δ rate of hosp (*J Allergy Clin Immunol* 2010;125:374)
- *Reassess after 60–90 min of Rx*
  Mild-mod exacerbation: cont SABA q1h
  Severe exacerbation: SABA & ipratropium q1h or continuously; ± Mg 2 g IV over 20 min (*Lancet* 2003;361:2114); ± heliox (60–80%)
- *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:** methylprednisolone 125 mg IV q6h (*Archives* 1983;143:1324)
- **Invasive ventilation:**
  large ET tube, P_{plat} <30 cm H_2O (predicts barotrauma better than PIP), max exp time PEEP individualized to Pt 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/SC 0.3–0.5 mL of 1:1000 dilution q5–20min; if HoTN 1 mg IVB q5min ± gtt
- **Airway:** suppl O_2 ± intubation or cricothyroidotomy (if laryngeal edema); β_2-agonists
- Fluid resuscitation w/ lg volume of crystalloid (may extravasate up to 35% of blood volume)
- Antihistamines relieve hives & itching, *no effect on airway or hemodynamics*
  H1RA (diphenhydramine 50 mg IV/IM) ± H2RA (eg, ranitidine 50 mg IV)
- Corticosteroids have no immediate effect but may help prevent relapse:
  methylprednisolone 125 mg IV q6h if severe or prednisone 50 mg PO
- 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
- At time of d/c: education re: allergen avoidance, instruction and Rx for EpiPen, allergist f/u

Angioedema (*Ann Allergy Asthma Immunol* 2000;85:521; *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)
- 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: synthetic C1 inhibitor cinryze (*NEJM* 2010;363:513)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and epidemiology (Lancet 2014;385:1778)

- 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 2003;362:1053)

- **Cigarette smoke** (centrilobular emphysema, affects 15–20% of smokers)
- Recurrent airway infections
- α_1-antitrypsin defic.: 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 important in genesis of COPD (*NEJM* 2015;373:111)
- Misc: biomass (eg, cooking fuels in enclosed space), chronic asthma (*Lancet* 2009;374:733)

Clinical manifestations

- Chronic cough, sputum production, dyspnea; later stages → freq exac., a.m. HA, wt loss
- Exacerbation triggers: infxn, other cardiopulmonary disease, incl. PE (*Annals* 2006;144:390)
  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

- 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
- ECG: PRWP, S1S2S3, R-sided strain, RVH, ↑ P waves in lead II ("P pulmonale")

Chronic treatment (Lancet 2015;385:1789)

- **Bronchodilators** (*first-line therapy*): **anticholinergics,** β_2-agonists (BA), theophylline
  Long-acting (LA) antimuscarinic (LAMA; eg, tiotropium): ↓ exac., ↓ admit, ↓ resp failure (*NEJM* 2008;359:1543), better than ipratropium or LABA as mono Rx (*NEJM* 2011;364:1093)
  LABA: ~11% ↓ in exacerbations, no ↑ in CV events (*Lancet* 2016;387:1817)
  LABA + inh steroid: ? ↓ mort. vs. either alone (*NEJM* 2007;356:775)
  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 exacerb & slow ↓ FEV_1; no Δ in risk of PNA or in mortality (*Lancet* 2016;387:1817)
- Roflumilast (PDE-4 inhibitor): ↑ FEV_1 & ↓ exacerbations when added to bronchodilator (*Lancet* 2009;374:685, 695 & 2015;385:857)
- Antibiotics: daily azithro ↓ exacerb, but not yet routine (*JAMA* 2014;311:2225)
- Mucolytics: no Δ FEV_1, but ? ↓ exacerbation rate (*Lancet* 2008;371:2013)
- **Oxygen:** if $P_aO_2 \leq 55$ mmHg or $S_aO_2 \leq 89\%$ (during rest, exercise, or sleep) to prevent cor pulmonale; only Rx proven to ↓ mortality (*Annals* 1980;93:391; *Lancet* 1981;i:681)
- **Prevention:** Flu/Pneumovax; smoking cessation (eg, varenicline, bupropion) → 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)

- Experimental
  - Lung volume reduction surgery: ↑ exer. capacity, ↓ mort. *if* FEV_1 >20%, upper-lobe, low exer. capacity (*NEJM* 2003;348:2059)
  - Bronchoscopic lung reduction w/ endobronchial valves or coils: ↑ lung fxn but significant complications (PTX, PNA) (*NEJM* 2015;373:2325; *Lancet* 2015;386:1066; *JAMA* 2016;315:175)
  - Nocturnal BiPAP: may improve survival, ? decrease QoL (*Thorax* 2009;64:561)
- Lung transplant: ↑ QoL and ↓ sx (*Lancet* 1998;351:24), ? survival benefit (*Am J Transplant* 2009;9:1640)

Staging and prognosis

- COPD assessment test (CAT): 8 question tool assessing cough, sputum, exercise capacity & energy, with score ranging 0–40 (http://www.catestonline.org)
- mMRC score: ≥2 defined as walking slowly b/c breathlessness or having to stop to catch breath walking level
- Ratio of diam PA/aorta >1 associated with ~3× ↑ risk of exacerbations (*NEJM* 2012;367:913)

COPD Staging and Recommended Therapies by GOLD Criteria

Stage	FEV_1	3-y mort	Exac. in past yr	CAT <10 or mMRC 0-1	CAT ≥10 or mMRC ≥2
I: Mild	≥80%	?	≤1 (and 0 hosp)	**A** Short-acting inh dilator prn	**B** Standing inh dilator (LAMA > LABA)
II: Mod	50–80%	~11%			
III: Severe	30–50%	~15%	≥2 or ≥1 hosp	**C** [ICS + LABA] or LAMA	**D** ICS + [LAMA and/or LABA] + Experimental as indicated
IV: Very severe	<30%	~24%			
				Consider adding PDE-4 inhib to bronchodilator	

Smoking cessation & vaccinations in all. Pulm rehab in groups B–D. Consider theophylline as alternative. O_2 as indicated per S_aO_2. (Adapted from Global Initiative for Chronic Obstructive Pulmonary Disease, 2016)

Exacerbation

COPD Exacerbation Treatment (*NEJM* 2002;346:988)

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	No consensus for optimal dose & duration (*Cochrane* 2009:CD001288) Consider: Prednisolone 30–40 mg/d × 10–14 d or even 5 d (*JAMA* 2013;309:2223) Methylprednisolone 125 mg IV q6h × 72 h for more severe exacerbations	↓ treatment failure, ↓ hospital stay, ↑ FEV_1 but no mortality benefit, ↑ complications (*Cochrane* 2009:CD001288) OutPt Rx after ED visit ↓ relapse (*NEJM* 2003;348:2618) ? use periph eos >2% to trigger use (*AJRCCM* 2012;186:48)
Antibiotics	Amox, TMP-SMX, doxy, clarithro, antipneumococcal FQ, etc., 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* freq. precipitants. ↑ 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 mod/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	

HEMOPTYSIS

Definition and pathophysiology

- Expectoration of blood or blood-streaked sputum
- **Massive hemoptysis:** –>600 mL/24–48 h; gas exchange more important than blood loss
- 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	**Vasc** (GPA, Goodpasture's, Behçet's; can be massive), 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

- Mechanism of death is asphyxiation not exsanguination; maintain gas exchange, reverse coagulation and treat underlying condition; cough supp. may ↑ risk of asphyxiation
- 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 flex. *Surgical resection.*

BRONCHIECTASIS

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

- Obstructive airways disease of bronchi and bronchioles, chronic transmural inflamm 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 myobact, 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 aspir.	Bronchoscopy

Treatment

- Treat underlying condition; mucolytics & bronchodilators
- Prophylactic azithro shown to ↓ exacerb. in non-CF bronchiectasis (*JAMA* 2013:1251)
- Antibiotics: at time of acute exacerbation directed against suspected or prior pathogens

Cystic fibrosis (*NEJM* 2015;372:351)

- Autosomal recessive genetic disorder due to mutations in chloride channel (CFTR gene)
- ↑ mucus thickness, ↓ mucociliary clearance, ↑ infections → bronchiectasis
- Clinical: recurrent PNA, weight loss, sinus infxns, infertility, pancreatic insuffic (fatty stools)
- Rx: airway clearance (chest PT, inh hypertonic saline, DNAse), abx for exacerb. for drug-resistant org. (eg, *Pseudomonas, Burkholderia*), gene targeted with CFTR potentiator (ivakaftor) & corrector (lumakaftor) (*NEJM* 2011;365:1663 & 2015;373:220), lung transplant

Non-tuberculous mycobacterium (NTM; ubiquitous hydrophilic bacteria)

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

SOLITARY PULMONARY NODULE

Principles

- Definition: single, <3 cm, surrounded by normal 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 Wegener's, rheumatoid nodule Lipoma, fibroma, amyloidoma, pneumonitis	**Bronchogenic carcinoma** (75%): adeno & large cell (peripheral) squamous & small cell (central) **Metastatic** (20%): breast, head & neck, colon, testicular, renal, sarcoma, melanoma Carcinoid, primary sarcoma

Initial evaluation

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

Diagnostic studies

- **PET:** detects metab. activity of tumors, 97% Se & 78% Sp for malig. (esp. if >8 mm) also 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 (for solid SPN >8 mm; if ≤8 mm, serial CT) (*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 ⊖

SLEEP APNEA

Definition and pathophysiology

- **Obstructive:** pharyngeal collapse → apnea (≥10 s) or hypopnea (↓ airflow) ± desaturation; risk factors: obesity (present in 70%), large neck, male sex, ↓ muscle tone, ↑ age, alcohol
- **Central:** ↓ neurologic feedback w/ oscillating drive. Apneas w/o resp effort ± subsequent ↑ resp rate. Associated with CHF & atrial fibrillation; worsened by sedatives.
- Complex: obstructive + central (nb, untreated obstructive → complex)
- Proposed mech: Apnea/arousals → sympathetic nervous system activation, negative intrathoracic pressure → ↑ preload, ↑ afterload. Consequently → HTN, pulm HTN.

Clinical manifestations (*Lancet* 2002;360:237; *Lancet Resp Med* 2013;1:61)

- Snoring, witnessed apneas/gasping, daytime sleepiness
- **Cardiovascular:** HTN (*JAMA* 2012;307:2169); a/w ↑ risk of stroke and death (*NEJM* 2005;353:2034) & possibly CAD & endothelial dysfxn (*AJRCCM* 2001;163:19; *Circ* 2008;117:2270)
- **Neurocognitive:** ↓ cognitive performance, ↓ QoL, ↑ motor vehicle and work accidents (*NEJM* 1999;340:847; *AJRCCM* 2001;164:2031)

Diagnosis and treatment (*JAMA* 2013;310:731 & *Lancet* 2014;383:736)

- **Polysomnography** (sleep study); can do home-testing
- **Obstructive: CPAP** ↓↓ apnea/hypopnea, ↓ BP (*JAMA* 2013;310:2407 & *NEJM* 2014;370:2276), ↓ sleepiness, ↑ performance (*AJRCCM* 2012;186:677), ↑ EF in Pts with CHF (*NEJM* 2003;348: 1233), ↓ metab syndrome (*NEJM* 2011;365:2277), ↓ mortality after stroke (*AJRCCM* 2009;180:36)
- Oral appliances if refusing CPAP; upper-airway stimulator under study (*NEJM* 2014;370:139)
- **Central:** adaptive servoventilation (ASV) if w/o CHF (nb, ↑ mortality if CHF; NEJM 2015;373:1095)
- Avoid alcohol and sedatives
- Surgery (eg, uvulopalatopharyngoplasty, UPPP) of limited benefit (*Chest* 1997;111:265)

WORKUP OF ILD (Thorax 2008;63:v1)

Broad categories

- **Sarcoid; exposure-related** (eg, drugs, toxins, hypersens. pneumonitis, pneumoconiosis); **collagen vasc. dis.** (eg, scleroderma, GPA); **idiopathic PNAs** (eg, IPF, COP); **misc.**

Rule out mimickers of ILD

- **Congestive heart failure** (✓ BNP, trial of diuresis)
- **Infection:** viral, atypical bacterial, fungal, mycobacterial, parasitic
- **Malignancy:** lymphangitic carcinomatosis, bronchoalveolar, leukemia, lymphoma

History and physical exam

- Occupational, travel, exposure (including tobacco), meds, FHx, precipitating event
- Tempo (acute → infxn, CHF, hypersens pneumonitis, eos PNA, AIP, COP, drug-induced)
- Extrapulmonary signs/sx (skin Δs, arthralgias/arthritis, clubbing, neuropathies, etc.)

Diagnostic studies (see Appendix & Radiology inserts)

- CXR and **high-resolution chest CT:** reticular, nodular or ground-glass pattern
  - Upper lobe-predominant → coal, silica, hypersens, sarcoid, TB, RA
  - Lower lobe-predominant → IPF, asbestos, scleroderma
  - Adenopathy → sarcoidosis, berylliosis, silicosis, malignancy, fungal infections
  - Pleural disease → collagen-vascular diseases, asbestosis, infections, XRT
- PFTs: ↓ D_LCO (*early sign*), restrictive pattern (↓ volumes), ↓ P_aO_2 (esp. w/ exercise); if also obstructive, consider sarcoid, LAM, silicosis
- Serologies: ✓ ACE, ANA, RF, ANCA, anti-GBM, HIV, ± myositis panel & other serologies
- Bronchoalveolar lavage: dx infxn, hemorrhage, eosinophilic syndromes, PAP
- Biopsy (transbronch, CT-guided, VATS, open) if no clear precipitant and w/u unrevealing

SPECIFIC ETIOLOGIES OF ILD

Sarcoidosis (Lancet 2014;383:1155)

- Prevalence: African-Americans, northern Europeans, and females; onset in 3rd–4th 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; anti-TNF, MTX, AZA, mycophenolate or cyclophosphamide 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**

Amio (dose & duration depend.): chronic interstitial PNA ↔ ARDS; Rx: d/c amio; steroids
Other drugs: nitrofurantoin, sulfonamides, thiazides, INH, hydralazine, gold
Chemo: **bleomycin** (triggered by hyperoxia), busulfan, cyclophosphamide, MTX, etc.
XRT: COP/BOOP w/ sharply linear, nonanatomic boundaries; DAH

- **Pneumoconioses** (inorganic dusts) (*NEJM* 2000;342:406; *Clin Chest Med* 2004:467)
  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 also → 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 ~67%; PHT seen in ~10% of CREST Pts
  PM-DM: ILD & weakness of respiratory muscles; MCTD: PHT & fibrosis
  SLE & RA: pleuritis and pleural effusions more often than ILD; SLE can cause DAH
- **Vasculitis** (can p/w *DAH*)
  GPA (Wegener's granulomatosis) (⊕ c-ANCA) w/ necrotizing granulomas
  EGPA (Churg-Strauss) (⊕ 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; *NEJM* 2014;370:1820)

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

IIPs

Type	Imaging/Histology	Clinical
UIP/IPF	Reticular opacities, honeycombing, traction bronchiectasis; periph, subpl., & basal	Sx >12 mo 5-y mort. ~80%
NSIP	Homogenous ground-glass opacities or consolid., reticular irreg lines; symmetric, periph, basal, subpl. Mimics CTD ILD. Cellular and fibrotic subtypes, latter similar to UIP but homogenous.	Sx mos–y 5-y mort. 10% (fibrotic = UIP)
COP/BOOP	Patchy bilat consolid., nodules; subpl. & peribronchial. Prolif of granulation tissue in small bronchioles & inflam of surrounding alveoli.	Can be post-infxn, HSCT, XRT, rxn to drugs. 5-y mort <5%.
AIP	Diffuse ground-glass opacities, consolid. w/ lobular sparing. Path similar to DAD.	Sx <3 wk 6-mo mort. 60%
DIP	Diffuse ground-glass opacities, reticular lines; lower zones, periph. Mϕ in alveoli.	30–50 yo smokers Sx wks–mos Death rare
RB-ILD	Bronchial thickening, centrilobular nodules, patchy ground-glass opacities. Mϕ in alveoli.	

UIP, usual interstitial PNA (IIP); IPF, idiopathic pulm fibrosis (*Lancet* 2011;378:1949); NSIP, nonspecific IP; COP, cryptogenic organizing PNA; BOOP, bronchiolitis obliterans w/ organizing PNA; AIP, acute IP (Hamman-Rich syndrome); DIP, desquamative IP; RB-ILD, resp bronchiolitis-assoc ILD.

- Rx for UIP/IPF: suppl O_2, pulm rehab, Rx for GERD, lung transplant referral
  Pirfenidone (antifibrotic) or **nintedanib** (tyrosine kin. 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
- 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 ± periph. 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): accum of surfactant-like phospholipids; ♂ smokers; 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%)
- Lymphocytic interstitial PNA: polyclonal B-cell infiltration (? lymphoma); Rx: steroids

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 (esp. after aggressive diuresis or if chronic), but ~75% of exudative effusions in CHF Pts found to have non-CHF cause (*Chest* 2002;122:1518)
- **Constrictive pericarditis** (knock on exam, calcification or thickening on imaging)
- **Cirrhosis** ("hepatic hydrothorax"): diaphragmatic pores allow passage of ascitic fluid often right-sided (⅔) & 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), Wegener's, Churg-Strauss
- **Gastrointestinal diseases:** pancreatitis, 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, postradiation 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

- **Thoracentesis** (*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
  parapneumonics 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} >⅔ ULN of LDH_{serum}; 97% Se, 85% Sp; best Se of all methods; however, will misidentify 25% of transudates as exudates; ∴ if clinically suspect transudate but meets criterion for exudate, confirm w/ test w/ higher Sp
  exudative criteria w/ better Sp: $chol_{eff}$ >55 mg/dL (95–99% Sp); $chol_{eff}$ >45 mg/dL *and* LDH_{eff} >200 (98% Sp); $chol_{eff}/chol_{serum}$ >0.3 (94% Sp); serum-effusion alb gradient ≤1.2 (92% Sp); serum-effusion TP gradient ≤3.1 (91% Sp)
  CHF effusions: *TP may* ↑ *with diuresis or chronicity* → "pseudoexudate"; alb gradient ≤1.2, $chol_{eff}$ >60 mg/dL (Se 54%, Sp 92%) or clin judgment to distinguish (*Chest* 2002;122:1524)
- **Complicated vs. uncomplicated parapneumonic** (*Chest* 1995;108:299)
  complicated = ⊕ Gram stain or culture *or* pH <7.2 *or* glucose <60
  complicated parapneumonic effusions usually require *drainage* to achieve resolution
  empyema = frank pus, also needs drainage to achieve resolution

- 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$_{all}$; 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 (*JAMA* 2012;307:2383); 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, inflamm., 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 med (immobile, h/o VTE, thrombophilia or cancer) & most surgery Pts	**UFH** 5000 U SC bid or tid, or **LMWH,** or fonda (if HIT ⊕), or mech Ppx (esp. if high bleed risk); ? extended Ppx w/ NOAC (*NEJM* 2016;375:534)
High-risk surg (trauma, stroke, spinal cord injury, h/o VTE/thrombophilia)	[LMWH or UFH SC] + mech Ppx
Orthopedic surgery	LMWH [or fonda, direct oral anticoag (qv) or warfarin (INR 2–3)] + mech Ppx NOACs overall appear favorable vs LMWH

For enoxaparin, 30 mg bid for highest risk or 40 mg qd for moderate risk or spinal/epidural anesth. Dose adjust: qd in CrCl <30 mL/min, ↑ 30% if BMI >40 (*Ann Pharmacother* 2009;43:1064).

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)

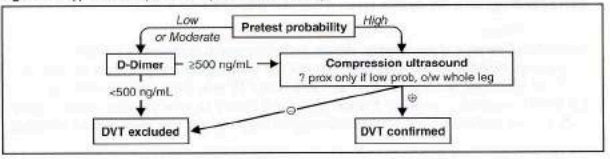
Score ≤0	Score 1 or 2	Score ≥3
Low probability (5%)	Moderate probability (17%)	High probability (53%)

- 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 (*Chest* 2012;141:e351S)



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

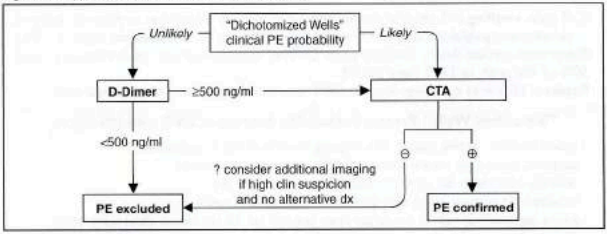
Dichotomized Wells Probability Assessment

≤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 (*JAMA* 2015;313:1668): high Se, poor Sp (~25%); ⊖ ELISA has >99% NPV ∴ use to r/o PE if "unlikely" pretest prob. (*JAMA* 2006;295:172) consider age-specific cut point: 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, but when added to CTA, does not Δ outcomes (*Lancet* 2008;371:1343)

Figure 2-4 Approach to suspected PE (*Annals* 2015;163:701)



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

- **Clinical:** hypotension and/or tachycardia (~30% mortality), hypoxemia
- **CTA:** RV/LV dimension ratio >0.9 (*Circ* 2004;110:3276)
- **Biomarkers:** ↑ troponin & ↑ BNP a/w ↑ mortality; w/ ⊖ Tn, decomp extremely unlikely (*Circ* 2002;106:1263 & 2003;107:1576; *Chest* 2015;147:685)
- **Echocardiogram:** RV dysfxn (even if normal troponin) (*Chest* 2013;144:1539)

Whom to treat (*Lancet* 2012;379:1835; *Chest* 2012;141:e419S)

- **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. If 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* 2012;141:e419S & 2016;149:315; *JAMA* 2014;311:717)

- *Initiate parenteral Rx immediately if high or intermed suspicion while dx testing underway*
- **Non-vitamin K antag oral anticoag** (*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 (espec in *cancer*) except: renal failure (CrCl <25), extreme obesity, hemodynamic instability or bleed risk (*Cochrane* 2004;CD001100)
  Can use as outpatient bridge to long-term oral anticoagulation
- If cancer, LMWH ↓ recurrence and mortality c/w UFH & warfarin (*NEJM* 2003;349:146; *Lancet Oncol* 2008;9:577); ✓ head CT for brain mets if melanoma, renal cell, thyroid, chorioCA
- **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, lepirudin) used in HIT ⊕ Pts
- **Warfarin** (goal INR 2–3): start same day as parenteral anticoag unless instability and ? need for lytic, catheter-based Rx or surgery; 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
- **Massive PE** (hemodynamic compromise): ↓ death and recurrent PE each by ~50% (*JAMA* 2014;311:2414; *EHJ* 2015;36:605) & lower PVR long term (*JACC* 1990;15:65)
- **Submassive PE** (hemodyn. stable but RV dysfxn on echo or enlargement on CTA, or ? marked dyspnea or severe hypoxemia): ↓ hemodyn. decompensation, ↑ ICH, ↓ mortality; consider if <75 y and/or low bleed risk (*NEJM* 2014;370:1402; *JAMA* 2014;311:2414). Some centers prefer catheter-directed therapy.
- **Moderate PE w/ large clot burden** (≥2 lobar arteries or main artery on CT or high-prob VQ w/ ≥2 lobes w/ mismatch): *low-dose lytic* (50 mg if ≥50 kg or 0.5 mg/kg if <50 kg; for both 10-mg bolus → remainder over 2 h) ↓ pulm HTN w/ = bleeding vs. heparin alone
- **DVT:** consider if (a) acute (<14 d) & extensive (eg, iliofemoral), (b) severe sx swelling or ischemia, (c) catheter-directed Rx not available, and (d) low bleed risk

Mechanical intervention

- **Catheter-directed** (fibrinolytic & thrombus fragmentation/aspiration; *Circ* 2012;126:1917)
  Consider if extensive DVT (see above) and to ↓ postthrombotic synd (*Lancet* 2012;379:31)
  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)
- **Thrombectomy:** if large, proximal PE + hemodynamic compromise + contra. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn (*J Thorac CV Surg* 2005;129:1018)
- **IVC filter:** use instead of anticoagulation if latter contraindicated
  No benefit to adding to anticoag (including in submassive) (*JAMA* 2015;313:1627)
  Consider removable filter for temporary indications
  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:
  full-dose NOAC: 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 (2.5 mg bid): 80% ↓ recur. VTE, w/o signif ↑ bleeding (*NEJM* 2013;368:699)
  warfarin, either regular (*JAMA* 2015;314:31) or low-intensity (*NEJM* 2003;348:1425)
  aspirin: 32% ↓ recurrent VTE (*NEJM* 2012;366:1959 & 367:1979)
- 2nd VTE event or cancer: indefinite (or until cancer cured) (*NEJM* 2003;348:1425)

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 ~3.8%, 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
PA mean = CO × PVR + PA wedge pressure. Trans pulm gradient = PA mean − PA wedge.

Etiologies (Revised WHO Classification) (Circ 2009;119:2250)	
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, 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; ~⅓ w/o clinical h/o PE (*NEJM 2011;364:351*) • Nonthrombotic emboli (tumor, foreign body, parasites)
Miscellaneous (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: dil. & 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 & restrict. 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, ↑ transpulm gradient (mean PAP-PCWP >12–15), ↑ 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 still concern
- Vasculitis labs: ANA (~40% ⊕ in PAH), RF, anti-Scl-70, anticentromere, ESR
- LFTs & HIV: r/o portopulmonary and HIV-associated PAH
- 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*)

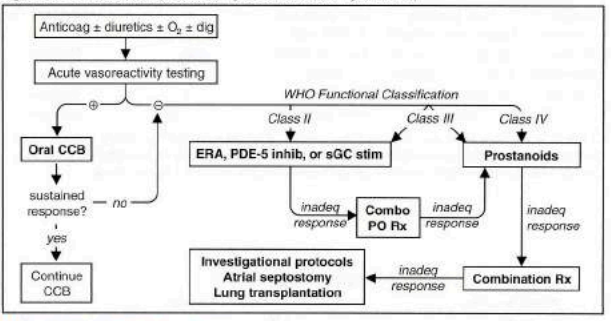
- Principles: 1) prevent & reverse vasoactive substance imbalance and vascular remodeling 2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq. systemic DBP
- **Supportive**
  Oxygen: maintain S_aO_2 >90–92% (reduces vasoconstriction)
  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent
  Digoxin: control AF, ? counteract neg. inotropic effects CCB
  Dobutamine and inhaled NO or prostacyclin for decompensated PHT
  Anticoag: not routinely used; ↓ VTE risk of RHF; ? prevention of *in situ* microthrombi; ? mort. benefit even if in NSR, no RCTs (*Circ 1984;70:580; 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 vasodil.

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; <½ long-term responder (NYHA I/II & near-nl hemodynamics) & have ↓ **mortality.** Not 1st line b/c side effects: HoTN, lower limb edema (*Circ* 2005;111:3105).

- 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 transplant (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.*
- May benefit from inotropes/chronotropes
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 100 mg over 2 h)

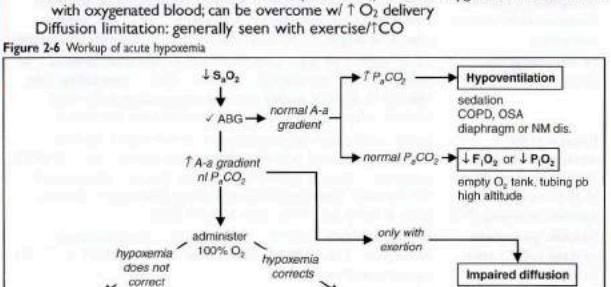
Prognosis

- 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;126:63-S)

$$\text{Hypoxemia} \rightarrow P_AO_2 = F_IO_2 \times (760 - 47) - \frac{P_aCO_2}{R}$$

- **A-a gradient = $P_AO_2 - P_aO_2$:** normal (*on room air*) = "4 + age/4" or "2.5 + (0.2 × age)"
- Hypoxemia + nl A-a gradient: problem is ↓ P_IO_2/F_IO_2 or ↑ P_aCO_2 (ie, hypoventilation)
- Hypoxemia + ↑ A-a gradient: problem is either
  - R → L shunt, anatomic (congen. 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 sat	CO-Ox sat	Treatment (+ 100% O_2)
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O_2
Methemoglobinemia	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.

$$\text{Hypercapnia} \rightarrow P_aCO_2 = k \times \frac{\dot{V}co_2}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

Etiologies of High ↑ P_aCO_2

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

↑ 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 approx 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, Δ**MS,** 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 patient to a standard ventilator Can receive PS ~20–30 cm H_2O, PEEP ~10 cm H_2O, F_iO_2 ~1.0 Used for short-term support (<24 h) for a reversible process
Conditions w/ strong evidence	**Cardiogenic pulmonary edema:** may ↓ intub. & mortality (*JAMA* 2005;294:3124; *Lancet* 2006;367:1155) although recent trial (w/ high crossover) did not show any mortality benefit (*NEJM* 2008;359:142)
Lancet 2000;355:1931 *AJRCCM* 2006;173:164	**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
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;148:340–355)

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 ↑ patient comfort (PSV) requiring less sedation
General principles	**Institutional/practitioner preference** and **patient 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 cc/kg IBW
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 Ø 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)
  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). Continue to ↑ PEEP until either can ↓ F_IO_2 to <0.6 or P_{plat} ≥30 cm H_2O. If PEEP 20 & F_IO_2 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see "ARDS").

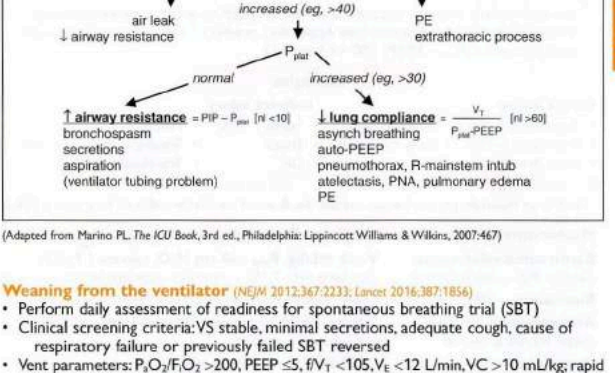
If ↑ PEEP yields no Δ *or* ↓ P_aO_2/F_IO_2 *or* ↑ P_aCO_2, suggests additional lung *not* recruitable and instead overdistending lung → ↑ shunt & dead space; ∴ ↓ PEEP

- 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 >7.15.

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*, 3rd ed., Philadelphia: Lippincott Williams & Wilkins, 2007:467)

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

- Perform daily assessment of readiness for spontaneous breathing trial (SBT)
- Clinical screening criteria: VS stable, minimal secretions, adequate cough, cause of respiratory failure or previously failed SBT reversed
- Vent parameters: P_aO_2/F_IO_2 >200, PEEP ≤5, f/V_T <105, V_E <12 L/min, VC >10 mL/kg; rapid shallow breathing index (f/V_T) >105 predicts failure, NPV 0.95 (*NEJM* 1991;324:1445)
- Daily awakening trial (d/c all sedation; *Lancet* 2008;371:126): open eyes & w/o: agitation, RR >35, S_aO_2 <88%, resp distress or arrhythmias (if fail, restart sedation at ½ prior dose).
- SBT = CPAP or T piece × 30–120 min
  failure if: deteriorating ABGs, ↑ RR, ↑ or ↓ HR, ↑ or ↓ BP, diaphoresis, anxiety
- Tolerate SBT → extubation. Fail SBT → ? cause → work to correct → retry SBT qd
- ? 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%/day, 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, stress-ulcer prophylaxis w/ ? sucralfate (↓ VAP, ↑ GIB) vs. H_2RA/PPI, ? silver-coated tubes (*JAMA* 2008;300:805)
- 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 patients in whom expect >14 d of mech vent → ↓ duration mech vent, ↓ # ICU days (*BMJ* 2005;330:1243); no benefit to performing at ~1 wk vs. waiting until ~2 wk (*JAMA* 2010;303:1483)
- Malnutrition (for all critically ill Pts): *enteral nutrition* initiated early is safe but not necessary (*JAMA* 2012;307:795), but bolus may ↑ risk of VAP & *C diff.* (*JPEN* 2002;26:174); no clear benefit to ✓ing gastric residuals (*JAMA* 2013;309:249); permissive enteral underfeeding (~½ of calculated caloric req) & standard enteral feeding w/ similar outcomes (*NEJM* 2015;372:2398); *parenteral nutrition* should be delayed until after day 8 to ↓ risk of infections, cholestasis, RRT, ventilator days (*NEJM* 2011;365:506)
- Oversedation/delirium: BDZs and polypharmacy are risk factors
  propofol: HoTN in ~25%; *propofol infusion syndrome* (PRIS) ? espec w/ high (>5 mg/kg/h) & prolonged (>48 h) infusions & concom vasopressors → ↑ AG, cardiac dysfxn, rhabdomyolysis, ↑ triglycerides, & renal failure (*Crit Care* 2009;13:R169)
  dexmedetomidine: ↑ vent-free days, but brady & HoTN c/w BDZ (*JAMA* 2012;307:1151 & 2016;315:1460)

ACUTE RESPIRATORY DISTRESS SYNDROME

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

- **Acute onset** within 1 wk 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
- Chest CT: heterogeneous lung with densities greater in dependent areas
- Lung bx: diffuse alveolar damage (DAD); Ø req. may give useful dx info (*Chest* 2004;125:197)

Pathophysiology

- ↑ 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

Etiologies

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

Treatment (primarily supportive) (*Lancet* 2007;369:1553; *NEJM* 2007;357:1113)

- 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 >7.15), ↓ 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

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)
- Esophageal balloon: used to determine true transpulmonary pressure, adjust PEEP according to esoph pressure (=pleural pressure) to maintain positive transpulm pressure and optimal PEEP; improves oxygenation and lung compliance but no effect on mortality (*NEJM* 2008;359:2095); helpful in obese Pts or w/ ↑ abdominal pressure

Other treatment considerations

- **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 using BNP >200 to trigger diuresis (UOP goal 4.5–9 mL/kg/h × 3 h)
- **Steroids:** debate continues. Adverse effects include neuromuscular weakness, poor glc control, ? infection. Benefit may vary by time since ARDS onset:
  <72 h: older studies w/o benefit (*NEJM* 1987;317:1565); ? ↓ mortality, ↑ vent/ICU-free days in more recent, controversial study (*Chest* 2007;131:954)
  7–13 d: ? benefit → ↑ vent/ICU-free days, no mortality difference (*NEJM* 2006;354:1671)
  ≥14 d: ↑ mortality (*NEJM* 2006;354:1671)
- **Paralysis:** if P_aO_2/F_IO_2 <150, cisatracurium × 48 h ↓ mortality by 32% (*NEJM* 2010;363:1107)
- **Proning:** if P_aO_2/F_IO_2 <150, prone-positioning ≥16 h ↓ mort. by ~50% (*NEJM* 2013;368:2159)
- **Experimental** (*JAMA* 2010;304:2521)
  Inhaled NO or prostacyclins: ↑ P_aO_2/F_IO_2, no ↓ mort. or vent-free days (*BMJ* 2007;334:779)
  Lung recruitment: apply CPAP 40–45 cm H_2O × 2 min to recruit lung and then ↑ PEEP to maintain; sicker Pts had ↑ recruitable lung (*NEJM* 2006;354:1775 & 1839)
  Driving pressure ($\Delta P = P_{plateau} - PEEP$): ↓ ΔP a/w ↑ survival; target <15 (*NEJM* 2015;372:747)
  V-V ECMO: may be useful in refractory ARDS, but no good trial data (*NEJM* 2011;365:1905)

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)

SEPSIS AND SHOCK

Definitions (*JAMA* 2016;315:801)	
Systemic inflammatory response synd. (SIRS)	≥2 of the following: (1) Temp >38 or <36°C; (2) HR >90; (3) RR >20 or P_aCO_2 <32; (4) WBC >12k or <4k or >10% bands
Sepsis	Life-threatening organ dysfxn (SOFA Δ ≥2) due to infxn qSOFA ≥2 useful in triage of potentially septic pts
Septic shock	Sepsis-induced circulatory abnl: pressor required for MAP ≥65 and lactate >2 despite adequate fluid resuscitation

Sequential [Sepsis-Related] Organ Failure Assessment (SOFA, 0-24 points)

Points	0	1	2	3	4
Resp: P_aO_2/F_iO_2	≥400	<400	<300	<200[a]	<100[a]
Coag: plt ($10^3/\mu L$)	≥150	<150	<100	<50	<20
Liver: bili (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥12
CV: MAP[b]	≥70	<70	dopa ≤5 or any DBA	dopa 5.1–15 or norepi/epi ≤0.1	dopa >15 or norepi/epi >0.1
Neuro: GCG	15	13–14	10-12	6-9	<6
Renal: Cr or UOP	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 <500	>5 <200

Quick SOFA (qSOFA): ≥2 of following: RR ≥22, ΔMS, SBP ≤110 mmHg

[a]w/ respiratory support; [b]catehcols (in μg/kg/min) for ≥1 h (*JAMA* 2016;315:762;775; & 801)

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

Fluids & Early Goal-Directed Therapy in Septic Shock (*JAMA* 2015;314:708)

- EGDT uses IVF & pressors to target MAP ≥65 mmHg, CVP 8–12 mmHg and UOP ≥0.5 mL/kg/h, and inotropes & PRBCs to achieve $S_{cv}O_2$ ≥70% in first 6 h (*NEJM* 2001;345:1368)
- Did not ↓ mortality c/w usual care in recent trials (*NEJM* 2014;371:1496, 2014;370:1683, & 2015;372:1301); however Pts had already rcvd >2 L fluid & abx, underscoring importance of these interventions (see below), and avg $S_{cv}O_2$ was >70%, ∴ no need for inotropes
- Lactate clearance (≥20%/2 h) as effective as $S_{cv}O_2$ to guide resusc. (*JAMA* 2010;303:739)
- Crystalloid as good as colloid for resuscitation (*JAMA* 2013;310:1809; *NEJM* 2014;370:1412)
- Predictors of fluid responsiveness: pulse pressure variation >13% w/ respiration (*Chest* 2008;133:252); resp. variation in IVC diam, & passive leg raise. Static CVP poor surrogate.
- Hb goal >7 g/dL as good as >9, except perhaps if coronary insuffic. (*NEJM* 2014;371:1381)
- After early resuscitation, if ALI/ARDS, target CVP 4–6 mmHg as additional fluids may be harmful → ↑ ventilator/ICU days (*NEJM* 2006;354:2564; *Chest* 2008;133:252)

Pressors (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: added to low-dose norepi not superior to high-dose norepi but ? benefit in less severe shock (norepi 5–14) (*NEJM* 2008;358:877); consider if HoTN catechol refractory

Antibiotics

- Start empiric IV abx w/in 1 h of recognition of severe sepsis or septic shock; every hour delay in abx admin a/w 8% ↑ in mortality (*Crit Care Med* 2006;34:1589)
- 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

Steroids (*NEJM* 2003;348:727 & 2008;358:111; *JAMA* 2000;283:1038 & 2009;301:2362)

- Cortisol secretion helps predict mortality, but treatment of adrenal insufficiency is unproven
- *Possible* mortality benefit w/in 8 h of severe septic shock (SBP <90 for >1 h despite fluids & pressors) if post ACTH stim cortisol Δ ≤ 9 μg/dL (*JAMA* 2002;288:862)
- No mortality benefit to early (<72 h) empiric corticosteroids in all Pts w/ septic shock, regardless of ACTH stim; faster resolution of shock, more superinfxn (*NEJM* 2008;358:111)
- Hydrocortisone 50–100 q6–8h ± fludrocortisone 50 μg daily in septic shock refractory to fluids & pressors, regardless of ACTH stim (*Crit Care Med* 2008;36:296)

Intensive glycemic control (*NEJM* 2010;363:2540)

- No clear benefit; reasonable to keep glc <150 mg/dL using validated protocol

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 antide-pressants	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	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 (relative), uncontrolled/unRx'd infxn, malig in prior 2 y, severe non-pulm dis., BMI ≥35, active smoking, drug dependence, med noncompliance, psychosocial

Posttransplant care

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

Complications

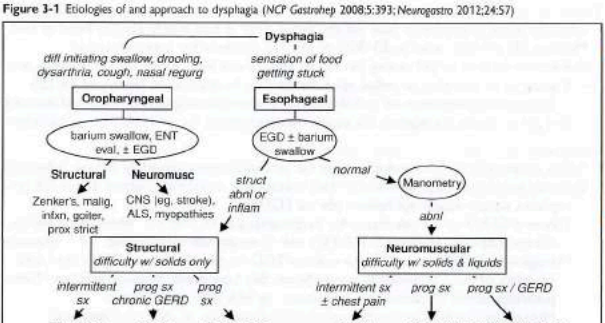
- Anastomotic: vascular (stenosis, thrombosis) and airway (infection, necrosis, dehiscence, granulation tissue, tracheobronchomalacia, stenosis, fistula)
- Acute rejection: ↓ lung fxn, cough, SOB, fever. Dx w/ trans-bronch bx. Rx immunosupp.
- Chronic rejection: bronchiolitis obliterans w/ obstruction. 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

DYSPHAGIA

Definitions

- 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 (*JAMA* 2015;313:18; *Gastro* 2014;147:1238)

- Caused by inflammatory or malignant changes in oropharynx/esophagus; *solids* > *liquids*
- Oropharyngeal
  - Zenker's diverticulum (post pharyngeal pouch): in elderly, a/w aspiration, dx w/ video fluoroscopy, Rx w/ endo/surg
  - malignancy, radiation injury, infection, goiter, osteophytes, proximal strictures/rings/webs
- Esophageal
  - rings (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: predominantly young or middle-aged ♂. Dx: >15 eos/hpf on bx, esoph dysfxn (ie, dysphagia, food impaction) & exclude GERD (empiric PPI trial). Rx: **3Ds**: 1st modify **D**iet (Ø milk, soy, eggs, wheat, nuts, fish); if no Δ, Rx w/ **D**rugs (swallow inh steroids); if ongoing sx & stricturing, **D**ilation.

Neuromuscular dysphagia

- Caused by aberrant motility or innervation of oropharynx/esophagus; *solids & liquids*
- Oropharyngeal: consider CNS disorders (eg, stroke, ALS, myopathies, CNS tumors)
- Esophageal: motility disorder a/w dysphagia, CP, GERD; dx via manometry or high-res esophageal pressure topography. Entities include:
  - *Distal spasm:* uncoordinated peristalsis w/ simultaneous contractions
  - *Hypercontractile:* high amp contractions; Rx w/PPI, nitrates/CCB/PDEi, TCA/SSRI
  - *Hypomotility:* ↓ amp of distal esoph contractions; seen in scleroderma, DM, hypothyroidism; Rx w/ PPI & Rx underlying disorder
  - *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 (*NEJM* 2011;364:1868); per oral endoscopic myotomy; CCB/nitrates/PDEi; Botox inj if not candidate for surgery

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:JTC1)
- Clinical diagnosis based on sx and response to empiric trial of PPI ("PPI test")
- EGD: if (1) Ø response to PPI; or if (2) ***alarm features:*** dysphagia, vomiting, ↓ wt, anemia
- If dx uncertain & EGD nl → esoph manometry w/ 24-h esoph pH monitoring ± impedance

Treatment (*Lancet* 2013;381:1933)
- 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 esoph hypersensitivity. Rx w/ TCA, SSRI or baclofen.

Complications (*NEJM* 2014;371:836; *Gastro* 2011;140:1084.e18 & 2015;149:1599)
- Reflux esophagitis (erosions/ulcers above GE jxn), strictures (caused by chronic inflamm)
- Barrett's esophagus (BE; *NEJM* 2014;371:836): metaplastic columnar mucosa above GE jxn replaces squam esoph epithelium (dx via EGD/bx)
  Screen if GERD w/ ≥1 risk factor for esophageal adeno.: >50 y, ♂, white, hiatal hernia, central adiposity, smoking. 0.1–0.3%/y risk of esoph adenocarcinoma, ↑ if ↑ dysplasia.
  Management: PPI. W/o dysplasia: surveillance EGD no sooner than q3–5y (limited data on utility of EGD screening in nondysplastic BE). Low-grade dysplasia: EGD q6–12mo; potential benefit of endoscopic eradication, eg RFA (*JAMA* 2014;311:1209).
  High-grade dysplasia: endoscopic eradication (resection or ablation treatment).

Peptic Ulcer Disease (PUD)

Definition & etiologies (*Lancet* 2009;374:1449)
- 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 ~80% of duodenal ulcers (DU) & ~60% 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 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 antigen or EGD + rapid urease test. False ⊖ if on abx, bismuth, PPI, so 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 above); 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.o.), or sx persist

Treatment (*NEJM* 2010;362:1597; *Gut* 2012;61:646; *BMJ* 2013;347:f4587)
- **If *H. pylori* ⊕, eradicate** ("test and treat") (*Gastro* 2016;151:51):
  Triple Rx: clarith + [amox, MNZ or levoflox] + PPI bid × 10–14 d (if clarith resist rate <20%)
  Quadruple Rx: MNZ + TCN + bismuth + PPI (if clarith resist rate >15% or amox allergy)
  erad vs. triple 93 vs. 70%, clarith sens 95 vs. 85%, resist 91 vs. 8% (*Lancet* 2011;377:905)
  Sequential Rx: PPI + amox × 7 d → PPI + clarith + MNZ × 7 d (*Lancet* 2013;381:205)
  Besides PUD, test & Rx if: gastric MALT lymphoma, atrophic gastritis, FHx gastric ca
- If *H. pylori* ⊖: gastric acid suppression w/ PPI
- 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)

Prophylaxis if ASA/NSAID required (*JACC* 2016;67:1661; *Aliment PharmRx* 2016;43:1262)
- PPI if (a) h/o PUD/UGIB; (b) also on clopidogrel (although ? ↓ antiplt effect); (c) ≥2 of the following: age >60, steroids or dyspepsia; prior to start test & Rx *H. pylori*
- Consider misoprostol; consider H2RA if ASA monotherapy (*Lancet* 2009;374:119)
- Consider Δ to COX-2 inhibit (↓ 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** = 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
- **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, occult blood
- **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:** BB sample for 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 (*NEJM* 2013;368:11)
- **Reverse coagulopathy:** FFP & vit K 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, if ongoing hematemesis, shock, poor resp status, Δ MS ? OutPt management if SBP ≥110, HR <100, Hb ≥13 (♂) or ≥12 (♀), BUN <18, Ø melena, syncope, heart failure, liver disease (*Lancet* 2009;373:42)

Diagnostic studies

- **Nasogastric tube** can aid localization: *fresh blood or coffee grounds* → active or recent UGIB; *nonbloody* → does not exclude UGIB (~15% missed). ⊕ occult blood test no value.
- 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 **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%) (*NEJM* 2016;374:2367) See "PUD"	*Treatment:* **PPI:** 80 mg IV bolus + 8 mg/h drip ≈ 40 mg IV BID boluses **Endoscopic therapy:** epi inj + bipolar cautery or hemoclip. Biopsies 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. 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 and ? discharge. Hold anticoag & antiplatelet Rx until hemostasis; can resume after hemostasis & PPI on board (*BMJ* 2012;344:e3412).
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 esophagitis (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%) (*Hep* 2007;46:922; *NEJM* 2010;362:823) See "Cirrhosis"		2° to portal HTN. If isolated gastric → r/o splenic vein thrombosis. *Pharmacologic* **Octreotide** 50 µg IV bolus → 50 µg/h infusion (84% success). Usually × 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 *Nonpharmacologic* **Endoscopic band ligation** (>90% success) or sclerotherapy Arteriography w/ coiling, or if available, endoscopic injection of cyanoacrylate (glue) for gastric varices Covered esophageal stent placement or balloon tamponade used for bleeding refractory to ligation as bridge to TIPS (consider early if persistent bleed on EGD or Child-Pugh C; *NEJM* 2010;362:2370) For persistent gastric variceal bleed: 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 d/t 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/ 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-sphincterotomy bleeding		Occurs in ~2% of cases, ↑ risk w/ more complicated procedure. Bleeding into duodenum. Rx w/ endo hemostasis.

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

Etiology LGIB	Comment & Treatment (*Am J Gastro* 2015;110:1265 & 2016;111:755)
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, painless hematochezia, ± abd cramping *Treatment:* Usually stops spont. (~75%) but may take hrs–days; ~20% recur. Can perform endo hemostasis w/ epi injections ± electrocautery (*NEJM* 2000;342:78), 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 (but can cause obscure GIB in adults). Dx w/ ^{99m}Tc-pertechnetate scintigraphy. Rx w/ angioembo, surgical resection.

Obscure GIB (*Gastro* 2007;133:1694; *GIE* 2010;72:471)

- **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 (*Gastro* 2009;137:1197)
  If still ⊖, consider ^{99m}Tc-pertechnetate scan ("Meckel's scan"), enteroscopy (single-balloon, double-balloon or spiral), tagged RBC scan and arteriography

Acute Diarrhea (<4 weeks' duration)

Acute Infectious Etiologies (*NEJM* 2014;370:1532; *JAMA* 2015;313:71)		
Pathogen		**Epidemiology & Clinical Sx**
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	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 (*Lancet* 2012;379:2466)	Contam H_2O, fish, shellfish; 50 cases/y in U.S. Gulf Coast. Severe dehydration & electrolyte depletion.
Parasitic	*Giardia*	Streams/outdoor sports, travel, outbreaks. Bloating. Acute (profuse, watery) → chronic (greasy, malodorous).
(± malab for mos after Rx)	*Cryptosporidia* (*NEJM* 2002;346:1723)	Water-borne outbreak; typically self-limited, can cause 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, travel to Asia; carried by puppies & kittens. Prodrome; abd pain → "pseudoappendicitis"; c/b GBS, reactive arthritis.
	Salmonella (nontyphoidal)	Eggs, poultry, milk. 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. 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)

- **History:** stool freq, bloody, 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:** ✓ **fecal WBC** (high false ⊕ & ⊖) or stool lactoferrin & calprotectin (PMN products; Se/Sp >90%), 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*)
- **Imaging/endoscopy** warranted if ***warning signs***: fever, signific abd pain, blood or pus in stools, >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)

- If none of the above warning signs *and* Pt able to take POs → supportive Rx only: oral hydration, loperamide, bismuth subsalicylate (avoid anticholinergics)
- If moderate dehydration: 50–200 mL/kg/d of oral solution (½ tsp salt, 1 tsp baking soda, 8 tsp sugar, & 8 oz OJ diluted to 1 L w/ H_2O) or Gatorade, etc. If severe: IV fluids.
- Fluoroquinolone or rifaximin if high suspicion for traveler's diarrhea
- If high suspicion for protozoal infection can consider metronidazole or nitazoxanide
- *Empiric* abx for non–hospital-acquired *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 as may ↑ risk of HUS

Clostridium Difficile-Associated Diarrhea (CDAD)

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/ all abx (esp. β-lactams, clinda, quinolones).
- Additional risk factors: elderly, nursing home residents, IBD, PPI (CID 2011;53:1173)

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** (colon dilatation ≥6 cm on KUB, colonic atony, systemic toxicity) and/or bowel perforation

Diagnosis

- Only test if *symptomatic* (diarrhea, s/s of colitis); test *liquid* stool (unless concern for ileus)
- **Stool EIA:** detects toxin B and/or A (1–2% strains make A); fast (2–6 h); ⊕ result highly Sp
- **Stool PCR:** has ↑ Se, but ⊕ if colonized in absence of active CDAD; should not necessarily Rx if ⊕ PCR w/ ⊖ neg toxin assay (JAMA IM 2015;175:1792)
- Consider flex sig if dx uncertain and/or evidence of no improvement w/ standard Rx

Treatment (NEJM 2015;372:1539; JAMA 2015;313:398)

- If possible d/c abx ASAP; stop antimotility agents
- **Non-severe:** vanco 125 mg PO q6h or MNZ 500 mg PO q8h × 10–14 d; equal cure rates, but MNZ less well tolerated
- **Severe** (any of the following: >12 BM/d, Temp >103°F, WBC >25, HoTN, ICU care required, ileus): vanco 125 mg PO q6h + MNZ 500 mg IV q8h
- If worsening (ileus, ↑ WBC, ↑ lactate, shock, toxic megacolon, peritonitis): abd CT & urgent surgical consult re: subtotal colectomy (? possible role for diverting loop ileostomy or colonic lavage); may also consider vanco PR
- If Pt needs to continue on abx, continue *C. diff.* Rx for ≥7 d post-abx cessation
- 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. Consider fecal microbial transplant (NEJM 2013;368:407 & JAMA 2016;315:142) or fidaxomicin (200 mg bid × 10 d). Pilot data for oral admin of nontoxigenic *C. diff* strain spores (JAMA 2015;313:1719).
- Probiotics w/o clear benefit (Lancet 2013;382:1249)

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), etc. → 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** (*NEJM* 2012;367:2419; *Gastro* 2015;148:1175)
  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 α-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* (*NEJM* 2007;365:55)
  Other s/s: fever, LAN, edema, arthritis, CNS Δs, gray-brown skin pigmentation, AI & MS, oculomasticatory myorhythmia (eye oscillations + mastication muscle contract)
  Rx: (PCN + streptomycin) or 3rd-gen ceph × 10–14 d → Bactrim for ≥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

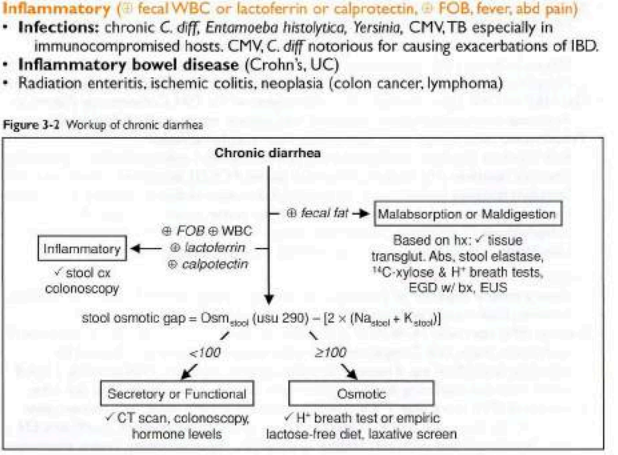
Maldigestion (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- 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 or 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



Functional GI Disease

- Recurrent GI sx caused by abnl gut–brain interactions rather than structural cause
- >20 types of FGIDs per Rome III criteria; now Rome IV (*Gastro* 2016;150:1257)
- **Irritable Bowel Syndrome (IBS)** (*JAMA* 2015;313:949)
  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 related to stress, diet, lifestyle, possibly microbiome.
  Treatment: exercise, cognitive behavioral Rx, Δ diet, probiotics, ? peppermint oil
  IBS-C: laxatives (eg, lubiprostone, linaclotide, PEG), biofeedback
  IBS-D: rifaximin or loperamide; eluxadoline, μ & κ agonist, δ antag (*NEJM* 2016:374:242)
- **Cyclical Vomiting Syndrome:** stereotypic episodes of acute recurrent vomiting; a/w marijuana use, family hx 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, thyroid disease, critical 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

Acute colonic pseudo-obstruction (Ogilvie's syndrome; *ANZ J Surg* 2015;85:728)

- Definition: loss of intestinal peristalsis in absence of mechanical obstruction
- Abd discomfort & distention, ↓ / absent bowel sounds, ± N/V, hiccups
- Typically in elderly, hospitalized, ill Pts, precipitated by: intra-abd process (surgery, pancreatitis, peritonitis, intestinal ischemia), severe medical illness (eg, sepsis), meds (opiates, CCB, anticholinergics), metab/endo abnl (thyroid, DM, kidney failure, liver failure), spinal cord compression/trauma, neurologic d/o (Parkinson's, Alzheimer's, MS)
- KUB or CT w/ colonic dilatation w/o mech obstruction; cecal diam >14 cm a/w high risk perf
- **Treatment:** conservative measures (NPO, avoid offending meds) usually effective; IV **neostigmine** (monitor for bradycardia), methylnaltrexone; bowel decompression w/ NGT, rectal tube, colonoscopy; if refractory, colostomy or colectomy

Constipation (*Annals* 2015;162:ITC1)

- Defined as dissatisfaction w/ defecation or (per Rome III): ≥2 of following during last 3 mo ≥25% of the time: straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate defecation, stool frequency <3/wk
- **Secondary etiologies** (4 M's)
  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:** diet change w/ ↑ fluid intake, fiber supplementation
  Bulk laxatives (psyllium, methylcelulose, polycarbophil): ↑ colonic residue, ↑ peristalsis
  Osmotic laxatives (Mg, sodium phosphate [avoid if CKD], lactulose): ↑ water in colon
  Stimulant laxatives (senna, castor oil, bisacodyl, docusate sodium): ↑ motility & secretion
  Enema/suppository (phosphate, mineral oil, tap water, soapsuds, bisacodyl)
  Lubiprostone (↑ secretion); methylnaltrexone and alvimopan for opioid-induced
  Linaclotide ↑ stool freq, ↓ straining/bloating (*NEJM* 2011;365:6:527)

Nutrition in critical illness (see "Mech Ventilation" as well) (*NEJM* 2014;370:1227)

- In theory, enteral superior to parenteral as maintains integrity and function of GI tract, however, both routes with similar outcomes (*NEJM* 2014;371:1673)
- **Enteral** (EN): start w/in 24–48 hr of ICU admission tends to ↓ infxn & mort. Contraindic. if obstruction, major GIB. Complications: ischemic bowel injury due to ↑ demand for splanchnic blood flow, esp. if hemodynamically unstable; aspiration PNA (possibly ↓ risk if jejunal feeds but conflicting data), nasopharyngeal ulceration/bleeding/pain to due tube.
- **Parenteral** (PN): start after 7 d if unable to tolerate enteral feeds, or ? sooner (*JAMA* 2013;309:2130); late (>day 8 of ICU stay) initiation of PN to supplement insufficient EN ↓ infxn & time on vent (*NEJM* 2011;365:506). 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.

DIVERTICULOSIS

Definition & pathophysiology (*Lancet* 2004;363:631)
- 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
- For asx diverticulosis, limited data for ↑ fiber diet or avoiding nuts/seeds (*JAMA* 2008;300:907)

DIVERTICULITIS

Pathophysiology (*NEJM* 2007;357:2057; *Gastroenterol* 2015;147:1944)
- 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 *contraindicated* acutely ↑ risk of perforation; do 6 wk after to r/o neoplasm

Treatment (*JAMA* 2014;311:287; *Dis Colon Rectum* 2014;57:284)
- 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 be needed for uncomplicated diverticulitis (*Cochrane* CD009092)
- 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)
  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
- Mesalamine ± rifaximin may provide sx relief in chronic/recurrent dis. (*Dig Dis Sci* 2007;52:2934)
- Risk of recurrence 10–30% w/in 10 y of 1st episode; more likely 2nd episode complicated

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 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 occurring anywhere in GI tract, *skip areas*

Epidem & pathophys *(NEJM 2009;361:2066; Gastro 2011;140:1785; Lancet 2016;387:156)*

- 1.4 million people in U.S.; prev 1:1000 UC & 1:3000 CD; ↑ incidence in Caucasians, Jews
- Age of onset 15–30 y in UC and CD; CD is bimodal and has second peak at 50–70 y
- 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 *(NEJM 2011;365:1713; Lancet 2012;380:1606)*

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)

Diagnosis

- **Colonoscopy:** involves rectum (95%) & extends proximally and *contiguously within colon*
- Classify by location: proctitis (25–55%), left-sided colitis (50–70%) and pancolitis (20%)
- Appearance: granular, friable mucosa with diffuse ulceration; *pseudopolyps*
- 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 (Se 77%, Sp 71%)

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 (5%): occurs in rectosigmoid after repeated episodes of inflammation
- CRC and dysplasia (see *below*)
- For patients 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% of Pts in remission at any given time; intermittent exacerbations in 90%; continual active disease in ~18%. Rate of colectomy at 10 y is 24%.
- Mortality rate of severe UC flare is <2%, & overall life expectancy in UC = non-UC Pts

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CROHN'S DISEASE *(Lancet 2012;380:1590)*

Clinical manifestations

- **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

Diagnosis

- **Ileocolonoscopy + bx** is gold standard; **small bowel imaging** (eg MR-enterography ~91% accuracy in identifying Crohn's compared to endoscopy); capsule endoscopy
- Classify by location: small bowel (47%), ileocolonic (21%), colonic (28%); upper tract rare
- Montreal classification: age at dx, disease location & behavior (stricturing vs. nonstricturing, penetrating vs. nonpenetrating), plus modifiers for upper tract & perianal disease
- 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
- Track disease severity w/ Crohn's Disease Activity Index (CDAI) questionnaire

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 ↓

Initial evaluation

- **H&P** (✓ for intestinal & extraintestinal manifestations) and **diagnostic studies** as above
- **Lab:** consider CBC/diff, LFTs, iron studies, B12, folate, vit D. Fecal calprotectin & lactoferrin have higher Se & Sp than ESR & CRP.
- **Exclude other etiologies:** infectious/ischemic colitis, intestinal lymphoma/carcinoma, CRC, IBS, vasculitis, Behçet's, celiac disease, small intestinal bacterial overgrowth
- **Rule out infection** (esp. CMV) before treating with immunosuppressants and biologics

Goals of treatment

- Induce remission of acute flare → maintain remission; mucosal healing 1° goal
- Convention is step up Rx (least → most toxic). Early combined immunosuppression Rx not yet widely adopted; consider if severe disease (*Lancet* 2015;386:1825).

Medical Therapy for IBD (in stepwise sequence)

	Ulcerative colitis
Mild	**5-ASA:** many formulations (sulfasalazine, mesalamine, olsalazine, balsalazide) depending on disease location. Used to induce remission & for maintenance. Complications: diarrhea, abd pain, pancreatitis.
Mild-Moderate	**MMX-budesonide:** oral formulation of budesonide released throughout entire 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. Complic: BM suppression, lymphoma, pancreatitis, hepatitis; ✓ TPMT levels prior to dosing to ↓ risk of generation of toxic metabolites. In selected cases can add allopurinol to boost activity in non-responders.
Severe or refractory disease	**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): 15–20% remission rates (*Gastro* 2012;142:257). For steroid-refractory flares or to maintain remission. Complic: reactivation TB (✓ PPD prior to Rx); exclude viral hepatitis; small ↑'d risk NHL; infusion & lupus-like rxn, psoriasis, MS, CHF. **Vedolizumab** (see *below*) Investigational: tofacitinib (janus kinase inhib; *NEJM* 2012;367:616), fecal transplant (*Gastro* 2015;149:102)
	Crohn's disease
Mild	**5-ASA:** Sulfasalazine 4–6 g/d may be useful in inducing remission **Abx:** FQ/MNZ or amox/clav for pyogenic complic (fistulas, perineal dis.)
Mild-mod	**Budesonide:** oral formulation able to reach ileum
Moderate-severe	**PO prednisone:** same as UC, for inducing remission, not maintenance **AZA/6-MP:** same as UC, for maintenance **MTX:** 15–25 mg IM/SC or PO qwk for maintenance; 1–2 mo to take effect
Severe or refractory disease	**Anti-TNF:** infliximab, adalimumab or certolizumab (pegylated) If flare on infliximab, ✓ trough & presence of anti-infliximab Ab. Low & ⊖ Ab → ↑ dose/freq. If ⊕ Ab → Δ to other biologic (*Am J Gastro* 2011;106:685). **Vedolizumab** (anti-α4β7 integrin) and **ustekinumab** (anti-IL 12/23) if refractory to anti-TNFs SMAD7 anti-sense oligonucleotide (*NEJM* 2015;372:1104) under study

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 biopsy is emerging technique. If high-grade dysplasia or dysplasia assoc. lesion/mass → colectomy. Chemoprophylaxis: 5-ASA & ursodeoxycholic acid (if PSC) ? beneficial (*AJG* 2011;106:731; *Aliment Pharmacol Ther* 2012;35:451).

ACUTE MESENTERIC ISCHEMIA

Definition and Causes

- 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
- **SMA thrombosis** (~60%): typically due to atherosclerosis at origin of SMA; other risk factors incl. vascular injury from abd trauma, infxn, or mesenteric dissections/aneurysms
- **SMA embolism** (~30%): embolic occlusion to SMA (has narrow take-off angle), often in setting of AF, valvular disease incl. endocarditis, atherosclerotic plaque in aorta
- **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 the small bowel** (<5%): vascular occlusion to small segments of the 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 (e.g. cardiac event or shock)

Physical Exam

- From unremarkable ± abd distention to peritoneal signs (bowel 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)*

- IVF, NPO, **optimize hemodynamics** (minimize pressors), **broad-spectrum abx, anti-coagulation** w/ heparin ± **tPA** (for occlusive disease), **IV papaverine** (vasodilator; for all)
- 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: angiography (gold std) ≈ gastric tonometry exercise testing + duplex U/S (if available)
- 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

Clinical manifestations, diagnosis, & treatment

- Disease spectrum: reversible colopathy (35%), transient colitis (15%), chronic ulcerating colitis (20%), resulting stricture (10%), gangrene (15%), fulminant colitis (<5%)
- Usually p/w **cramping LLQ pain w/ overtly bloody stool;** fever and peritoneal signs should raise clinical suspicion for infarction
- 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

ACUTE PANCREATITIS (AP)

Pathogenesis

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

Etiologies (*Lancet* 2015;386:85)

- **Gallstones** (40%): ♀ > ♂, usually small stones (<5 mm) or microlithiasis/sludge
- **Alcohol** (30%): ♂ > ♀, 1st attack after ~10 y heavy use; usually chronic w/ acute flares
- Anatomic: divisum, annular pancreas, duodenal duplication cysts, Sphincter of Oddi dysfxn
- Autoimmune: can p/w chronic disease, panc mass or panc duct strictures, ↑ IgG4, ⊕ ANA
- Drugs: 5-ASA, 6-MP/AZA, ACEI, cytosine, didanosine, dapsone, estrogen, furosemide, isoniazid, metronidazole, pentamidine, statins, sulfa, thiazides, tetracycline, valproate
- Familial: a/w mutations in *PRSS 1, CFTR, SPINK 1;* suspect if early onset (age <20 y)
- Infections: ascariasis, clonorchiasis, coxsackie, CMV, HIV, mumps, mycoplasma, TB, toxo
- Ischemia: vasculitis, cholesterol emboli, hypovolemic shock, cardiopulmonary bypass
- Metabolic: hypertriglyceridemia (TG >1000; type I and V familial hyperlipemia), hyperCa
- Neoplastic: panc/ampullary tumors, mets (RCC most common, breast, lung, melanoma)
- Post ERCP (5%): Ppx w/ PR indomethacin (*NEJM* 2012;366:1414), panc duct stent if high risk
- Post trauma: blunt abdominal trauma, pancreatic/biliary surgery
- Toxins: organophosphates, scorpion toxin, methanol

Clinical manifestations

- **Epigastric abdominal pain (90%),** only 50% p/w classic bandlike pain radiating to back
- 10% pain-free (due to analgesic/steroid use, immunosuppressed, ΔMS, ICU, post-op).
  ∴ ✓ amylase/lipase in Pts w/ unexplained shock (*Am J Gastro* 1991;86:322).
- **Nausea and vomiting (90%)**
- Abdominal tenderness/guarding, ↓ bowel sounds (ileus), jaundice if biliary obstruction
- Signs of retroperitoneal hemorrhage (Cullen's = periumbilical; Grey Turner's = flank) rare
- Ddx: acute cholecystitis, perforated viscus, SBO, mesenteric ischemia, IMI, AAA leak, distal aortic dissection, ruptured ectopic pregnancy

Diagnostic studies

- **Dx requires 2 of 3:** characteristic abd pain; lipase or amylase >3× ULN; ⊕ imaging
- Laboratory (*Am J Gastro* 2013;108:1400)
  levels of both amylase and lipase do *not* correlate w/ severity of disease
  ↑ **amylase:** >3× ULN >90% sensitive, >70% specific for acute pancreatitis
  false ⊖: acute on chronic (eg, alcoholic); hypertriglyceridemia (↓ amylase activity)
  false ⊕: other abd or salivary gland process, acidemia, renal failure, macroamylasemia
  ↑ **lipase:** >3× ULN 99% sensitive, 99% specific for acute pancreatitis
  false ⊕: renal failure, other abd process, diabetic ketoacidosis, HIV, macrolipasemia
  longer half-life than amylase: useful in Pts w/ delayed presentation after onset of sx
  lipase >10,000 has 80% PPV for biliary dx, 99% NPV for EtOH (*Dig Dis Sci* 2011;56: 3376)
  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 with AP 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): limited role; useful for occult biliary disease (microlithiasis)

Severity (*Am J Gastro* 2009;104:710)

- 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

- Scoring systems (*Crit Care Med* 1999;27:2272; *Am J Gastro* 2009;104:966)
  Ranson's/APACHE II: earliest scoring systems predicting severity at 48 h using multiple physiological criteria; may have poor PPV for severe AP
  BISAP: simple 5-point scoring system (BUN >25, impaired MS, SIRS, age >60, pleural effusion) used w/in first 24 h; score ≥3 predicts ↑ risk of organ failure, mortality
  CTSI: uses CT findings at 48–72h (fluid collections, necrosis) to predict mortality
- Other criteria: SIRS >48 h, rising BUN/Hct, obesity, comorbid disease predict ↑ mortality

Treatment (*Clin Gastro Hepatol* 2011;9:710; *Am J Gastro* 2012;107:1146; *NEJM* 2014;370:150)

- **Fluid resuscitation:** *early aggressive IVF,* titrate to UOP ≥0.5 mL/kg/h, goal to ↓ BUN & Hct over first 12–24 h. LR may be superior to NS (↓ SIRS, CRP at 24 h; avoid if ↑ Ca)
- **Nutrition** (*Clin Gastro Hepatol* 2007;5:946; *Intern Med* 2012;51:523; *Crit Care* 2013;17:R118)
  Early enteral feeding encouraged (maintains gut barrier, ↓ bacterial translocation) though new data suggest may not be superior to oral feeding at 72 h (*NEJM* 2014;317:1983)
  Mild: Start feeding once pain-free w/o ileus. Low-fat low-residue diet as safe as liquid diet.
  Severe: early (w/in 48–72 h) enteral nutrition indicated and preferred over TPN b/c ↓ infectious complications, organ failure, surgical interventions, and mortality.
  Nasogastric feeding shown to be non-inferior to nasojejunal feeding
- **Analgesia:** IV opioids (monitor respiratory status, adjust dosing if ↑ renal impairment)
- **Gallstone pancreatitis:** urgent (w/in 24 h) ERCP w/ sphincterotomy if cholangitis, sepsis, or Tbili ≥5. For mild disease, CCY during initial hosp to ↓ risk of recurrence (*Lancet* 2015;386:1261); defer surgery if necrotizing AP 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 Gastroenterol* 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 antibiotics
  Infected necrosis (5% of all cases, 30% of severe): high mortality. Rx w/ carbapenem or MDZ+FQ. "Step-up" Rx w/ perc drainage and minimally invasive surg debridement or endoscopic necrosectomy superior to open necrosectomy (*NEJM* 2010;362:1491)
  Pancreatic abscess: circumscribed collection of pus (usually w/o pancreatic tissue), usually seen ≥4 wk into course. Rx with abx + drainage (CT-guided if possible).

Chronic Pancreatitis

Pathogenesis & Etiology

- Often, but not always, recurrent acute attacks → inflammatory infiltrate → fibrosis → pancreatic insufficiency (need to lose 90% of panc fxn to develop DM, fat/protein malabs.)
- Toxins (60–80% due to EtOH; smoking also important risk factor), idiopathic, genetic, autoimmune, relapsing AP, obstruction

Clinical manifestations

- Sxs include epigastric pain, N/V; over time will be painless and p/w steatorrhea and wt loss

Diagnostic studies

- Labs: amylase/lipase ↑ early, may be nl later. ⊕ fecal fat, ↓ stool elastase & A1AT.
  ✓ A1c, consider IgG4/ANA & genetic testing (CFTR, SPINK1, PRSS1) if young or ⊕ FHx.
- Imaging: Ca^{2+} on KUB/CT. ERCP/MRCP/EUS high Sens for dx: stricture, dilated ducts

Treatment (*Lancet* 2016;387:1957)

- Pancreatic enzyme replacement (may ↓ pain by reducing CCK)
- Pain control: smoking & EtOH cessation, analgesics, ESWL for duct stones, celiac nerve plexus block, thoracoscopic splanchnicectomy, resection.

Complications

- Pseudocysts, pseudoaneurysms, pancreatic ascites or pleural effusion, ↑ **risk of panc Ca**

Autoimmune Pancreatitis

Pathogenesis

- Lymphoplasmacytic sclerosing pancreatitis w/ dense fibrosis and ↑ IgG4 (type 1), or granulocytic epithelial lesions with minimal IgG4 cells (type 2)

Clinical Manifestations

- **Abdominal pain,** can p/w obstructive jaundice and panc mass mimicking panc Ca.
- Extrapancreatic: Sjögren's, 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, immunomodulators (AZA, MMF, cyclophosphamide) if relapse

ABNORMAL LIVER TESTS

Tests of hepatocellular injury or cholestasis

- **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

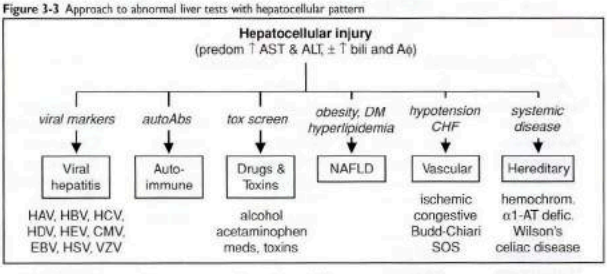
- **Albumin:** marker for liver protein synthesis, ↓ slowly in liver failure ($t_{½}$ ~15–18 d)
- **Prothrombin time** (PT): depends on synthesis of coag factors by liver (except FVIII); b/c $t_{½}$ of some factors (eg, V, VII) is short, ↑ PT can occur w/in hrs of liver dysfxn

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		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



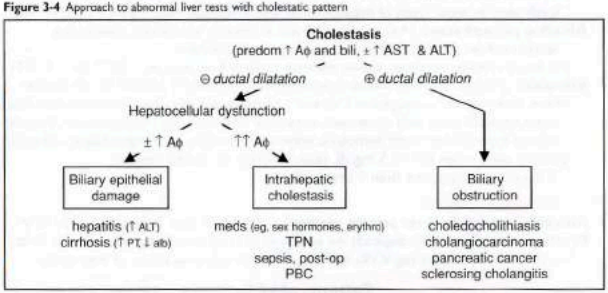
- **Workup for *acute* enzyme elevation** (often symptomatic)
  Severe ALT & AST elevation (>1000):
  toxins (usu. acetaminophen) → ✓ tox screen, EtOH, acet. levels. Other toxins: INH, disulfiram, pyrazinamide, OTC/herbal, fenofibrate, niacin, amiodarone, MDMA.
  ischemia (eg, sepsis, hypotension, Budd 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 (rare cause of liver dis); thyroid studies; see "Cirrhosis"

If ⊖ evaluation → lifestyle modification (wt loss, DM control) & repeat testing 3–6 mo

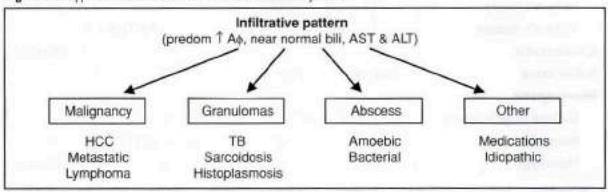
If evidence of chronic liver disease or persistent lab abnl, consider liver bx

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



- **Workup for cholestatic pattern:** ✓ RUQ U/S to assess for ductal dilatation.
  If ⊕ (extrahepatic obstruction) → Pt may need ERCP ± imaging (MRCP, CT) for dx/Rx
  If no dilatation on U/S → ✓ AMA (for PBC), viral serologies (Hep A-E, EBV, CMV); if work-up negative, consider MRCP and liver bx. See offending med list below.

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



- **Workup for infiltrative pattern:** ✓ GGT level to ensure GI source of Aϕ elevation.
  If ⊕ (↑ GGT & ↑ Aϕ) → often imaging first step (RUQ U/S or CT; consider MRCP if these studies negative); ✓ SPEP (for amyloid), often need liver bx for definitive diagnosis.

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

Hepatocellular		Cholestatic		Mixed
Acarbose	Prednisone	ACE inhibitors	6-MP	Amox-Clav
Acetaminophen	Protease Inhibitors	Anabolic Steroids	OCP	Azathioprine
Allopurinol	Pyrazinamide	Azathioprine	Penicillins	Carbamazepine
Amiodarone	Risperidone	Chlorpromazine	Protease Inhibitors	Clindamycin
Azathioprine	Statins	Estrogens	Sulfonamides	Mirtazapine
Clindamycin	Sulfonamides	Macrolides	Terbinafine	Nitrofurantoin
Fibrates	Tamoxifen	Methimazole	Tricyclics	Penicillins
Hydralazine	Tetracyclines			Phenobarbital
Isoniazid	TNF-alpha inhibitors			Phenytoin
Ketoconazole	Trazodone			Protease Inhibitors
Methotrexate	Tricyclics			Sulfonamides
Mirtazapine	Valproic Acid			Trazodone
Nitrofurantoin				Tricyclics
(Some) NSAIDs				Valproic acid
Phenytoin				Verapamil

VIRAL

Hepatitis A (ssRNA; 30–45% of acute viral hepatitis in U.S.)

- Transmission: fecal–oral route; contaminated food, water, shellfish; daycare center outbreaks
- Incubation: 2–6 wk; no chronic carrier state
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, jaundice; rarely fulminant (↑ 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 fulminant hepatitis
- 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.; *Lancet* 2014;384:2053)

- Transmission: blood (IVDU, transfusion), sexual, perinatal
- Incubation: 6 wk–6 mo (mean 12–14 wk)
- Acute infxn: 70% subclinical, 30% jaundice, <1% fulminant hepatitis (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* 2014;161:58 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

Phase	ALT (ULN*)	HBV DNA (IU/mL)	HBeAg	Liver Histology (inflammation/fibrosis)	Progression to cirrhosis
Immune-tolerant	NI	≥10^6	⊕	Minimal	<0.5%/y
Immune-active HBeAg ⊕	≥2×	≥20k	⊕	Moderate-to-severe	2–5.5%/y
Inactive	NI	≤2k	⊖	Min necroinflam.; variable fibrosis	0.05%/y
Immune Reactivation; HBeAg ⊖ 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.

- 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% (*Gastro* 2012;142:1360; *Lancet* 2013;381:468). Tenofovir preferred if h/o lamivudine resistance.
- **PEG IFN-α2a:** At 2 y, HBeAg seroconversion is 27%; contraindicated if autoimmune disease, uncontrolled psych disorder, seizures, decompensated cirrhosis

- 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 (*NEJM* 2007;356:1445)
- Immunosuppression: prior to initiating chemoRx, anti-TNF, steroids (>20 mg/d > 1 mo), screen Pts for HBV; Rx if moderate to high risk of reactivation (*Gastro* 2015;148:215)
- 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; fulminant hepatitis 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)
  Acute: if no spont. clearance at 12–16 wk, can Rx w/ same regimens for chronic HCV
  Chronic: Rx recommended for all except those with ↓ life expectancy
- Rx: NS3/4A protease inhibitors ("…previr"; PI), NS5a inhibitors ("…asvir"; NS5ai), RNA polymerase inhibitors ("…buvir"; RNAPi), ribavirin (RBV), pegylated-interferon (PEG-IFN)

Approved HCV Regimens for Treatment-Naïve Patients

PI	NS5ai	RNAPi	RBV	PEG-IFN	Genotypes
	Daclatasvir	Sofosbuvir	±		1a, 1b, 2, 3
	Ledipasvir	Sofosbuvir			1a, 1b, 4, 5, 6
	Velpatasvir	Sofosbuvir			1, 2, 3, 4, 5, 6
Paritaprevir*	Ombitasvir	Dasabuvir	±		1a, 1b
Paritaprevir*	Ombitasvir		±		4
Simeprevir		Sofosbuvir	±		1a, 1b
		Sofosbuvir	⊕	±	2, 3, 4, 5, 6
Grazoprevir	Elbasvir		±		1, 4

*Boost with ritonavir. www.hcvguidelines.org. *NEJM* 2014;370:211, 220, 1483, 1574, 1879, 1889, 1973, 1983, 1993 & 2015;373:2608 & 2618; *Lancet* 2014;384:1756.

- Monitoring on Rx: CBC, INR, LFTs, GFR, HCV VL, and TSH (if IFN is used) prior to starting Rx. PIs contraind. 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, Alb, INR after 4 wk.
- Goal is *sustained virologic response* (SVR) = Ø 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; 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; *NEJM* 2012;367:1237; *Lancet* 2012;379:2477)

- Most common cause of acute viral hepatitis in endemic areas
- Transmission: fecal–oral; travelers to central & SE Asia, Africa and Mexico, exp. to swine
- 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* 2011;55:171; *Hep* 2010;51:2193)

- Type 1: antismooth muscle Ab (ASMA), ANA; antisoluble 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-methyl DOPA, statins

Diagnosis and treatment (*Lancet* 2013;382:1433)

- 70% female; 40% present w/ severe AIH (3% fulminant) w/ ALT >10 × ULN; 34–45% asx
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs' ⊕ hemolytic anemia
- Dx: scoring system combining serologies, ↑ IgG, Ø viral hepatitis, & liver bx (interface hepatitis & lymphoplasmacytic infiltrate) has high Sp & mod Se (*Hep* 2008;48:169)
- 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 Hep* 2012;57:399; *Hep* 2010;51:307)

- 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 un Rx'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) ↓ death but ↑ rate of infections (*NEJM* 1992;326:507 & 2015;372:1619)
  - Contraindications: active GIB, pancreatitis, untreated HBV, uncontrolled infections
  - Pentoxifylline of no benefit alone or when added to steroids (*NEJM* 2015;372:1619)
  - Addition of NAC to steroids ↓ 1-mo but not 6-mo mortality (*NEJM* 2011;365:1781)

Acetaminophen hepatotoxicity (*NEJM* 2008;359:285; *BMJ* 2011;342:2218)

- 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; delayed ↑↑ Tbili
- Seen in HoTN & CHF; often requires ↑ venous + ↓ portal/arterial pressure + hypoxia

Nonalcoholic fatty liver disease (*Hep* 2012;55:2005)

- Definition: fatty infiltration of liver *and* absence of EtOH or other cause of steatosis
  NAFL = steatosis, Ø 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. NAFLD fibrosis score = clinical variables to predict NASH w/ advanced fibrosis with PPV >80% (www.nafdscore.com).
- Rx: wt loss (ideally ≥10%, *Gastro* 2015;149:367), exercise, DM control (liraglutide, *Lancet* 2016;387:679 or pioglitazone). statins (*Lancet* 2010;376:1916); vit E ↓ steatosis but not fibrosis in Pts w/o DM (*NEJM* 2010;362:1675). HCC is a complication of NAFLD that has progressed to NASH cirrhosis but can occur in absence of advanced liver disease.

ACUTE LIVER FAILURE (ALF)

Definition

- Acute insult to liver + coagulopathy + encephalopathy; most w/o known preexisting liver dis.
- *Fulminant* if encephalopathy w/in 8 wk from jaundice onset; *subfulminant* if 8 wk to 6 mo
- Acute on chronic liver failure: acute insult to liver in Pt w/ underlying chronic liver disease

Etiology (*Lancet* 2010;376:190)

- **Drugs/toxins** (nearly 80% of cases in U.S.; *Hepatology* 2010;52:2065)
  - 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 US): 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's 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): esp. 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 (*Hepatology* 2012;55:965)

- CBC, PT/PTT, LFTs, lytes, BUN/Cr, pH, lactate, NH_3, acetaminophen level, 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 (*NEJM* 2013;369:2525)

- **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
- 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. Daily blood cultures.
- Rx of specific causes: NAC if acetaminophen-related; antiviral (eg, entecavir) for HBV; plasma exchange can be temporizing measure for Wilson's; 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 (*Gastro* 2009;137:856)
- **Liver transplantation** if poor prognosis but could survive surgery

Prognosis

- Non-acetaminophen ALF mortality ~80%, acetaminophen-induced ALF mortality ~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
- ~25–30% of Pts undergo liver transplantation w/ 5-y survival rate of 70%
- BMI >30, Cr >2, age >50 y, need for pressors/vent support a/w poorer acute transplant outcome

CIRRHOSIS

Definition (*Hep* 2011;54:1864 & 2012;56:1983; *J Hep* 2012;56:513)

- 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's 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

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 as 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)

Workup (*Lancet* 2014;383:1749)

- 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

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)	<4	4–6	>6
or INR	<1.7	1.8–2.3	>2.3
	Classification		
	A	**B**	**C**
Total points	5–6	7–9	10–15
1-y survival	100%	80%	45%

- **MELD** (**M**odel for **E**nd-Stage **L**iver **D**isease): used to stratify Pts on liver tx list & to predict 3-mo survival in Pts w/ cirrhosis and some acute forms of liver disease. Based on Cr, INR, & total bili. Calculator: www.mayoclinic.org/meld/mayomodel6.html (*Gastro* 2011;14:1952). If MELD <21 additional predictors of mortality include Na <130 (*NEJM* 2008;359:1018; *Clin Gastroenterol Hepatol* 2009;7:1236), refractory ascites, ↑ HVPG and low QoL.

Ascites (see "Ascites" for details on dx evaluation; *Am J Gastro* 2009;104:1802)

- 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 cirrhotic Pts as interfere w/ diuretic action and are nephrotoxic
- **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)
  Med mgmt: conflicting evid. for d/c ↑ing βB (*Hep* 2016;63:1968); if limited by HoTN, 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 as ↑ risk of AKI.
  Transjugular intrahepatic portosystemic shunt (TIPS) (*Clin Gas Hep* 2011;9:936)
  ↓ 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%, hemolysis (*Hep* 2010;51:306)
  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)
  Spontaneous *empyema* can occur (even w/o SBP) → dx thoracentesis; Rx abx

Spontaneous bacterial peritonitis (SBP; see "Ascites" for details; *J Hep* 2010;53:397)

- 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 encephalopathy or AKI) can use FQ but avoid if already on for ppx or if in ↑ FQ resistance area.
  IV albumin 1.5 g/kg at time of dx & 1 g/kg on day 3 → ↑ survival (*NEJM* 1999;341:403)
  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;4993) → cipro 500 mg qd or Bactrim DS qd.
  Short-term Ppx: CTX 1 g IV × 7 d if GIB; cipro 500 mg PO qd × 1 y if ascitic fluid TP <1.5

Gastroesophageal varices ± UGIB (see also "GIB"; *Lancet* 2014;383:1749)

- 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 or propranolol typically used, titrate to max tolerated dose; carvedilol can be considered in nonresponders or if systemic HTN (α_1 blockade → ↓ intrahepatic vasc resistance, *Gut* 2013;62:1634). EGD not req. to document improvement.
  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 (*Hepatol* 2008;47:1764); using both βB and EVL for primary prevention currently not recommended
- 2° prevention: for all Pts after 1st bleed, given ~50% risk of rebleed & ~30% mortality
  βB + EVL > either alone (*Annals* 2008;149:109); TIPS if refractory, or consider in Child B or C w/in 72 h of admission for esoph variceal bleed (↑ 1-y survival; *NEJM* 2010;362:2370)

Portosystemic encephalopathy (PSE) (*Clin Gas Hep* 2012;10:1208)

- 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; rifaximin + lactulose may be more effective than lactulose alone; *Am J Gastro* 2013;108:1458); acarbose & probiotics may benefit
- 2° prevention: lactulose or rifaximin 550 bid (*Gastro* 2009;137:885; *NEJM* 2010;362:1071)

Hepatorenal syndrome (HRS) (*NEJM* 2009;361:1279; *Crit Care* 2012;16:R23(1))

- Pathophys: splanchnic vasodilation and renal vasoconstriction w/ ↓ renal blood flow
- Criteria: (1) cirrhosis w/ ascites; (2) **acute kidney injury** (serum Cr ↑ ≥0.3 mg/dL w/in 48 h or ≥50% ↑ in serum Cr from baseline; *Gut* 2015;64:531); (3) Ø improvement in Cr after d/c

diuretic & volume expansion (1 g/kg/d of albumin × 2 d); (4) Ø shock (prerenal azotemia/ATN); (5) Ø nephrotoxic meds; (6) Ø intrinsic kidney disease

Type I: development in <2 wk; usually occurs in severe liver failure, often following precipitating event (see later); median survival 2 wk

Type II: more indolent course, median survival 6 mo; liver failure present < in type I

- 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 (Hep 2010;51:576).
  May need dialysis or TIPS as bridge to liver transplant.

Hepatocellular carcinoma (HCC) (Hep 2011;53:1020; Lancet 2012;379:1245)

- Epi: worldwide, 6th most prevalent cancer; 3rd most frequent cancer-related death, 80% of cases due to HCV/HBV cirrhosis, in which annual risk of HCC is ~3–8% (Gastro 2012;142:1264). ↑'d risk w/ cirrhosis of any type but esp. w/ viral, HFE, PBC, ? α1-AT.
- Clinical: asx vs. hepatic decompensation (eg, ascites, PSE), PVT w/ tumor thrombus
- Dx: screen cirrhotics q6mo w/ U/S ± AFP, though many centers choose dual phase CT/MRI (if arterial enhancing & venous phase or delayed washout, no bx req for dx)
- Rx: *radiofrequency ablation* (RFA) for HCCs <3 cm in size; consider *resection* if single lesion <2 cm and Child-Pugh A w/o portal HTN; *transarterial chemoembolization* (TACE) preferred for large cancers (not curative) or if not amenable to RFA (near IVC/lung); consider *liver transplant* if up to 3 HCCs ≤3 cm or 1 HCC ≤5 cm (Milan criteria)

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 and diastolic fxn, prolonged QT, hyperkinetic circulation; ↑ troponin, BNP (JACC 2010;56:539)
- **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 insufficiency (Hep 2012;55:1282)
- 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
- 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), acute liver failure
- Contraindic: inadequate social support, active substance abuse (EtOH w/in 6 mo), sepsis, advanced cardiopulm dis., extrahepatic Ca, cholangio Ca, hemangiosarcoma, persistent noncompliance, AIDS, fulminant LF 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's disease *(J Hep 2012;56:671)*

- Recessive disorder of copper transport (mutation in *ATP7B*) → **copper overload;** primarily affects liver, but also other tissues (brain, eye)
- Epidemiology: 1 in 30,000, majority present b/t 5 & 35 y/o, only 3% of Pts present >40 y/o
- 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*, Alϕ/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); 2nd-line 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 fulminant LF 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 found to have chronic liver dis) & M (malton) *(Am J Respir Crit Care Med 2013;137:502)*. 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/o; 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: ↑ Alϕ, ↑ 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
  ~25% complete response, ↑ survival & ↓ histologic change & complications (eg, varices) *(Gastro 2005:128:297)*. Budesonide may benefit in short term.
  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) *(Lancet 2013;382:1587; World J Hepatol 2016;8:265)*

- 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: ♂ > ♀ (20–50y) ~70% Pts w/ PSC have IBD (usually UC); only 1–4% w/ UC have PSC.
- 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) *(Gastro 2008;134:706)*
- Dx: MRCP ± ERCP → *multifocal beaded bile duct strictures*, but may miss dx if confined to small intrahepatic ducts (~2% "small duct PSC": better prognosis, ? different disease). 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) (Hepatology 2009;49:1729 & 2015;61:660)

- Definition: thrombosis, constriction or invasion of portal vein → portal HTN → varices. Isolated splenic vein thrombosis (eg, 2° to pancreatitis) → isolated gastric varices.
- Etiologies: cirrhosis, neoplasm (pancreas, HCC), abdominal infxn, hypercoag states, pancreatitis, collagen vascular diseases, Behçet's, IBD, surgery, trauma, OCPs, preg
- Clinical manifestations
  - **acute:** can p/w abd or lumbar pain; often 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
- Diagnostic studies: LFTs usually normal; U/S w/ Doppler, MRA, CT (I°), angiography; "portal cavernoma" network of hepatopetal collaterals in chronic PVT—can rarely cause biliary obstruction and cholestatic LFTs = portal cholangiopathy (may require surgery)
- Treatment:
  - **Acute:** If noncirrhotic, LMWH → warfarin × 6 mo, or indefinitely if irreversible cause. If cirrhotic, preliminary studies support anticoag if no contraindications; should screen for high-risk varices prior to initiation (*Nat Rev Gastroenterol Hepatol* 2014;11:435).
  - **Chronic:** Anticoag if noncirrhotic or hypercoag state; screen for varices prior to anticoag. Esophageal varices: 1° Ppx recommended; if bleed, endoscopic Rx and βB. If refractory bleed consider TIPS, shunt.
    Isolated gastric varices 2° splenic vein thrombosis: splenectomy is curative

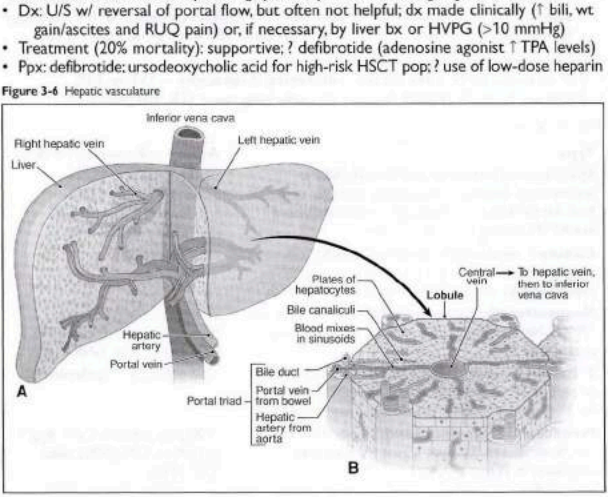
Budd-Chiari syndrome (Hepatology 2009;49:1729)

- Occlusion of hepatic vein(s) or IVC → sinusoidal congestion and portal HTN
- Etiologies: ~50% due to myeloproliferative d/o a/w *JAK2* mutations (esp. *P. vera*), other hypercoag state, tumor invasion (HCC, renal, adrenal), IVC webs, trauma, 25% idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals, acute liver failure
- Dx: ± ↑ aminotransferases & A_0; 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) (Hepatology 2009;49:1729)

- Occlusion of hepatic venules and sinusoids (formerly **veno-occlusive disease**)
- 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)
- Treatment (20% mortality): supportive; ? defibrotide (adenosine agonist ↑ TPA levels)
- Ppx: defibrotide; ursodeoxycholic acid for high-risk HSCT pop; ? use of low-dose heparin

Figure 3-6 Hepatic vasculature



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

ASCITES

Pathophysiology

- Portal hypertension → systemic vasodilatation (? due to release of NO) → ↓ effective arterial volume → renal Na retention → volume overload and ascites
- In malignant or inflammatory ascites, pathophysiology related to leaking of proteinaceous material from tumor or from inflamed/infected/ruptured intraabdominal structures

Etiologies

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

Symptoms

- ↑ abd girth, wt gain, new abd hernia, abd pain, dyspnea, nausea, early satiety

Evaluation (*JAMA* 2008;299:1166; *Hepatology* 2009;29:2087)

- Physical exam: flank dullness (NPV ~90%; >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)
  If ≥1.1 g/dL → cause of ascites likely portal HTN (~95% accuracy; *Annals* 1992;117:215)
  If <1.1 g/dL → non–portal hypertension related
  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 is fluid.

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)

Type	Ascites cell count/mm^3 & cx
Spontaneous bacterial peritonitis (SBP): spontaneous bacterial translocation from gut to ascitic fluid. Ascitic fluid in cirrhosis has ↓ opsonins (esp. if low AFTP), leading to ↑ risk of infxn.	≥250 polys; Cx ⊕ (1 org.) *E. coli* (37%), *Klebs* (17%), *S. pneumo* (12%), misc. GPC (14%), misc. GNR (10%)
Culture-⊖ neutrocytic ascites (CNNA): cell counts suggest infxn but cx ⊖. No recent abx, w/o other explanation for counts. Rare when sens cx methods.	≥250 polys; Cx ⊖
Nonneutrocytic bacterascites (NNBA): ⊕ cx w/o ↑PMNs. Natural course may resolve w/o tx or may progress to SBP.	<250 polys; Cx ⊕ (1 org.) Misc. GPC (30%), *E. coli* (27%), *Klebs* (11%), misc. GNR (14%)
2° bacterial peritonitis: caused by intraabd abscess or perf. AFTP >1 g/dL, glc <50 mg/dL, LDH >225 U. Rx 3rd-gen ceph. + MNZ; urgent abd imaging ± ex lap.	≥250 polys; Cx ⊕ (polymicro)
Peritoneal dialysis-associated: cloudy fluid, abd pain, fever, nausea. Rx: vanc + gent (IV load, then administer in PD)	≥100, poly predom. Cx ⊕ (typ. 1 org.). Misc. GPC (50%), misc. GNR (15%).

CHOLELITHIASIS (GALLSTONES)

Epidemiology & pathogenesis (*J Hep* 2008;48:S124)

- >10% adults in the U.S. have gallstones; a/w ↑ overall mortality (*Gastro* 2011;140:508)
- Bile = bile salts, phospholipids, cholesterol; ↑ cholesterol saturation in bile + accelerated nucleation + gallbladder hypomotility → gallstones
- Risk factors: ♀; South, Central, Native American; ↑ age (>40 y), obesity, pregnancy, TPN, rapid ↓ wt; drugs (OCPs, estrogen, clofibrate, octreotide, ceftriaxone); ileal disease
- ? statin use >1 y ↓ risk of sx gallstones & cholecystectomy (*JAMA* 2009;302:2001)

Types of gallstones

- 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 & infection in bile ducts → bacteria deconjugate bilirubin → precipitates w/ calcium; seen w/ duodenal diverticula, biliary strictures, parasites

Clinical manifestations

- Asx in 80% of cases; biliary pain in ~2%/y; once sx, rate of complications ~2%/y
- **Biliary pain ("colic") = episodic RUQ or epigastric abd pain** that begins abruptly, is continuous, resolves slowly and lasts for 30 min–3 h; ± radiation to scapula; **nausea**
- May be precipitated by **fatty foods**
- Physical exam: afebrile, ± RUQ tenderness or epigastric pain

Diagnostic studies

- 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

Treatment (*J Hepatol* 2016;65:146)

- Cholecystectomy (CCY), usually laparoscopic, if symptomatic
- CCY in asx Pts w/: GB calcification (~7% risk of ca) (Surgery 2001;129:699), GB polyps >10 mm, Native American, stones >3 cm or bariatric surgery or cardiac transplant candidates
- 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
- Biliary pain: NSAIDs (eg, diclofenac 50 mg IM) drug of choice, efficacy = opiates & ↓ complications (*Aliment Pharmacol Ther* 2012;35:1370)

Complications

- Cholecystitis: 20% of sx biliary pain → cholecystitis w/in 2 y
- Choledocholithiasis → cholangitis or gallstone pancreatitis
- Mirizzi syndrome: common hepatic duct compression 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 (*NEJM* 2008;358:2804)

Pathogenesis

- Acute cholecystitis: stone impaction in cystic duct → inflammation behind obstruction → GB swelling ± secondary infection (50%) of biliary fluid
- Acalculous cholecystitis: gallbladder stasis and ischemia → inflammatory response; occurs mainly in critically ill, hosp. Pts (postop major surgery, TPN, sepsis, trauma, burns, opiates, immunosuppression, infxn [eg, CMV, *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: ↑ WBC, ± mild ↑ bilirubin, Aϕ, ALT/AST and amylase; 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 biliary tree). In acute cholecystitis, HIDA enters BD but not GB. 10–20% false ⊕ (cystic duct obstructed from chronic cholecystitis, lengthy fasting, liver disease).

Treatment

- 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 (*Ann Surg* 2013;258:385)
- 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 (*NEJM* 2015;373:357)
- Intraoperative cholangiogram or ERCP to r/o choledocholithiasis in Pts w/ jaundice, cholangitis or stone in BD on U/S

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

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Choledocholithiasis

Definition

- Gallstone lodged in common bile duct (CBD)

Epidemiology

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

Clinical manifestations

- Asymptomatic (50%)
- RUQ/epigastric pain 2° obstrxn of bile flow → ↑ CBD pressure, jaundice, pruritus, nausea

Diagnostic studies

- Labs: ↑ bilirubin, Aϕ; transient spike in ALT or amylase suggests passage of stone
- RUQ U/S: BD stones seen ~50% of cases; usually inferred from dilated CBD (>6 mm)
- ERCP preferred dx modality when likelihood high; cholangiogram (percutaneous, operative) when ERCP unavailable or unsuccessful; EUS/MRCP to exclude BD stones when suspicion low

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
- Labs: ↑ WBC, bilirubin, Aϕ, amylase; ⊕ 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
- **Acidosis** → process that increases $[H^+]$; **alkalosis** → process that decreases $[H^+]$
- Primary disorders: metabolic acidosis or alkalosis, respiratory acidosis or alkalosis
- Compensation
  - respiratory: hyper- or 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 minutes; renal compensation takes hours to 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, ICa, 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 (*JASN* 2010;21:920)

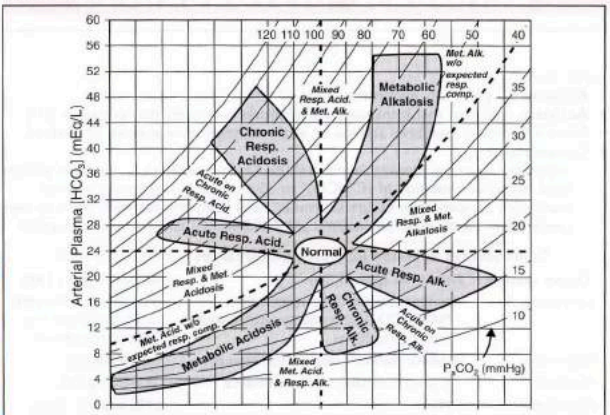
Primary disorder	Expected compensation
Metabolic acidosis	↓ $P_aCO_2 = 1.2 \times \Delta HCO_3$ or $P_aCO_2 = (1.5 \times HCO_3) + 8 \pm 2$ (Winters' formula) (also, P_aCO_2 = last 2 digits of pH)
Metabolic alkalosis	↑ $P_aCO_2 = 0.7 \times \Delta HCO_3$
Acute respiratory acidosis	↑ $HCO_3 = 0.1 \times \Delta P_aCO_2$ (also, ↓ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory acidosis	↑ $HCO_3 = 0.35 \times \Delta P_aCO_2$ (also, ↓ pH = $0.003 \times \Delta P_aCO_2$)
Acute respiratory alkalosis	↓ $HCO_3 = 0.2 \times \Delta P_aCO_2$ (also, ↑ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory alkalosis	↓ $HCO_3 = 0.4 \times \Delta P_aCO_2$

- **Alternative approaches**
  - Base excess/deficit (*Curr Opin Crit Care* 2006;12:569; *Am J Emerg Med* 2016;34:626)
  - Strong Ion Difference or "Stewart Method" (*NEJM* 2014;371:1821)

Mixed disorders (more than 1 primary disorder at the same time)

- If compensation less or greater than predicted, may be 2 disorders:
  - P_aCO_2 too low → concomitant 1° resp. alk.
  - P_aCO_2 too high → concomitant 1° resp. acid.
  - HCO_3 too low → concomitant 1° met. acid.
  - HCO_3 too high → concomitant 1° met. alk.
- Normal pH, *but* . . .
  - ↑ P_aCO_2 + ↑ HCO_3 → resp. acid. + met. alk.
  - ↓ P_aCO_2 + ↓ HCO_3 → resp. alk. + met. acid.
  - normal P_aCO_2 & HCO_3, *but* ↑ AG → AG met. acid. + met. alk.
  - normal P_aCO_2, HCO_3, & AG → no disturbance *or* non-AG met. acid. + met. alk.
- *Cannot* have resp. acid. (hypoventilation) and resp. alk. (hyperventilation) simultaneously

Figure 4-1 Acid-base nomogram



(Adapted from Brenner BM, ed., *Brenner & Rector's The Kidney*, 8th ed., 2007; Ferri F, ed. *Practical Guide to the Care of the Medical Patient*, 7th ed., 2007)

- **ABG vs. VBG:** concordant for pH (~0.04), HCO_3 (~2 mEq) but **not** PCO_2 (~8±17 mmHg) VBG can be used to *screen* for hypercarbia w/ PCO_2 cutoff ≥45 mmHg (100% Se), **but** may not accurately assess *degree* of hypercarbia (*Am J Emerg Med* 2012;30:896).

Metabolic Acidosis

Initial workup (*NEJM* 2014;371:1434)

- ✓ **anion gap** (AG) = $Na^+ - (Cl^- + HCO_3^-)$ = unmeasured anions − unmeasured cations
  - if ↑ glc, use measured *not* corrected Na
  - expected AG is [albumin] × 2.5 (ie, 10 if albumin is 4 g/dL, 7.5 if albumin is 3 g/dL)
  - ↑ AG → ↑ unmeasured anions such as organic acids, phosphates, sulfates
  - ↓ AG → ↓ alb or ↑ unmeasured cations (Ca, Mg, K, Li, bromide, iodide, immunoglobulin)
- If ↑ AG, ✓ **delta-delta** ($\Delta\Delta = \Delta AG/\Delta HCO_3$) to assess if there is an additional metabolic acid-base disturbance; ΔAG = (calculated AG − expected AG), $\Delta HCO_3 = (24 - HCO_3)$
  - $\Delta\Delta$ = 1–2 → pure AG metabolic acidosis
  - $\Delta\Delta$ < 1 → AG metabolic acidosis *and* simultaneous non-AG acidosis
  - $\Delta\Delta$ > 2 → AG metabolic acidosis *and* simultaneous metabolic alkalosis

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	**Diabetes mellitus,** alcoholism, starvation (*NEJM* 2014;372:546)
Lactic acidosis (*NEJM* 2014; 371:2309)	**Type A:** impairment in tissue oxygenation eg, **circulatory or respiratory failure, sepsis,** ischemic bowel, carbon monoxide, cyanide **Type B:** no impairment in tissue oxygenation. ↓ 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 such as phosphates, sulfates, urate, etc.
Ingestions	**Methanol** (windshield fluid, antifreeze, solvents, fuel): metab to formic acid **Ethylene glycol** (antifreeze): metab to glycolic and oxalic acids **Propylene glycol** (pharmaceutical solvent, eg, IV diazepam, lorazepam, and phenobarbital; antifreeze): lactic acidosis **Salicylates:** metabolic acidosis (from lactate, ketones) + respiratory alkalosis due to stimulation of CNS respiratory center **Glutathione depletion:** acetaminophen → ↑ endogenous organic acid 5-oxoproline in susceptible hosts (malnourished, female, renal failure)

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**
- **Osmolal gap** (OG) = measured osmoles − calculated osmoles
  calculated osmoles = (2 × Na) + (glucose/18) + (BUN/2.8)
  (can + [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)
  for methanol/ethylene glycol: early on, OG precedes AG; later OG may be nl with ⊕ AG

Ingestions			
AG	**OG**	**Ingestion**	**Other manifestations**
↑	nl	Acetaminophen	Hepatitis
		Salicylates	Fever, tachycardia, tinnitus; met. acid. + resp. alkalosis
↑	↑	Ethanol	Alcoholic fetor, ΔMS, hepatitis; keto + lactic acidosis ± met. alk. (vomiting)
		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
nl/↑	↑	Isopropyl alcohol	ΔMS, fruity breath (acetone)

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 (*CJASN* 2012;7:671)

- Evaluate history for causes (see above)
- ✓ **urine anion gap** (UAG) = $(U_{Na} + U_K) - U_{Cl}$
  UAG = unmeasured anions − unmeasured cations; as NH_4^+ is primary unmeasured cation, UAG is indirect assay for renal H^+ excretion as NH_4^+ (*NEJM* 1988;318:594)
- ⊖ UAG → ↑ renal NH_4^+ excretion → appropriate renal response to acidemia
  Ddx: GI causes, proximal RTA, ingestions or dilutional
- ⊕ UAG → failure of kidneys to generate NH_4^+
  Ddx: distal or hypoaldo RTA, early renal failure
  nb, plasma K usually ↓ in distal and ↑ in hypoaldo RTA
- UAG evaluation assumes Pt volume replete (U_{Na} >25), U_{pH} <6.5 & no AG met. acidosis (which causes ⊕ UAG due to excretion of organic anions)

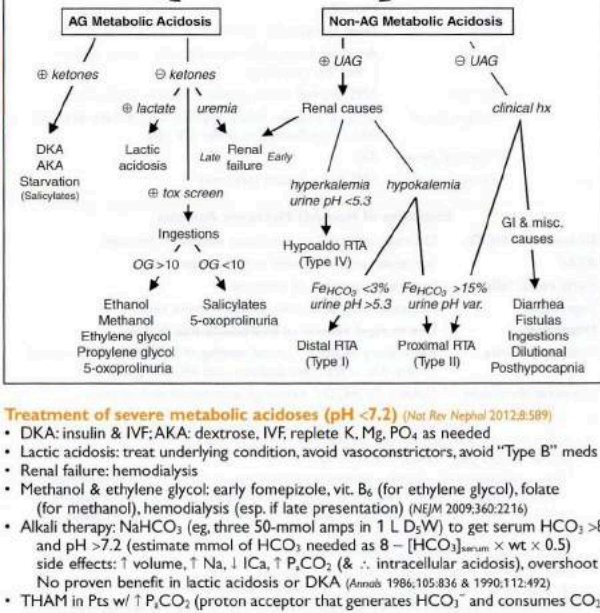
Renal tubular acidoses (RTAs) (*JASN* 2002;13:2160; *Int J Clin Pract* 2011;65:350)

- **Proximal** (Type II): ↓ proximal reabsorption of HCO_3
  1° (Fanconi's syndrome = ↓ proximal reabsorption of HCO_3, PO_4, glc, amino acids), paraprotein (multiple myeloma, amyloidosis), meds (acetazolamide, heavy metals, ifosfamide), renal transplant, ↓ Vit D, NRTIs
- **Distal** (Type I): defective distal H^+ secretion
  1°, autoimmune (Sjögren's, RA), nephrocalcinosis, meds (ampho, Li, ifosfamide); normally a/w ↓ K; if with ↑ K → sickle cell, obstruction, SLE, renal transplant
- **Hypoaldo** (Type IV): ↑ K → ↓ NH_3 synthesis/delivery → ↓ urine acid carrying capacity
  ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV
  normal renin, ↓ aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin
  ↓ response to aldosterone
  meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors
  tubulointerstitial disease: sickle cell, SLE, amyloid, diabetes
- 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**	**UpH**	**Fe_{HCO_3}[b]**	**Serum K**
Proximal	II	Moderate	±	<5.3[a]	>15%	↓
Distal	I	Severe	⊕	>5.3	<3%	↓[c]
Hypoaldo	IV	Mild	⊕	<5.3	<3%	↑

[a]Urine pH will rise above 5.3 in the setting of HCO_3 load
[b]Fe_{HCO_3} 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 Nephol 2012;8:589)*

- DKA: insulin & IVF; AKA: dextrose, IVF, replete K, Mg, PO_4 as needed
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors, avoid "Type B" meds
- Renal failure: hemodialysis
- Methanol & ethylene glycol: early fomepizole, vit. B_6 (for ethylene glycol), folate (for methanol), hemodialysis (esp. if late presentation) *(NEJM 2009;360:2216)*
- Alkali therapy: $NaHCO_3$ (eg, three 50-mmol amps in 1 L D_5W) to get serum HCO_3 >8 and pH >7.2 (estimate mmol of HCO_3 needed as $8 - [HCO_3]_{serum} \times wt \times 0.5$)
  side effects: ↑ volume, ↑ Na, ↓ ICa, ↑ P_aCO_2 (& ∴ intracellular acidosis), overshoot
  No proven benefit in lactic acidosis or DKA *(Annals 1986;105:836 & 1990;112:492)*
- THAM in Pts w/ ↑ P_aCO_2 (proton acceptor that generates HCO_3^- and consumes CO_2)

Metabolic Alkalosis

Pathophysiology

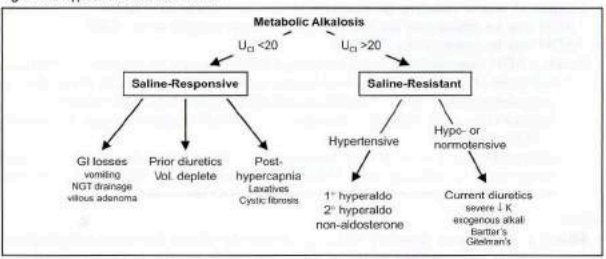
- Saline-responsive etiologies require *initiating event* and *maintenance phase*
- *Initiating event:* gain of HCO_3 or loss of acid
  loss of H^+ from GI tract or kidneys
  exogenous alkali: iatrogenic HCO_3 administration, milk alkali syndrome
  contraction alkalosis: diuresis → excretion of HCO_3-poor fluid → extracellular fluid "contracts" around fixed amount of HCO_3 → ↑ HCO_3 concentration
  posthypercapnia: respiratory acidosis → renal compensation with HCO_3 retention; rapid correction of respiratory disorder (eg, with intubation) → transient excess HCO_3
- *Maintenance phase*
  volume depletion → ↑ proximal reabsorption of $NaHCO_3$ and ↑ aldosterone (see next)
  hyperaldosteronism (either 1° or 2°) → distal Na reabsorption in exchange for K^+ and H^+ excretion (and consequent HCO_3 retention)
  hypokalemia → transcellular K^+/H^+ exchange; intracellular acidosis in renal proximal tubular cells promotes bicarbonate reabsorption and ammoniagenesis

Etiologies of Metabolic Alkalosis	
Saline-responsive	**GI loss of H^+**: vomiting, NGT drainage, villous adenoma **Diuretic use** Posthypercapnia, laxatives, cystic fibrosis
Saline-resistant	*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; exogenous alkali load Bartter's syndrome (loop-like); Gitelman's syndrome (thiazide-like)

Workup

- Check **volume status** and **U_{Cl}**
  - U_{Cl} <20 mEq/L → saline-responsive
  - U_{Cl} >20 mEq/L → saline-resistant (unless currently receiving diuretics)
  - (U_{Na} unreliable determinant of volume status as alkalemia → ↑ HCO_3 excretion → ↑ Na excretion; negatively charged HCO_3 "drags" Na^+ along)
  - If U_{Cl} >20 and volume replete, ✓ **blood pressure**

Figure 4-3 Approach to metabolic alkalosis



Treatment of severe metabolic alkalosis (pH >7.6)

- If volume depletion: d/c diuretics and correct volume deficit with isotonic saline
  If cardiopulmonary disease precludes hydration, can use KCl, acetazolamide, HCl
- If NGT drainage that cannot be stopped: PPI
- Hyperaldosteronism: treat underlying condition

Respiratory Acidosis

Etiologies (also see "Hypercapnia")

- **CNS depression:** sedatives, CNS trauma, O_2 in chronic hypercapnia (↓ hypoxemic drive), central sleep apnea
- **Neuromuscular disorders:** myasthenia gravis, Guillain-Barré, poliomyelitis, ALS, muscular dystrophy, severe hypophosphatemia, high spinal cord injury, drugs (paralytics)
- **Upper airway abnormalities:** acute airway obstruction, laryngospasm, obstructive sleep apnea, esophageal intubation
- **Lower airway abnormalities:** asthma, COPD
- Lung parenchyma abnormalities (often cause hypoxia → ↑ RR → resp. alk., but eventual muscle fatigue → resp. acid.): pneumonia, pulmonary edema, restrictive lung disease
- Thoracic cage abnormalities: pneumothorax, flail chest, kyphoscoliosis
- Post infusion of bicarbonate in acidemic Pt w/ limited ability to ↑ minute ventilation

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Respiratory Alkalosis

Etiologies (*NEJM* 2002;347:43)

- **Hypoxia → hyperventilation:** pneumonia, pulm. edema, PE, restrictive lung disease
- **Primary hyperventilation**
  CNS stimulation, pain, anxiety, fever, trauma, stroke, voluntary
  drugs: salicylates, progesterone, methylxanthines, nicotine
  pregnancy, sepsis, hepatic failure, 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 for secretion: hyperosmolality, ↓↓ effective arterial volume (EAV), angiotensin II
  Action: insertion of aquaporin-2 channels in collecting ducts → passive water reabsorption
  urine osmolality is an indirect functional assay of the ADH-renal axis
  U_{osm} range: 60 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 reabsorption of sodium in exchange for potassium or H^+

HYPONATREMIA

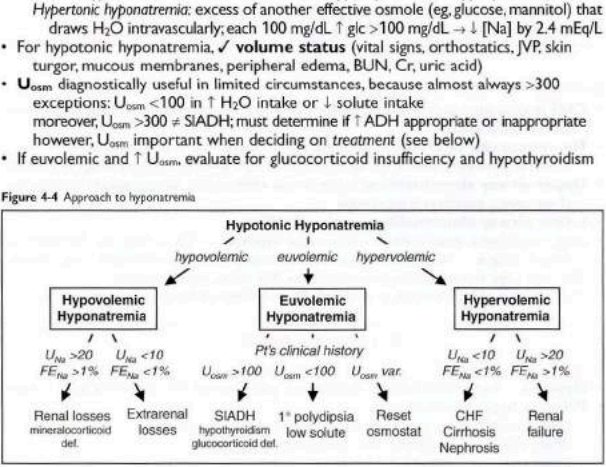
Pathophysiology (*NEJM* 2015;372:1349)

- **Excess of water relative to sodium;** almost always 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 >12 L/d) of free H_2O overwhelms diluting ability of kidney (normal dietary solute load ~750 mOsm/d, minimum U_{osm} = 60 mOsm/L → excrete in ~12 L; if H_2O ingestion exceeds this amount → 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} = 60 mOsm/L → excrete in ~4 L; if H_2O ingestion exceeds this amount → H_2O retention)

Workup (*JASN* 2012;23:1140; *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 hyponatremia most common scenario; true excess of free H_2O relative to Na
  Isotonic hyponatremia: rare lab artifact from hyperlipidemia or hyperproteinemia
  Hypertonic hyponatremia: excess of another effective osmole (eg, glucose, mannitol) that draws H_2O intravascularly; each 100 mg/dL ↑ glc >100 mg/dL → ↓ [Na] by 2.4 mEq/L
- For hypotonic hyponatremia, ✓ **volume status** (vital signs, orthostatics, JVP, skin turgor, mucous membranes, peripheral edema, BUN, Cr, uric acid)
- **U_{osm}** diagnostically useful in limited circumstances, because almost always >300
  exceptions: U_{osm} <100 in ↑ H_2O intake or ↓ solute intake
  moreover, U_{osm} >300 ≠ SIADH; must determine if ↑ ADH appropriate or inappropriate
  however, U_{osm} important when deciding on *treatment* (see below)
- If euvolemic and ↑ U_{osm}, evaluate for glucocorticoid insufficiency and hypothyroidism

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, as loop diuretics ↓ tonicity of medullary interstitium and impair urine concentrating ability), salt-wasting nephropathy, cerebral salt wasting, mineralocorticoid deficiency
- **Extrarenal losses** (U_{Na} <10 mEq/L, FE_{Na} <1%): hemorrhage, GI loss (diarrhea), third-spacing (pancreatitis), ↓ PO intake, insensible losses

Euvolemic hypotonic hyponatremia (ie, ↑ TBW relative to total body Na)

- **SIADH** (euvolemia or mild hypervolemia, **inapprop ↑ U_{osm},** approp U_{Na}, ↓ BUN & UA)
  malignancy: lung, brain, GI, GU, lymphoma, leukemia, thymoma, mesothelioma
  pulmonary: pneumonia, TB, aspergillosis, asthma, COPD, PTX, ⊕ pressure ventilation
  intracranial: trauma, stroke, SAH, seizure, infxn, hydrocephalus, Guillain-Barré synd.
  drugs: antipsychotics, antidepress. (esp. *SSRIs*), chemotherapy, AVP, MDMA, NSAIDs
  miscellaneous: pain, nausea, postoperative state
- **Endocrinopathies:** ↑ ADH activity seen in *glucocorticoid deficiency* (co-secretion of ADH & CRH) and *severe hypothyroidism/myxedema coma* (↓ CO & ↓ GFR)
- **Psychogenic polydipsia** (U_{osm} <100, ↓ uric acid): usually requires intake >12 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 → activation of RAAS → ↑ aldosterone *and* ↑↑ ADH
- **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 (*Crit Care* 2013;17:206; *NEJM* 2015;372:55)

- **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 of ↑ Na *should not exceed 6* (chronic) to *8* (acute) mEq/L/d to avoid central pontine myelinolysis/osmotic demyelination syn. (CPM/ODS: paraplegia, dysarthria, dysphagia)
  If severe (<120) or neuro sx: consider 3% NaCl + dDAVP (to prevent rapid overcorrection) in consultation w/ nephrology (*AJKD* 2013;61:571)
- **Frequent lab draws** and **IVF rate adjustments** are cornerstones of treatment
- **Overly rapid correction:** can lead to CPM/ODS. Should be emergently reversed w/ dDAVP ± D_5W; partial neurologic 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 entire infusate retained *without any output of Na or H_2O*
if Pt euvolemic, as in SIADH, infused Na will be excreted
eg, 1 L NS (154 mEq of Na or 308 mOsm of solute in 1 L free H_2O) given to Pt with SIADH with U_{osm} = 616 → 308 mOsm solute excreted in 0.5 L H_2O →
net gain 0.5 L H_2O → ↓ $[Na]_{serum}$
∴ normal saline can *worsen* hyponatremia from SIADH if U_{osm} > $infusate_{osm}$

- **Hypovolemic hyponatremia:** volume repletion with normal saline at a **slow rate.**
  Once volume replete → stimulus for ADH removed (w/ very short ADH $t_{1/2}$) → kidneys excrete free H_2O → serum Na will correct rapidly (D_5W ± ddAVP if overcorrection)
- **SIADH** (*NEJM* 2007;356:2064; *AJKD* 2015;65:435): **free water restrict** + treat underlying cause
  hypertonic saline (± loop diuretic) if sx or Na fails to ↑ w/ free H_2O 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: particularly if chronic and no CHF
  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**
  mobilize excess Na & H_2O (use loop diuretics; avoid thiazides) & ↑ EAV (vasodilators to ↑ CO in CHF, colloid infusion in cirrhosis)
  aquaresis: vaptans sometimes used; however, no proven mortality benefit, hypoNa recurs after stopping drug, risk of overcorrection, contraindicated in cirrhosis, and expensive (*NEJM* 2015;372:2207)

HYPERNATREMIA

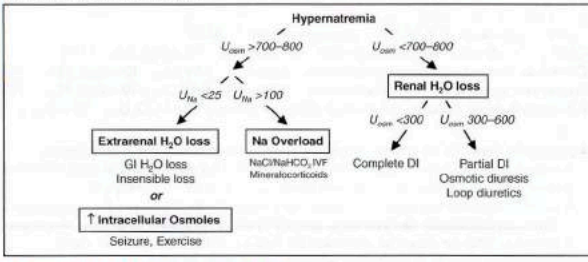
Pathophysiology (Crit Care 2013;17:206; NEJM 2015;372:55)

- 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
- ***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

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
- **Insensible loss:** fever, exercise, ventilation

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, tumors, infiltrative/IgG4); also idiopathic, hypoxic encephalopathy, anorexia, EtOH
  Nephrogenic (*Annals* 2006;144:186)
  congenital (ADH receptor V2 mutation, aquaporin-2 mutation; *Ped Nephrol* 2012;27:2183)
  drugs: **lithium,** amphotericin, demeclocycline, foscarnet, cidofovir
  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

- **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):

$$\text{Free } H_2O \text{ deficit (L)} = \frac{[Na]_{serum} - 140}{140} \times TBW$$

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) = $([Na]_{serum} - 140)/3$

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

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 ↓ of Na should not exceed 0.5 mEq/L/h** to avoid cerebral edema
  shortcut: 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

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

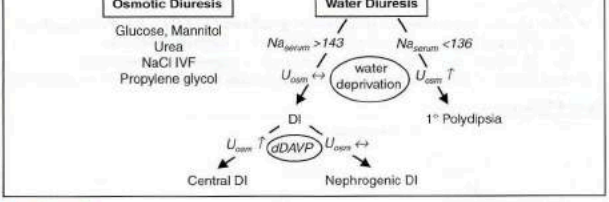
Osmotic diuresis

- Etiologies
  Glucose (uncontrolled diabetes mellitus)
  Mannitol
  Urea: recovering AKI, ↑ protein feeds, hypercatabolism (burns, steroids), GI bleed
  NaCl administration
  Propylene glycol

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 μg 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

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)
  nephrogenic DI: treat underlying cause if possible; Na restriction + thiazide (mild volume depletion → ↓ delivery of filtrate to dysfunctional diluting segment of kidney), consider amiloride for lithium-induced DI (*Kid Int* 2009;76:44)
  pregnancy-induced DI: due to vasopressinase from placenta, ∴ Rx w/ dDAVP

POTASSIUM HOMEOSTASIS

Overview (*NEJM* 2015;373:60)

- Renal: potassium excretion regulated at **distal nephron** (collecting tubule)
  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 ($U_{K:Cr}$ <20 mEq/g)

- Alkalemia, insulin, catecholamines, hypokalemic/thyrotoxic periodic paralysis, acute ↑ in hematopoiesis (megaloblastic anemia Rx w/ B_{12}, AML crisis), hypothermia, chloroquine, barium/cesium intoxication, antipsychotic overdose (risperidone, quetiapine)

GI potassium losses (U_K <25 mEq/d, $U_{K:Cr}$ <20 mEq/g, TTKG <3)

- 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 >30 mEq/d, ? $U_{K:Cr}$ >20 mEq/g, TTKG >7)

- Hypotensive or normotensive
  acidosis: DKA, RTA [proximal RTA (type II) and some distal RTAs (type I)]
  alkalosis: diuretics, vomiting/NGT drainage (via 2° hyperaldosteronism)
  Bartter's syndrome (loop of Henle dysfxn → furosemide-like effect; *NEJM* 1999;340:1177)
  Gitelman's syndrome (distal convoluted tubule dysfxn → thiazide-like effect)
  ↓ Mg: ? release Mg-mediated inhib. of ROMK channel ∴ ↑ K secretion (*JASN* 2007;18:2649)
- 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, exogenous mineralocort., licorice, congenital adrenal hyperplasia)

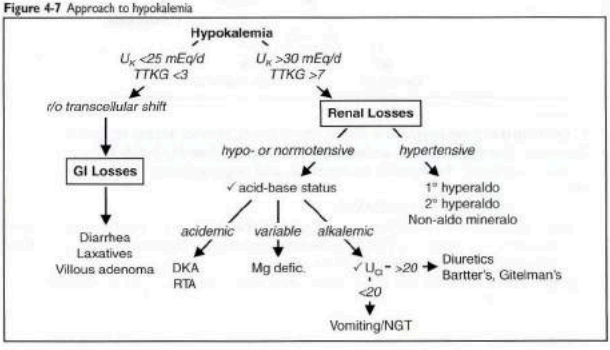
Clinical manifestations

- Nausea, vomiting, ileus, weakness, muscle cramps, rhabdomyolysis, polyuria
- ECG: can have no Δs, U waves, ↑ QT interval, ventricular ectopy (PVCs, VT, VF)

Workup (*Nat Rev Neph* 2011;7:75)

- Rule out transcellular shifts
- ✓ 24-h $\mathbf{U_K}$ and **transtubular potassium gradient** (TTKG) = $(U_K/P_K)/(U_{osm}/P_{osm})$
  U_K >30 mEq/d, ? $U_{K:Cr}$ >20 mEq/g, or TTKG >7 → suggests renal loss
  U_K <25 mEq/d, $U_{K:Cr}$ <20 mEq/g, or TTKG <3 → suggests extrarenal loss
- If renal losses, ✓ **BP, acid-base, $\mathbf{U_{Cl}}$** (U_{Na} unreliable for volume status w/ alkalemia)

Figure 4-7 Approach to hypokalemia



Treatment

- *If true potassium deficit:* **potassium repletion** (↓ 1 mEq/L ≈ 200 mEq total body loss) KCl 40 mEq PO q4–6h if nonurgent, KCl 10 mEq/h IV if urgent, recheck K freq
- Beware of excessive potassium repletion if transcellular shift cause of hypokalemia
- Treat underlying cause (if hydration needed, avoid dextrose-containing solutions as dextrose → ↑ insulin → intracellular potassium shifts)
- Replete low Mg: IV $Mg\text{-}SO_4$ 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 defic. (DM), β-blockers, dig intox. (blocks Na-K ATPase), massive cellular release (tumor lysis, rhabdo, ischemic bowel, hemolysis, transfusions, resorbing hematomas, hyperthermia, rewarming), hyperkalemic periodic paralysis, succinylcholine

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: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV
  normal renin, ↓ aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin
  ↓ 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
- ECG: peaked T waves, ↑ PR interval, ↑ QRS width, loss of P wave, sine wave pattern, PEA/VF (ECG: low sensitivity, cardiac arrest can be first electrical manifestation!)

Workup (*Crit Care Med* 2008;36:3246)

- Rule out pseudohyperkalemia (IVF with K, hemolysis during venipuncture, ↑ plt or WBC)
- Rule out transcellular shift
- **Assess GFR,** if normal, then consider ↓ distal Na delivery and urine flow. ✓ transtubular K gradient (TTKG) = $(U_K/P_K)/(U_{osm}/P_{osm})$ <6 c/w hypoaldo (*JASN* 2006;19:424).

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 10 U IV + 1–2 amps $D_{50}W$	15–30 min	transient effect (30–60 min) drives K into cells
Bicarbonate (esp. if acidemic)	1–2 amps IV	15–30 min	transient effect (60 min) exchange K for H^+ in cells
β2 agonists	albuterol 10–20 mg inh. or 0.5 mg IV	30–90 min	transient effect (~2 h) drives K into cells
K-binding resins	Kayexalate[b] 30–90g PO/PR ? Na zirconium 1.25–10 g/tid PO Patiromer 8.4–25.2 g/d PO	hrs hrs hrs-d	exchange K for cations in gut (Na, Ca, H); ↓ total body K; (*NEJM* 2015;372:211 & 222)
Diuretics	furosemide ≥40 mg IV	30 min	↓ total body K
Hemodialysis			↓ total body K

[a]Calcium chloride contains more calcium and is typically reserved for use in codes (↑ risk of tissue necrosis)
[b]? rare a/w intestinal necrosis esp. with postoperative ileus or obstructive bowel disease (*AJKD* 2012;60:409)

- *Rate of onset* important to note when establishing a treatment plan
- Calcium helps prevent/treat cardiac complications; ∴ should be initial Rx, esp. if ECG Δs
- Insulin, bicarbonate (esp. if acidemic), and β2 agonists should follow to ↓ plasma K
- Treatments that **eliminate total body K essential,** as other Rxs will wear off with time; Kayexalate or Na zirconium ± diuretics may be effective in many cases, but emergent hemodialysis should be considered in life-threatening situations
- Patient information for diet education: http://www.kidney.org/atoz/content/potassium.cfm

Acute Kidney Injury (AKI)

Definition (*CJASN* 2008;3:844; *KI Suppl* 2012;2:19)

- AKI: abrupt (<48 h) ↑ Cr ≥0.3 mg/dL, ↑ Cr ≥50%, or UOP <0.5 mL/kg/h for ≥6 h
  additional gradations based on further ↑ Cr & ↓ UOP but not used clinically
- *Cannot* estimate GFR using Cr in setting of AKI or Δ'ing Cr (requires steady state)

Workup (*NEJM* 2007;357:797; *Lancet* 2012;380:756)

- **H&P:** recent procedures & meds; thirst; VS & vol status; s/s of obstruction, vasc or systemic dis.; ischemia (prerenal & ATN) accounts for >50% of in-hospital AKI
- **Urine evaluation:** output, urinalysis, **sediment,** electrolytes, and osmolality
- **Fractional excretion of sodium (FE_{Na})** = $(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$
  <1% → prerenal, contrast, HRS or glomerulonephritis; >2% → ATN
  In setting of diuretics. ✓ $FE_{UN} = (U_{UN}/P_{UN})/(U_{Cr}/P_{Cr})$; <35% → prerenal
- Renal U/S or CT: r/o obstruction & eval kidney size to estimate chronicity of kidney disease
- Serologies (if indicated): see "Glomerular Disease"
- Renal biopsy (light microscopy, IF, and EM): may be necessary if etiology remains unclear (esp. if hematuria and/or proteinuria). Relative contraindications: SBP>150, ASA/NSAID or anticoag use. Consider dDAVP (0.3 μg/kg 30–60 min prior) for severe uremia.

Etiologies and Diagnosis of Acute Kidney Injury (*Lancet* 2012;380:756)

	Etiologies	U/A, Sediment, Indices
Prerenal	↓ **Effective arterial volume** (*NEJM* 2007;357:797) Hypovolemia, ↓ cardiac contractility (eg, CHF), systemic vasodilatation (eg, sepsis)	Bland Transparent hyaline casts FE_{Na} <1%
	Renal vasoconstriction: NSAIDs, ACEI/ARB, contrast, calcineurin inhib., HRS, hyperCa	BUN/Cr >20 U_{Na} <20
	Large vessel: RAS (bilateral + ACEI), vasculitis, dissection, abd compartment synd., renal venous congestion, VTE	U_{osm} >500
Intrinsic	**Acute tubular necrosis (ATN)** *Ischemia:* progression of prerenal disease *Toxins* Drugs: AG, amphotericin, cisplatin, HES (starch) Pigments: Hb, myoglobin (*NEJM* 2009;361:62) Monoclonal: Ig light chains (*Blood* 2010;116:1397) Crystals: UA, ACV, MTX, indinavir, oral $NaPO_4$ *Contrast-induced AKI (CIAKI):* ↓ RBF + toxin	Pigmented granular muddy brown casts in ~75% (± in CIAKI) ± RBCs & protein from tubular damage FE_{Na} >2%, BUN/Cr <20, U_{Na} >20 (except pigment, CIAKI) U_{osm} <350
	Acute interstitial nephritis (AIN) *Allergic:* β-lactams, sulfa drugs, NSAIDs, PPIs *Infection:* pyelonephritis, 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, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	± RBCs ⊕ urine eos in chol emboli
	Glomerulonephritis (see "Glomerular Disease")	Dysmorphic RBCs, RBC casts
Post	**Bladder neck:** BPH, prostate cancer, neurogenic bladder, anticholinergic meds	Bland ± nondysmorphic RBCs
	Ureteral (bilateral or unilateral in single kidney): malig, LAN, retroperitoneal fibrosis, nephrolithiasis	FE_{Na} variable

General treatment (*CJASN* 2008;3:962)

- Prerenal: isotonic IVF ≈ alb (*NEJM* 2004;350:22), HES (starch) nephrotoxic (*NEJM* 2012;367:124)
- Avoid nephrotoxic insults; review dosing of renally cleared drugs
- Optimize hemodynamics (both MAP & CO)
- *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: generally hyperkalemia; occasionally hypercalcemia, tumor lysis

Intoxications (http://www.extrip-workgroup.org/): contact Poison Control (1-800-222-1222)
Indicated for: methanol, ethylene glycol, metformin, Li, valproic acid, salicylates, barbiturates, theophylline, thallium
Also consider for: carbamazepine, acetaminophen, dig (also give Digibind), dabigatran (also give idarucizumab)
Overload of volume (CHF)
Uremia: pericarditis, encephalopathy, bleeding

- Data on benefit of early RRT remains mixed (*NEJM* 2016;375:122 & *JAMA* 2016;315:2190)

Disease-Specific Management

Cardiorenal syndrome (CRS) (*Nat Rev Neph* 2009;5:641 & 2013;9:99; *CJASN* 2013;8:1800)

- 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)
- Treatment: **IV loop diuretics** (bypass potential gut edema; see below for dosing); no diff. between high vs. low dose and bolus vs. gtt (*NEJM* 2011;364:797). No clinical benefit with vaptans (ADH receptor antag; *JAMA* 2007;297:1319), dopamine or nesiritide (*NEJM* 2011;365:32; *JAMA* 2013;310:2533), or ultrafiltration (*NEJM* 2012;367:2296).
- Prognosis: 7% ↑ mortality a/w each 10 mL/min ↓ eGFR in ADHF (*JACC* 2006;47:1987)

Contrast-induced acute kidney injury (CIAKI); (*Circ* 2015;132:1931)

- Risk factors: CKD, DM, CHF, age, hypotension, ↑ contrast volume (*JACC* 2004;44:1393)
- Clinical: AKI w/in 48 h of contrast exposure, peaks in 3–5 d, resolves in 7–10 d (if does not resolve, consider cholesterol emboli or other etiology)
- Prevention: consider when eGFR <60 or diabetes (*CJASN* 2013;8:1618)
  Isotonic IV fluids (unless contraindic, eg, CHF)
  Outpatients: 3 mL/kg/h × 1 h before, 1–1.5 mL/kg/h × 6 h after (*JAMA* 2004;291:2328)
  Inpatients: 1 mL/kg/h × 6–12 h before, during, and 6–12 h after;
  if undergoing cardiac cath, consider rate of IVF based on LVEDP:
  5, 3, or 1.5 mL/kg/h if LVEDP <13, 13–18, or >18 mmHg (*Lancet* 2014;383:1814)
  $NaHCO_3$ similar to NaCl (*CJASN* 2015;10:1519).
  Hold ACEI/ARB (*AJKD* 2012;60:576). NSAIDs, diuretics. ? high-dose statin (*Circ* 2012;126:3008)
  Minimize contrast volume and use iso-osmolar contrast (*JACC* 2006;48:692)
  N-acetylcysteine 600–1200 mg PO bid on day prior to & day of contrast; benefit in some but not all studies (*Annals* 2016;164:406); as safe, reasonable to consider in high-risk Pts
  No proven benefit to Ppx RRT in addition to above, may be harmful (*Am J Med* 2012;125:66)
- Gadolinium: can cause AKI in stage IV CKD (*Neph Dial Trans* 2006;21:697), no effective Ppx
  Nephrogenic systemic fibrosis: fibrosis of skin, joints, eyes, and internal organs –2–4 wk post exposure in Pts w/ mod-severe CKD (*JACC* 2009;53:1621). Postgado HD encouraged albeit no data. Physical therapy. Can be irreversible.

Hepatorenal syndrome (HRS; see "Cirrhosis"; *AJKD* 2013;62(6):1198)

- Albumin + either octreotide & midodrine or IV vasopressors

Rhabdomyolysis (*NEJM* 2009;361:62)

- Multifactorial 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)
- Generally low risk of AKI when CK <5000, but correlation imperfect. Rhabdo & risk of AKI/death calculator: http://www.brighamandwomens.org/research/rhabdo/default.aspx
- Aggressive IVF resuscitation and augmenting UOP (tailor IVF to target UOP ~3 mL/kg and ensure ↓ CK). If urine pH <6.5, can consider $NaHCO_3$ solutions and watching pH.
  ✓ K & Ca frequently. Monitor for compartment syndrome.

Acute interstitial nephritis (AIN; *KI* 2008;73:940 & 2010;77:956)

- Commonly drug-induced: β-lactams, sulfa drugs, NSAIDs, PPIs
- If suspected, prompt removal of offending drug, consider early steroids w/in 7 d of dx

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

Obstructive diseases

- Dx: imaging w/ renal U/S if undifferentiated or abd/pelvic CT (I^-) if suspect nephrolithiasis
- Treatment: Foley catheter vs. percutaneous nephrostomy for decompression
- Following decompression, at risk of:
  Hypotonic diuresis (2° buildup of BUN, tubular damage); Rx w/ IVF (eg, ½ NS)
  Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly

Chronic Kidney Disease (CKD)

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

- ≥3 mo of **reduced GFR** (<60) *and/or* **kidney damage** (path, markers, imaging)
- Prevalence 13% in U.S.

- Cr poor estimate of GFR, use equation (www.kidney.org/professionals/KDOQI/gfr_calculator.cfm) CKD-EPI preferred over MDRD as 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), congenital, drugs, myeloma, progression of AKI (*JAMA* 2009;302:1179)
- Presence and degree of albuminuria a/w worse outcomes independent of GFR
- Rates of all-cause mortality and CV events increase with each stage of CKD & albuminuria and are greater than rate of progression to kidney failure (*NEJM* 2004;351:1296)

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

Albuminuria stage based on albuminuria (mg/d) or spot urine alb (μg) to Cr (mg) ratio: nl or mildly ↑ (<30); mod ↑ or microalbuminuria (30–299); or severely ↑ or macroalb (≥300)

Signs and Symptoms of Uremia (*NEJM* 2007;357:1316)	
General	Nausea, anorexia, malaise, fetor uremicus, metallic taste, susceptibility to drug O/D, decreased temperature
Skin	Uremic frost (white crystals in & on skin), pruritus, calciphylaxis, NSF
Neurologic	Encephalopathy (Δ MS, ↓ memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
Cardiovascular	Pericarditis, accelerated atherosclerosis, hypertension, hyperlipidemia, volume overload, CHF, cardiomyopathy (esp. LVH)
Hematologic	Anemia, bleeding (due to platelet dysfunction and Epo deficiency)
Metabolic	↑ K, ↑ PO_4, acidosis, ↓ Ca, 2° hyperparathyroidism, osteodystrophy

Complications & treatment (*Annals* 2009;150:ITC2-1; *NEJM* 2010;362:57)

- **General:** nephrology referral when GFR <30 and access planning (avoid subclavian lines; preserve an arm for access by avoiding blood draws, BP measurements, IVs); Rx CV risk factors (eg, smoking, LDL-C; *Lancet* 2011;377:2181), vaccines (flu, PNA, HBV)
- **Dietary restrictions:** Na (if HTN), K (if oliguric or hyperkalemic), PO_4, ? moderate protein restriction, strict glc control in DM, avoid herbal and unknown OTCs
- **BP Control:** goal <130/80, ? <120/80 if tolerated (*NEJM* 2015;373:2103); start w/ ACEI (or ARB), effective in DM & nondiabetic CKD (*NEJM* 2004;351:1952); no benefit of ACEI + ARB combined and a/w adverse outcomes (*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** (qv)
- **Anemia:** goal Hb ~10 g/dL, worse outcomes if target higher (*NEJM* 2009;361:2019) epoetin (start 80–120 U/kg SC, divided 3×/wk) or darbepoetin (0.45 μg/kg q wk) 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	150–300

  phosphorus binders (*take with meals!*) (*NEJM* 2010;362:1312)
  - if ↑ PO_4 and ↓ Ca → calcium acetate (PhosLo) or calcium carbonate
  - if refractory ↑ PO_4 or in setting of ↑ Ca → sevelamer (Renagel), lanthanum (Fosrenol)
  - 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) before adding 1,25-(OH)D analogue (paricalcitol); stop if ↑ Ca (*AJKD* 2009;53:408)
  - cinacalcet (parathyroid calcium-sensing receptor agonist) if ↑ PTH despite phosphorus binders ± vit. D analogue (*CJASN* 2016;11:161); consider parathyroidectomy
- **Calciphylaxis** (calcific uremic arteriopathy):
  - Pathophys: calcification of media of small- to med-sized blood vessels of dermis & SC fat → ischemia and skin necrosis w/ *painful* lesions (*NEJM* 2007;356:1049)
  - Risk Factors: uremia in ESRD (↑ PO_4, ↑ Ca, ↑ PTH), ♀>♂,DM, obesity, warfarin
  - Diagnosis: skin bx gold standard; bone scan used in support of dx

Treatment: multidisciplinary wound care, manage hyperPTH, avoid vit D & Ca suppl., IV & intralesional Na thiosulfate, cinacalcet; NOAC rather than warfarin
Prognosis: a/w 60% 1-y mort. in ESRD Pts (*AJKD* 2015;66(1):133)

- **Transplant evaluation**

Diuresis

General considerations

- Increases Na 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* 1998;339:387)

- **Drugs:** furosemide (Lasix), torsemide, bumetanide (Bumex), ethacrynic acid
- **Mech:** inhib Na-K-2Cl transporter in thick ascending limb (ThAL); 20–25% Na reabsorp.
  Transient, immediate venodilation may aid in pulmonary congestion (*NEJM* 1973;288:1087)
  Response is fxn of amt of drug excreted; ∴ ↑ dose needed in renal insufficiency, CHF
  Sigmoidal dose response curve; ∴ ↑ dose until induce diuresis, ↑↑ dose beyond that point yields diminishing returns compared with ↑ frequency of dosing
- **Dosing:** PO bioavailability of furosemide ~50%, ∴ IV dose ~2× as potent as PO dose
  torsemide & bumetanide ~90% bioavailability; use ethacrynic acid if sulfa allergy
  40 mg furosemide PO ≈ 20 mg furosemide IV ≈ 20 mg torsemide PO ≈ 1 mg bumetanide
  dose furosemide bid-qid; qd dosing can lead to initial diuresis → antinatriuresis
  Continuous vs. bolus IV: similar results in acute CHF (*NEJM* 2011;364:797)
  ? ↑ diuresis w/ co-administration of albumin if ↓ serum albumin (*Crit Care Med* 2005;33:1681)

Thiazide diuretics (*NEJM* 2009;361:2153)

- **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 prior to loop diuretic, typically ~30 min before

K-sparing diuretics

- **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.

Approach to Diuresis (if inadequate diuresis, go to next step)

Step	Action
1	**Loop diuretic PO:** ✓ response at 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 needed w/ ↑ Cr; initial effective IV Lasix dose ≈ 30 × Cr (ie, if Cr = 4 → 120 mg IV lasix)
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) + 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

Adverse effects

- Loop: ± ↑ Na, ↓ K, ↓ Mg, ↓ Ca, hyperuricemia, ototoxicity, hypersensitivity (sulfa)
- Thiazide: ↓ Na, ↓ K, ↓ Mg, ↑ Ca, hyperlipidemia, pancreatitis, ↑ glucose, hypersensitivity
- K-sparing: ↑ K (esp. w/ ACEI), metabolic acidosis, gynecomastia (spironolactone)

Renal Replacement and Dialysis

General

- Substitutes for renal solute and fluid removal
- Acute indications: see "AKI"; choices CVVH vs HD
- Chronic indications: time of RRT initiation should factor in Pt QoL, uremic sx, risk of development of urgent/acute indications; choices PD vs. HD

Hemodialysis (HD) (*NEJM* 2010;363:1833)

- Physiology: blood flows along one side of *semipermeable* membrane, dialysate along other
  Fluid removal (ie, Na + H_2O) via transmembrane pressure (TMP) gradient

Solute removal via transmembrane concentration gradient and inversely proportional to size (∴ effective removal of K, urea, and Cr, but not PO_4)

- Typical orders: duration, volume removal goals, K and Ca in dialysate bath, anticoagulation
- 6× vs. 3×/wk improved HTN, LV mass, QoL, but ↑ vasc issues (*NEJM* 2010;363:2287); w/ 3×/wk HD, ↑ adverse outcomes after 2-d interval (*NEJM* 2011;365:1099)
- Complications: HoTN, arrhythmia, access issues (clot, stenosis, infxn, recirculation), disequilibrium syndrome (sx of cerebral edema due to H_2O shifts after removal of plasma urea during dialysis, esp. in new HD Pts w/ ↑↑ BUN), high-output HF
- Fever w/ catheter: empiric abx (vanc + GNR coverage qHD). GPC > GNR > mixed/fungal. Catheter removal, replacement, or "lock" abx. Consider metastatic infxn w/u (*AJKD* 2004;44:779; *JASN* 2014;25:2927).

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)

- Physiology: *hemofiltration* rather than dialysis. Blood under pressure passes down one side of *highly permeable* membrane allowing H_2O and solutes to pass across membrane via TMP gradient (convective clearance). Filtrate discarded. Replacement fluid infused (solute concentrations similar to plasma, except no urea, Cr, PO_4). Fluid balance precisely controlled by adjusting filtrate/replacement fluid.
- Access: double-lumen central venous catheter
- Typical orders: volume goals, replacement fluid buffer: **HCO_3** (requires heparin to prevent machine from clotting, although can be run heparin-free) **vs. citrate** [hepatically metabolized (∴ cannot be given in cirrhosis/liver failure) to HCO_3; provides anticoagulation w/in machine via Ca chelation]
- Complications: hypotension, ↓ PO_4, access complications; ↓ ICa (citrate toxicity in Pts with hepatic dysfunction → look for ↓ ICa but normal/ ↑ serum Ca and AG met acidosis)
- Potential advantages over HD: less hypotension, better volume control, removal of inflammatory mediators; however, no survival advantage (*Lancet* 2006;368:379)
- No advantage for high-intensity CVVH over standard intensity (*NEJM* 2008;359:7)

Peritoneal dialysis (PD) (*Perit Dial Int* 2001;21:25; *Perit Dial Int* 2009;29:S59)

- Physiology: peritoneum acts as membrane. Fluid balance controlled by choosing dialysate [glucose] (higher concentrations pull more fluid into peritoneum); longer dwell times pulls first more and then less fluid as glc equilibrates across peritoneum
- Access: permanent catheter inserted in OR
- Typical orders for CAPD (continuous ambulatory peritoneal dialysis):
  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
- Can use overnight cycler device that infuses & drains more rapidly, with shorter dwells, while Pt sleeps. Called automated or continuous cycling peritoneal dialysis (APD, CCPD).
- Complications: hypoalbuminemia; right-sided pleural effusion
  Peritonitis: abd pain, tenderness, cloudy drainage (WBC >100 and >50% PMNs)
  spectrum: 60–70% GPC, 15–20% GNR, remainder no bacteria or fungal
  Rx: abx IV or in PD, catheter removal for certain pathogens (eg, yeast, *Pseudomonas*)
  Hyperglycemia: exacerbated by inflammation, long dwell times, and higher [glucose]

Kidney transplantation (*Med Clin N Am* 2016;100:435)

- Rx of choice for ESRD; contraindic: active malig, infxn, ischemia, noncompl, subst use
- Immunosupp.: calcineurin inhib (tacrolimus, CsA) or CTLA4 inhib (*NEJM* 2016;374:333), antimetabolite (AZA, MMF), prednisone, ± mTOR inhibitor (sirolimus) (*NEJM* 2004;351:2715)
- Late renal dysfxn: usual AKI causes + calcineurin tox, rejection (*NEJM* 2010;363:1451), BK virus, recurrence of 1° disease; usual w/u + immunosupp levels, BK virus load, U/S, then bx if no other cause (*CJASN* 2008;3:S56; *CJASN* 2011;6:1774)
- ↑ risk of infxn (incl opportunistic such CMV, JC, BK viruses; *CJASN* 2012;7:2058) & malignancy (incl PTLD)
- ↑ CVD risk due to HTN (calcineurin inhib, RAS), DM & dyslipidemia (immunosupp meds)

GLOMERULONEPHRITIS (GN)

Definition (*Lancet* 2016;387:2036)

- *Pathologically:* intraglomerular inflammation (ranging from focal proliferative [<50% of glomeruli] to diffuse proliferative to crescentic) (*Lancet* 2006;368:404)
- *Clinically:* hematuria w/ dysmorphic RBCs or RBC casts, ± subnephrotic proteinuria often w/ AKI, HTN, edema
- *Progression:* acute GN = days; rapidly progressive GN (RPGN) ~6 wks; chronic GN ≈ mos; can simply have asx hematuria
- Crescentic GN (pathologic description) ≈ RPGN (clinical description)

ANCA ⊕ Vasculitis (pauci-immune, minimal staining) ~40–45% of total

Pathogen:? bacterial infxn, drugs (hydral, allopurinol, contam cocaine) (*CJASN* 2011;6:2799)

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 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

Anti-GBM Disease (linear staining) <15% of total

Disease	Glomerulonephritis	Pulm hemorrhage	Anti-GBM
Goodpasture's	⊕	⊕	⊕
Anti-GBM disease	⊕	—	⊕

Immune Complex (IC) Disease (granular staining) ~40–45% of total	
Renal-limited diseases	**Systemic diseases**
Infection-related GN (*Staph* & *Strep*; ↓ C3, ± ASLO)	**SLE** (⊕ ANA, ⊕ anti-dsDNA, ↓ C3, ↓ C4)
Membranoproliferative GN (MPGN) (↓ C3)	**Cryoglobulinemia** (⊕ cryocrit, ⊕ RF, ⊕ HCV, SPEP, ↓ C3, ↓ C4)
Fibrillary and Immunotactoid GN (normal C3)	**Endocarditis** (fever, ⊕ BCx, valvular disease, ↓ C3)
IgA nephropathy (normal C3) (*NEJM* 2013;368:2402)	**Henoch-Schönlein purpura** (IgA nephropathy + systemic vasculitis w/ IgA deposits, nl C3)

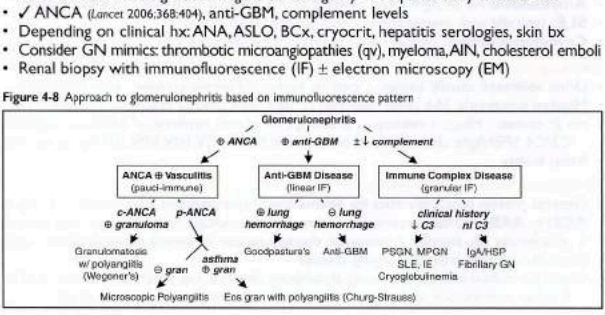
Oncology-related glomerulopathy (*Kid Int* 2013;84:34; *CJASN* 2012;7:1701)

- 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)

Workup (*Archives* 2001;161:25; *AJKD* 2014;63(4):656)

- *Acute GN/RPGN ± lung hemorrhage is an emergency* → requires early Dx and Rx
- ✓ ANCA (*Lancet* 2006;368:404), anti-GBM, complement levels
- Depending on clinical hx: ANA, ASLO, BCx, cryocrit, hepatitis serologies, 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 (*Kid Int Sup* 2012;2:143; *AJKD* 2014;63(4):656)

- 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 (*JASN* 2010;21:2028)
- ANCA ⊕ or anti-GBM: pulse steroids + CYC (or rituximab) ± plasma exchange (*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 hematuria 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* 2006;17:813)

IgA nephropathy (*NEJM* 2013;368:25; *KI Suppl* 2012;2:143; *CJASN* 2014;9:617)

- 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 (30–40%), chronic GN (10%), nephrotic syndrome (5%), RPGN (<5%)
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: 20–40% will reach ESRD w/in 20 y of presentation
- Rx: ACEI/ARB (*JASN* 1999;10:1772); steroids if proteinuria (*JASN* 2012;23:1108; *NEJM* 2015;373:2225); ± cytotoxic Rx for crescentic GN & nephrotic sx, consider for prog. chronic GN

Nephrotic Syndrome

Definition (*NEJM* 1998;338:1202)

- *Pathologically:* abnormal glomerular podocyte permeability to protein
- *Clinically:* proteinuria >3.5 g/d, albumin <3.5 g/dL, edema, ↑ cholesterol, hypertension

Primary glomerular diseases (grouped by pathology)

- **Focal segmental glomerulosclerosis** (40%; *NEJM* 2011;365:2398): 1° (? ↑ soluble urokinase receptor; *Nat Med* 2011;17:952), HIV (collapsing variant), NSAIDs, lymphomas, pamidronate, heroin, congenital, ↑ filtration from prior nephron loss, obesity, vesicoureteral reflux, anabolic steroids, *ApoL1* mutation in AA (*JASN* 2015;26:1443)
- **Membranous nephropathy** (30%; *CJASN* 2014;9:609; *Lancet* 2015;385:1983): idiopathic (auto Ab to phospholipase A_2 or thrombospondin; *NEJM* 2009;361:11 & 2014;371:2277), infxn (esp. HBV, also HCV, syphilis), autoimmune (eg, SLE), carcinomas, drugs (NSAIDs, penicillamine)
- **Minimal change disease** (20%, more common in children; *NDT* 2003;18:vi52) idiopathic, NSAIDs, Hodgkin's disease, & other lymphoproliferative disorders
- **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-med (rare); abnl C3 convertase activity, dense deposit dis, C3GN
- **Fibrillary-immunotactoid glomerulopathy** (1%; *Kid Int* 2003;63:1450)
- **Mesangial proliferative GN** (? atypical forms of MCD/FSGS, 5%) IgM, C1q nephropathy

Systemic diseases with secondary glomerular involvement

- **Diabetes mellitus:** nodular glomerulosclerosis (Kimmelstiel-Wilson lesion); large kidneys hyperfiltration → microalbuminuria → dipstick ⊕ → nephrotic range (10–15 y) concomitant 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:** typically with membranous nephropathy (WHO class V)
- **Cryoglobulinemia:** typically with membranoproliferative GN

Workup (*Archives* 2001;161:25; *BMJ* 2008;336:1185)

- Urine sediment: usually benign; ± oval fat bodies ("Maltese crosses"; *NEJM* 2007;357:806)
- Measure proteinuria: 24-h urine collection or spot urine prot/Cr ratio (not accurate in AKI)
- r/o 2° causes: ↑ Hb_{A1C} + retinop. → presumpt. dx of diab. nephrop.; ✓ ANA, anti-dsDNA, C3/C4, SPEP/light chains, fat pad bx, cryocrit, HBV/HCV, HIV, RPR, $APLA_2$ recept. Ab
- Renal biopsy

Treatment (*Kid Int Sup* 2012;2:143; *NEJM* 2013;368:10)

- General: protein suppl.; diuretics for edema; treat hyperlipidemia, Na restriction (<2 g/d)
- **ACEI** or **ARB:** decrease proteinuria → slow nonimmunologic progression of renal disease
- 1° glomerular dis: steroids ± cytotoxic therapy; cancer screening if membranous neph.
- Secondary causes: treat underlying disease
- Watch for malnutrition (protein loss), thrombosis (in ~25%, esp. renal vein, b/c loss of ATIII & other endogenous anticoags), infxn (esp. encaps. organisms b/c loss of Ig)

URINALYSIS

Urine Dipstick

Measurement	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
Protein	Detects albumin (marker for glomerular dysfxn); see "Proteinuria"
Blood	See "Hematuria"; can also be ⊕ w/ few RBCs on sediment review in myoglobinuria (rhabdomyolysis) False ⊖: semen, dilute urine (→ osmotic cell lysis), ↑ pH, vaginal blood
WBC	Suggests inflammation (UTI, interstitial nephritis, GN)
Ketones	Detects acetoacetate (ie, ketoacidosis) but *not* β-hydroxybutyrate
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

Urine Sediment (microscopic examination) (*Am J Kidney Dis* 2008;51:1052)

Method: Centrifuge fresh sample (prox. port if Foley) × 3–5 min at 1500–3000 rpm; pour off supernatant in one motion; resuspend pellet by agitating base of tube; pour suspension onto slide w/ coverslip; view under "high dry" power; phase contrast for RBC morphology

Cells	RBCs: assess amount & morphology (many dysmorphic → glomerular) WBCs: PMNs (UTI) vs. eosinophils (AIN; may require special stain) Epithelial cells: tubular (ATN), transitional (bladder or ureters), squamous
Casts *(see urinalysis photo inserts in appendix)*	*Proteins molded in lumen of renal tubule ± entrapped cellular elements* RBC → GN WBC → AIN, pyelonephritis, GN Granular ("muddy brown"): degenerating cellular casts → ATN Tubular cell → ATN Hyaline: Tamm-Horsfall protein (nonspecific) Waxy and broad → advanced chronic kidney disease
Crystals *(see urinalysis photo inserts in appendix)*	Calcium oxalate monohydrate: spindle, oval, or dumbbell shaped Calcium oxalate dihydrate: envelope shaped or octahedral Uric acid: variable shape; polychromatic under polarized light Cystine: hexagon shaped Struvite: coffin-lid shaped; seen in chronic UTI with urea-splitting organisms Drugs: sulfa, protease inhibitors: "shocks of wheat"; acyclovir: fine needles

Proteinuria

Etiologies of Proteinuria

Category	Description	Etiologies
Glomerular (can be >3.5 g/d)	Disruption of filtration barrier → lose albumin	Glomerulonephritis Nephrotic syndrome
Tubulointerstitial (usually <1–2 g/d)	↓ reabsorption of freely filtered proteins → lose globulins	ATN; AIN Fanconi's syndrome
Overflow	↑ production of freely filtered proteins	Multiple myeloma Myoglobinuria
Isolated	By def'n: asx, normal renal fxn, sed, & imaging, no h/o renal disease	Functional (fever, exercise, CHF) Orthostatic (only when upright) Idiopathic (transient or persistent)

- **Urine dipstick**
  1+ ≈30 mg/dL, 2+ ≈100 mg/dL, 3+ ≈300 mg/dL, 4+ >2 g/dL; interpretation depends on SG; eg, 3+ in very concentrated urine might not indicate heavy proteinuria
  Insensitive for microalbuminuria and myeloma light chains (Bence-Jones protein)
- **Spot urine:** protein (mg/dL)/creatinine (mg/dL) ≈ g/d of proteinuria (*NEJM* 1983;309:1543)
  unlike urine dipstick, will accurately measure myeloma light chains
  reliable surrogate for 24-hr urine, esp. 1st morning void (*JASN* 2009;20:436); inaccurate if AKI depends on Cr production, ∴ underestimates if muscular, overestimates if cachectic
- **Microalbuminuria** (30–300 mg/24h or mg/L or μg/mg of Cr): early sign of glomerular vascular disease; marker for ↑ risk of CV adverse outcomes (*JAMA* 2001;286:421)
- Orthostatic proteinuria: typically in adolescents; ~90% of young ♂ with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously

Etiologies of Hematuria	
Extrarenal (far more common)	**Intrarenal**
Nephrolithiasis	Nephrolithiasis or crystalluria
Neoplasm: transitional cell, prostate	Neoplasm
Infxn: cystitis, urethritis, prostatitis	Trauma/exercise (? extrarenal component)
Foley trauma	Vascular: renal infarcts, renal vein thromb., sickle cell, ruptured hemangioma
BPH	Glomerular: IgA, thin BM > others; ? loin pain synd.
Schistosoma haematobium	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* 2015;314:1865 & 2016;315:2276; *Annals* 2016;164:488)
- **Urine dipstick:** ⊕ if ≥3 RBCs; ⊕ dipstick and ⊖ sediment → myo- or hemoglobinuria
- **Urine sediment:** dysmorphic RBCs or RBC casts → GN → consider renal bx
- If no evidence of glomerulonephritis:
  r/o UTI and non-GU causes (GI or vaginal bleed)
  Urine cytology (Se ~70%, Sp ~95%), not adequate substitute for cystoscopy
  Renal imaging: helical CT ± contrast (r/o nephrolithiasis and neoplasia of upper tract), cystoscopy (r/o bladder neoplasia, esp. ≥35 y), ± MRI, retrograde pyelogram, U/S

NEPHROLITHIASIS

Types of stones and risk factors (*J Clin Endocrinol Metabol* 2012;97:1847)
- **Calcium** (Ca oxalate > Ca phosphate): **70–90% of kidney stones**
  Urine findings: ↑ Ca, ↑ oxalate (Ca-ox only), ↑ pH (Ca-phos only), ↓ citrate, ↓ volume
  2° hypercalciuria: 1° hyperparathyroidism, distal RTA, sarcoid
  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
- **Noncontrast helical CT scan** (ureteral dilation w/o stone suggests recent passage) 97% sens. 96% spec. (*AJR* 2008;191:396); U/S appears comparable (*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 (*NEJM* 2004;350:684)
- Analgesia (narcotics ± NSAIDs; combination superior, *Ann Emerg Med* 2006;48:173), ensure adequate fluid repletion, antibiotics if UTI
- Consider alpha blocker > CCB to promote ureteral relaxation (*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), stent, perc nephrostomy, ureteroscopic removal

Chronic treatment (*J Clin Endocrinol Metabol* 2012;97:1847)
- Increase fluid intake (>2 L/d) for goal UOP 2 L/d
- Calcium stones: 24-h urine identifies **specific urinary risk factors to treat**
  ↓ Na and meat intake (*NEJM* 2002;346:77), thiazides: decrease urine Ca
  Depending on 24-h urine: K-citrate, dietary oxalate restriction, allopurinol
  High dietary Ca is likely beneficial by ↓ oxalate absorp., unclear role of Ca supplements
- Uric acid: urine alkalinization (K-citrate), allopurinol
- Magnesium ammonium phosphate: antibiotics to treat UTI, urologic intervention, acetohydroxamic acid: urease inhibitor, reserve for experienced clinician, poorly tolerated
- Cystine: urine alkalinization (K-citrate), D-penicillamine, tiopronin

ANEMIA

↓ in RBC mass: Hct <41% or Hb <13.5 g/dL (men); Hct <36% or Hb <12 g/dL (women)

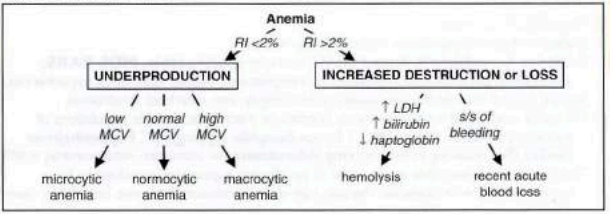
Clinical manifestations

- 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

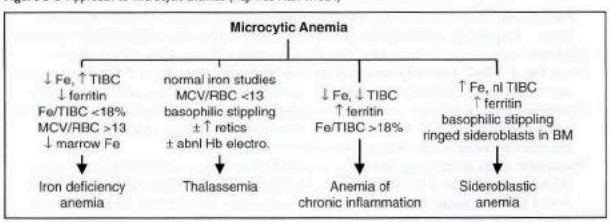
- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including **pica**), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- **Reticulocyte index** (RI) = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor
  maturation factors for a given Hct: 45% = 1, 35% = 1.5, 25% = 2, 20% = 2.5
  RI >2% → adequate marrow response; RI <2% → hypoproliferation
- **Peripheral smear:** select area where RBCs evenly spaced and very few touch each other; ✓ RBC size, shape, inclusions (see "Appendix" & "Peripheral Smear" inserts), 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



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., Epo). Iron-refractory iron-defic. anemia (IRIDA; rare Fe refractory 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 sprue labs (**anti-TTG**, antigliadin, antiendomysial Ab)
  Cytogenetics & molecular testing as indicated

- Treatment oral Fe tid (~6 wk 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* 2011;379:373)

- ↓ 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
- Severe clinical manifestations: chipmunk facies, pathologic fractures, hepatosplenomegaly (due to extramedullary hematopoiesis), high-output CHF, bilirubin gallstones, Fe overload
- Diagnosis: MCV <70, **normal Fe, 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

Anemia of chronic inflammation (see below)

Sideroblastic anemia

- Defective heme biosynthesis within RBC precursors
- Etiologies: **hereditary/X-linked** (*ALAS2* mutations), **idiopathic, MDS-RARS, reversible** (alcohol, lead, isoniazid, chloramphenicol, copper deficiency, hypothermia)
- Special clinical manifestations: hepatosplenomegaly, iron overload syndromes
- Dx: social, work & TB hx; can be micro-, normo- or macrocytic; variable populations of hypochromic RBCs; ↑ Fe, nl TIBC, ↑ ferritin, basophilic stippling, RBC **Pappenheimer bodies** (Fe-containing inclusions), **ring sideroblasts** (w/ iron-laden mitochondria) in BM
- Treatment: treat reversible causes; trial of pyridoxine, supportive transfusions for severe anemia with chelation therapy; high-dose pyridoxine for some hereditary cases

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Normocytic Anemias

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 (*Blood* 1997;89:1052).
- 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). Unclear if one should treat highly sx Pts w/ goal Hb 10–12 g/dL; weigh risk of thrombosis.

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, or parathyroid disease → ↓ Epo; can be normocytic or macrocytic

Sideroblastic anemia (see above)

Pure red cell aplasia

- Destructive antibodies or lymphocytes → ineffective erythropoiesis
- Associated with thymoma, CLL 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 infection; immunosuppression/chemoRx if CLL or idiopathic; supportive care w/ PRBC transfusions; ? erythropoietin receptor agonist if due to antierythropoietin Ab (*NEJM* 2009;361:1848) consider hematopoietic cell transplantation.

Macrocytic Anemias

includes megaloblastic and nonmegaloblastic causes

Megaloblastic anemia

- **Impaired DNA synthesis** → cytoplasm matures faster than nucleus → ineffective erythropoiesis and macrocytosis; due to **folate** or **B_{12} deficiency;** also in **MDS**
- ✓ **folate** and **vitamin B_{12};** ↑ LDH & indirect bilirubin (due to ineffective erythropoiesis)
- Smear: **neutrophil hypersegmentation, macro-ovalocytes,** anisocytosis, poikilocytosis

Folate deficiency

- Folate present in leafy green vegetables and fruit; total body stores sufficient for **2–3 mo**
- Etiologies: **malnutrition** (alcoholics, anorectics, elderly), ↓ absorption (sprue), impaired metabolism (methotrexate, pyrimethamine, trimethoprim; *NEJM* 2015;373:1649), ↑ requirement (chronic hemolytic anemia, pregnancy, malignancy, dialysis)
- Diagnosis: ↓ folate; ↓ RBC folate, ↑ homocyst. but nl methylmalonic acid (unlike B_{12} defic.)
- Treatment: folate 1–5 mg PO qd for 1–4 mo or until complete hematologic recovery; *critical to r/o B_{12} deficiency first (see below)*

Vitamin B_{12} deficiency (*NEJM* 2013;368:149)

- B_{12} present only in foods of animal origin; total body stores sufficient for **2–3 y**
- Binds to **intrinsic factor** (IF) secreted by gastric parietal cells; absorbed in terminal ileum
- Etiologies: malnutrition (alcoholics, vegans), **pernicious anemia** (PA, autoimmune disease against gastric parietal cells, a/w polyglandular endocrine insufficiency and ↑ risk of gastric carcinoma), other causes of ↓ absorption (gastrectomy, sprue, Crohn's disease), ↑ competition (intestinal bacterial overgrowth, fish tapeworm)
- Clinical manifestations: **neurologic** changes (**subacute combined degeneration**) affecting peripheral nerves, posterior 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

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** (⅓ – ⅔ 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) an option in refractory disease (*Blood* 2014;123:1818)
  - **supportive care:** transfusions, antibiotics, possible utility of G-CSF and 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

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), **infection, DKA** or **foods** (fava beans)
- 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* as older RBCs have already lysed and young RBCs may still have near normal levels)

Sickle cell anemia (*Lancet* 2016;387:2545, 2554 & 2565)

- 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 and infarction:** painful crises, acute chest syndrome, CVA, splenic sequestration, hand-foot syndrome, renal papillary necrosis, aseptic necrosis, priapism
- **Infection:** splenic infarction → overwhelming infection by **encapsulated organisms;** infarcted bone → **osteomyelitis** (*Salmonella, Staph. aureus*)
- Diagnosis: sickle-shaped RBCs and Howell-Jolly bodies on smear; Hb electrophoresis
- Treatment: **hydroxyurea** causes ↑ HbF → ↓ painful crises, acute chest episodes and may ↓ mortality (*NEJM* 2008;358:1362); allogeneic HSCT may have a role in young Pts w/ severe disease (*Blood* 2000;95:1918) and adults (*NEJM* 2009;361:2309; *Blood* 2012;120:4285)
- Supportive care: folic acid qd; pneumococcal, meningococcal, *H. flu* & HBV vaccination; pain crises Rx'd w/ **hydration, O_2 & analgesia;** simple or exchange transfusion for TIA or stroke, severe acute chest syndrome, or preop (goal Hb 10 g/dL; *Lancet* 2013;381:930)

Hereditary spherocytosis (HS) (*Br J Hematol* 2004;126:455)

- 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
- **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: 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, antibody-mediated, RBC destruction precipitated by a medication:
  abx: cephalosporins, 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.

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)

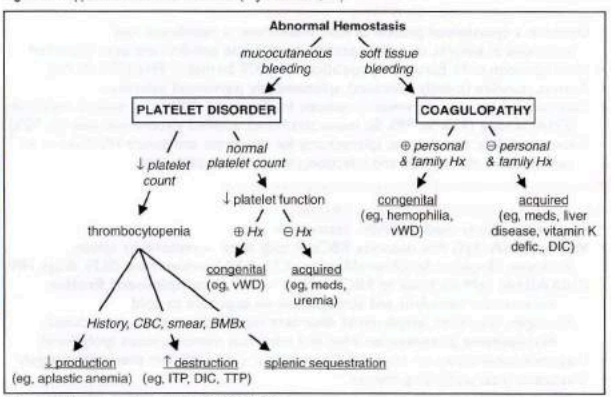
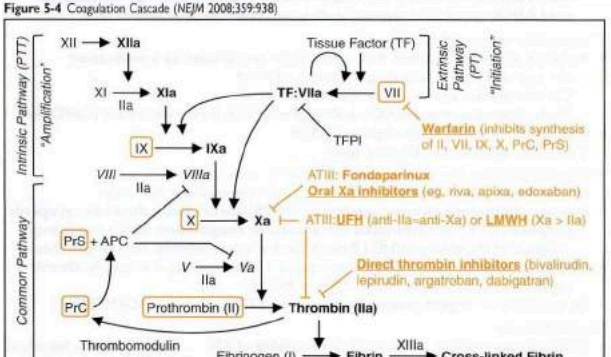


Figure 5-4 Coagulation Cascade (*NEJM* 2008;359:938)



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)

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

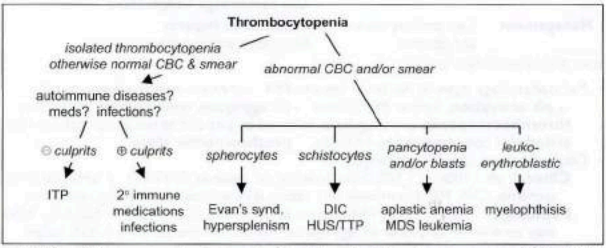
Etiologies

- ↓ **production**
  - **hypocellular bone marrow:** aplastic anemia (qv), rarely MDS, drugs (eg, thiazides, antibiotics), 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
- **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**
  ↑ 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*)
  r/o **pseudothrombocytopenia** due to platelet clumping (✓ platelet count in non–EDTA-containing tube, eg, citrate or heparin-containing tube)

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)

- Primary ITP: isolated thrombocytopenia due to immune plt *destruction* & ↓ *production* (auto-Ab to megakaryocytes); (2° ITP a/w disease/drug exposure; Rx underlying disorder)
- Primary ITP is *diagnosis of exclusion;* no robust clinical or lab parameters, but typically:
  CBC: isolated ↓ plt (<100,000/μL); 10% have ITP + AIHA = Evans syndrome
  Peripheral smear: large platelets
  BM bx: ↑ megakaryocytes; perform in adults >60 y to r/o myelodysplasia
  R/o other etiologies: viral serologies (**HIV, HCV,** HBV, EBV), *H. pylori* Ab, ANA, pregnancy test, APLA, TSH, parvovirus, & CMV PCR. *Anti-plt Ab tests not useful.*

- Clinical manifestations: insidious onset of mucocutaneous bleeding; ♀:♂ = 3:1
- Treatment: goals based on individual Pt
  rarely indicated if plt >50,000/μL unless bleeding, trauma/surgery, anticoag, comorbidities
  steroids, IVIg, & splenectomy mainstay of initial Rx; romiplostim/eltrombopag if refractory

Treatment of Primary ITP in Adults

Approach	Treatment	Notes
First-line	**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% initial response ~20% sustained remission
	Anti-Rh(D) Ig 75 μg/kg/d IV	For Rh(D) ⊕ Pts w/ spleen Ab-coated RBCs overwhelm Mϕ FcR
	IVIg (1 g/kg/d IV × 2–3 d) *consider if need rapid ↑ in plt*	Blocks Mϕ FcR, ↓ anti-plt Ab Up to 80% initial response
Second-line	**Splenectomy** (*? for ITP >6 mo*)	~65% long-term remission
	Rituximab (anti-CD20) ± dex	anti–B-cell Ab
	Romiplostim or **eltrombopag**	TPO-R agonists → ↑ plt prod
	Azathioprine, cyclophosphamide	Immunosuppressants
	Danazol, vincristine	↓ plt clearance
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)
Refractory	Romiplostim or eltrombopag	See above
	Autologous HSCT	Limited data, investigational

(*NEJM* 2003;349:831; 2010;464:1889 & 2011;365:734; *Blood* 2013;121:537)

Overview of Heparin-Induced Thrombocytopenias

Feature	Type I (historic)	HIT (formerly type II)
Mechanism	Direct effect of heparin (nonimmune)	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

(*Chest* 2012;141:e495S; *NEJM* 2015;373:252)

- 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
Thrombocytopenia	↓ >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 (*NEJM* 2014;371:654)

- Includes hemolytic-uremic syndrome (HUS) & thrombotic thrombocytopenic purpura (TTP)
- Definition: vascular occlusive disorders w/ systemic (TTP) or intrarenal (HUS) plt aggreg. → thrombocytopenia & mechanical injury to RBCs (MAHA) (*NEJM* 2002;347:589)
  HUS triad = thrombocytopenia + MAHA + renal failure
  TTP pentad (all 5 in only ~5%) = ↓ plts + MAHA (100%) ± Δ MS (65%) ± renal failure (50%, late feature) ± fever (25%)
- Pathophysiology: mechanism in most HUS cases is distinct from TTP (*NEJM* 1998;339:1578)
  HUS: Shiga toxin binds & activates renal endothelial cells & plts → intrarenal thrombi
  TTP: ↓ ADAMTS13 protease activity *or* inhibitor→ persistence of large vWF multimers on endothelial surface → adhesion and aggregation of passing platelets → thrombosis
- Clinical manifestations and associations
  HUS: usually in children; prodrome of bloody diarrhea due to enterohemorrhagic *E. coli*
  TTP (low ADAMTS13): usually in adults; **idiopathic,** autoimmune dis., familial, preg
  TTP-like (nl ADAMTS13): **drugs** (CsA, tacrolimus, gemcitabine, mitomycin-C, ticlopidine, clopidogrel, quinine), HIV, HSCT, malig
- Dx: unexplained **thrombocytopenia** (typically <20k) + **MAHA** → *sufficient for dx*
  ⊕ **schistocytes** (>2–3/hpf), ⊖ Coombs, normal PT/PTT & fibrinogen, ↓↓ ADAMTS13 ↑↑ 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 (*Blood* 2010;116:4060); ? eculizumab in HUS & ? caplacizumab in TTP (*NEJM* 2013;368:2169 & 2016;374:511); *plt transfusions contraindic.* → ↑ 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* 2004;351:683 & 2012;367:1954)

- 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

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

- 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
- Rx: purified/recomb. factor VIII (*NEJM* 2016;374:2054) or IX; desmopressin (mild dis.); amino-caproic acid; cryo (FVIII); recomb. factor VII or IX-Fc fusion proteins have ↑ $t_{1/2}$, so 1–2×/wk dosing for Ppx (*NEJM* 2013;369:2313); ? emicizumab (binds FIX & X; *NEJM* 2016;374:2044)

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
Fondaparinux	24°, K	anti-Xa*	? Dialysis
Warfarin	36°, L	↑ PT	*No bleeding:* INR 4.5–10, Ø Rx or **vit. K** 2.5 mg PO; INR >10 give 5 mg PO (sup to SC, = IV at 24 h) *Bleeding:* **vit. K** 10 mg IV + **FFP** 2–4 U IV q6–8h; PCC (eg, KCentra) faster; ↓ tfn (*Circ* 2013;128:360)
Fibrinolytic	20′, LK	↓ fbgn	**Cryoprecipitate, FFP,** ± aminocaproic acid
Dabigatran	~12°, K	↑ PTT*	Idarucizumab (*NEJM* 2015;373:511)
Rivaroxaban Apixaban Edoxaban	8–12°, K > L	↑ PT* anti-Xa*	Anti-fibrinolytic agent; consider PCC; specific reversal agents (eg, andexanet) under development (*NEJM* 2015;373:2413; *J Thromb Haemost* 2015;13:S187)

*Routine monitoring not performed. Mode of excretion: K, kidney; L, liver; RES, reticuloendothelial system. 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

Prevalence is in Caucasians. (*NEJM* 2001;344:1222; *JAMA* 2005;293:2352)

Vascular Beds Affected by Inherited and Acquired Hypercoagulable States		
	Venous	**Venous and Arterial**
Inher.	**Factor V Leiden**	? factor V Leiden + smoking
	Prothrombin mutation	Hyperhomocysteinemia (inherited or acquired)
	↓ protein C, S or AT III	Dysfibrinogenemia
Acquired	Stasis: immobilization, surgery, CHF	Platelet defects: myeloproliferative disorders, HIT, PNH (although venous > arterial)
	Malignancy	Hyperviscosity: polycythemia vera, Waldenström's macroglobulinemia, sickle cell, acute leukemia
	Hormonal: OCPs, HRT, tamoxifen, pregnancy	Vessel wall defects: vasculitis, trauma, foreign bodies
	Nephrotic syndrome	Others: **antiphospholipid syndrome**, IBD

Diagnostic evaluation (not routinely required for initial VTE)

- 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) (*J Thromb Haemost* 2006;4:295; *NEJM* 2013;368:1033)

- 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 after thromboembolic event (lifelong for most Pts)
  - Intensity of anticoagulation controversial (*Nat Rev Rheum* 2015;11:586)
  - 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, although some treat to INR 3–4
  - *Recurrent thrombosis* on warfarin: consider INR 3–4 vs. LMWH or fondaparinux (*Arth Rheum* 2007;57:1487)
  - Consider ASA prophylaxis for high-risk asx Pt (eg, SLE); no current evidence for NOACs

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

Blood Products and Indications (*Lancet* 2013;381:1845)	
Packed red blood cells (PRBCs) (*Annals* 2012;157:49)	For acute blood loss or to ↑ O_2-carrying capacity if end organ ischemia. 1 U PRBC → ↑ Hb by ~1 g/dL. Conservative Hb goal >7 g/dL adequate for UGIB & critically ill Pts (*NEJM* 2013;368:11 & 2014;371:1381; *BMJ* 2015;350:h1354). Controversy remains re: coronary ischemia, although Hb >8 may be adequate (*JAMA Int Med* 2013;173:132), but perhaps not peri-cardiac surgery (*NEJM* 2015;372:997; *Anesth* 2016;125:46).
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 *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 and fever (cytokine release) and carry CMV. For chronically transfused Pts, potential transplant recipients, h/o febrile nonhemolytic transfusion reaction, cases in which CMV-negative products are 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; ratio of PRBC:plt:FFP repletion controversial, follow labs (*J Trauma* 2006;60:S91 & 2008;65:272).

Transfusion Complications (*NEJM* 1999;340:438; *JAMA* 2003;289:959)			
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, hypotension
- **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 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: >10,000 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 RAEB-2	EB-1: 5–9% BM/2–4% PB blasts, no Auer rods EB-2: 10–19% BM/5–19% PB blasts or Auer rods
MDS, unclassifiable (MDS-U)	MDS-U	w/ 1% PB blasts, single lineage dysplasia & pancytopenia, or defining cytogenetic alteration

Certain cytogenetics [eg, t(15;17), t(8;21), inv16, t(16;16), or MLL rearrangement] classified as AML, regardless of BM blast count. 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; *NEJM* 2006;355:1456); DNA hypomethylating agents (azacitidine or decitabine)
  - Intermediate/high risk → DNA hypomethylating agents (survival advantage w/ azacitidine; *Lancet Oncol* 2009;10:223), combination **chemo** (akin to AML Rx) or **allogeneic HSCT**
  - Hypoplastic MDS (rare) → consider **immunosuppression** (CsA, ATG, pred), HSCT
- Prognosis: IPSS-R correlates with **survival** and **progression to AML**

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 (*Am J Hematol* 2012;87:285; *JAMA Oncol* 2015;1:97; *Blood* 2016;127:2391)

- 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 (PM); chronic myelogenous leukemia (CML), BCR-ABL1 ⊕; chronic neutrophilic leukemia (CNL); 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
  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

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
- Ruxolitinib (JAK1/2 inhibitor) if poor response, intolerant of hydroxyurea (*NEJM* 2015;372:426)
- PEG IFNα-2a yields high response rate w/ limited toxicity (*Blood* 2008;112:3065)
- 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%; higher if previous cytoreductive chemo)

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 and very rarely, minor increase in reticulin fibers; normal iron stores
- ***JAK2* V617F** present in ~50% of ET; ***MPL*** or ***CALR*** mutations in majority of JAK2 wt
- 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 × 10^6/μL *and* no CV risk factors	Consider for vasomotor symptoms	No
Int.	Neither low nor high	±	Consider if plt >1.5 × 10^6/μL
High	Age ≥60 or h/o thrombosis or plt >1.5 × 10^6/μL	⊕ (consider holding if plt >1 × 10^6/μL and lab evid. of acquired vWD)	**Hydroxyurea.** Goal plt <0.4 × 10^6/μL or sx free. IFNα if young or pregnant.

Imetelstat (telomerase inhib) under investigation (*NEJM* 2015;373:92)

Prognosis

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

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;** inconsistent benefit from androgens or Epo; ? 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)
- Thalidomide and lenalidomide ± steroids may improve red cell count
- Imetelstat (telomerase inhibitor) under investigation (*NEJM* 2015;373:908)

Complications and prognosis

- Median survival ~6 y; transformation into AML occurs at a rate of ~8%/y
- Dynamic International Prognostic Scoring System (DIPPS plus): age >65, WBC >25k, Hgb <10, blasts >1%, ⊕ symptoms, RBC Tx, Plt <100K, karyotype (*JCO* 2011;29:392). IWG-MRT allows prognostication at any point during clinical course (*Blood* 2010;115:1703).

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): ~21k cases/y in U.S.; median age 67 y; >80% of adult acute leukemias
- Acute lymphocytic (ALL): ~6k cases/y in U.S.; median age 14 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

Clinical manifestations
- Cytopenias → **fatigue** (anemia), **infection** (neutropenia), **bleeding** (thrombocytopenia)
- More common in **AML**
  - **leukostasis** (more often when blast count >50,000/μL): occluded microcirculation → local hypoxemia and hemorrhage → dyspnea, hypoxia, headache, blurred vision, TIA/CVA; look for *hyperviscosity retinopathy* (vascular engorgement, exudates, hemorrhage)
  - **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, lymphadenopathy, hepatosplenomegaly (also in monocytic AML)
  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:** hypercellular with >20% blasts; 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; *NEJM* 2015;373:1136)

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) cytochemistry: ⊕ **myeloperoxidase** and/or **nonspecific esterase**
- Immunophenotype: myeloid: CD13, CD33, CD117; monocyte: CD11b, CD64, CD14, CD15
- Cytogenetics: important for prognosis. Intermed. risk = no favorable/unfavorable features.

WHO 2016 Classification of AML (*Blood* 2016;127:2391)

4 Major Subtypes	Examples
Recurrent genetic abnl	t(8;21); inv(16); *PML-RARA*; t(9;11), t(6;9), inv(3), t(1;22), mutation in *NPM1*, biallelic mutation in *CEBPA*
Myelodysplasia-related Δ	w/ or w/o antecedent MDS or MPN
Therapy-related	eg, alkylating agents or topoisomerase inhibitors
Not otherwise specified	w/ min differentiation; w/ or w/o maturation; myelomonocytic; monoblastic/cytic; pure erythroid; megakaryoblastic
Also: myeloid sarcoma, myeloid proliferations of Down's syndrome	

AML Genetics (*Blood* 2010;115:453 & 116:354; *NEJM* 2016;374:2209)

	Favorable prognosis	Unfavorable prognosis
Karyotype	t(15;17) in APL; t(8;21); inv(16)/t(16;16)	−5; −7; 3q26 aberrations; t(6;9); 11q23 aberrations; complex karyotype
Gene mutations	*NPM1*+; biallelic *CEBPA*	*FLT3* ITD; *MLL*-PTD; *TP53*, *RUNX1*
Recurrent somatic mutations: *DNMT3A; TET2; ASXL1; RAS; WT1; IDH1/2*; spliceosome		

Treatment (*Lancet* 2013;381:484)

- Induction chemo followed by consolidation; if unfit, hypomethylating agents or clinical trial
- **Induction chemo:** "7 + 3" = cytarabine × 7 d + ida/daunorubicin × 3 d. Daunorubicin dose: age <60 → high (90 mg/m²); age >60 → standard (60 or 45 mg/m²) (*NEJM* 2009;361:1249). Gemtuzumab ozogamicin (α-CD33) ? benefit in fav/int risk AML (*Lancet* 2012;379:1508).
- ✓ for complete remission (CR) = ANC >1000, plts >100, off RBC Rx, <5% BM blasts **CR ≠ cure;** ∴ must always f/u induction with **consolidation Rx**
- If ⊕ CR: consolidation Rx per Pt risk (age, genetics, PS): chemo (eg, high-dose cytarabine, HiDAC) if favorable risk; *poor risk* → allo-HSCT; int risk depends on mutat., donors, PS
- If ⊖ CR: reinduce w/ altern. Rx [eg, MEC (mitoxantrone, etoposide, cytarabine)], HiDAC
- If relapse after CR: salvage chemo or clinical trial → allogeneic HSCT
- Supportive care: hydration + allopurinol or rasburicase for tumor lysis prophylaxis; transfusions; antibiotics for fever and neutropenia; antifungals for prolonged fever & neutropenia; hydroxyurea ± leukapheresis for leukostasis (avoid pheresis in APL)

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 >75% for younger Pts w/ favorable prognostic factors
- Poor prog. factors: age >60, unfavorable cytogenetics, poor performance status, antecedent MDS/MPN, tAML; genetics (*NEJM* 2016;374:2209; *JAMA* 2015;314:811); residual dis. eg, persistent *NPM1*-mut. transcripts a/w ↑ relapse, ↓ survival (*NEJM* 2016;374:422)

Acute promyelocytic leukemia (APL) (*Blood* 2009;113:1875)

- Rare disease, approx. 8% of total AML cases in U.S. *but biologically and clinically distinct*
- Atypical promyelocytes (large, granular cells; bilobed nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: **t(15;17); *PML-RAR*α** (>95% of cases)
- **Medical emergency** with **DIC** and **bleeding** common; supportive care measures crucial
- Remarkable responses to **all-*trans*-retinoic acid (ATRA),** which induces differentiation, and **arsenic trioxide (ATO);** early initiation of ATRA critical as soon as APL *suspected;* ATO highly active as first-line therapy or in treatment of refractory disease.
- Induction: ATRA + ATO → CR ~100%, ↑ 2-y event-free survival (*NEJM* 2013;362:111); anthracycline + ATRA ± cytarabine → CR in ~90%, favored in high-risk APL (WBC >10k)
- 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)
- Consolidation: daunorubicin + ATRA (*Blood* 2010;116:3751) or ATRA+ATO (*NEJM* 2013;369:111)
- Role of maintenance Rx (eg, ATRA + 6MP + MTX) controversial; not w/ ATRA/ATO Rx
- Best prognosis of all AMLs: >90% cure; WBC >10,000/μL = ↓ prognosis (*Blood* 2000;96:1247)

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 & <20% BM blasts. ALL and LBL are considered the same disease with different clinical presentations.
- Morphology: **no granules** (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL
- Cytogenetics (*Blood* 2010;115:206): t(9;22) = Philadelphia chrom (Ph) –25% of adults w/ ALL; "Ph-like" ALL gene expression: worse prognosis, ? role of TKI (*NEJM* 2014;371:1005)
- Immunohistochem.: 2 major phenotypes (Burkitt's treated differently; see "Lymphoma")

WHO Immunophenotype Classification of ALL (*Blood* 2016;127:2375)

WHO type	Adult freq.	Immunohistochemistry
B cell	75%	⊕ TdT, ⊕ CD19; variable CD10, CD20
T cell	25%	⊕ TdT, ⊕ T-cell Ag (CD2, cytoplasmic CD3, CD5, CD7)

Treatment (*JCO* 2011;29:532; *Leukemia* 2013;29:526)

- **Induction chemo:** regimens typically include combination of anthracycline, vincristine, steroids, cyclophosphamide, ± asparaginase; based on pediatric regimens
- **CNS prophylaxis:** intrathecal MTX/cytarabine ± cranial irradiation *or* systemic MTX
- **Postremission therapy** options:
  consolidation/intensification chemo (~7 mo) followed by maintenance chemo (~2–3 y)
  high-dose chemo w/ allo HSCT considered for Pts in CR1 w/ available donor
  pediatric regimens in adults (*Leukemia* 2015;29:526); consider allo SCT if <50 (controversial)
- If relapse → salvage (eg, chemo or CAR-T or inotuzumab), then allogeneic HSCT if able
- Ph ⊖ t(9;22) primary refractory/relapsed B-cell ALL: blinatumomab (*Lancet Oncol* 2015;16:57)
- Ph ⊕ t(9;22) → add imatinib or dasatinib, followed by allogeneic HSCT

- MLL-AF4 t(4;11), hypodiploidy (<44 chromosomes), min residual disease → consider allo-HSCT
- Infusion of chimeric antigen receptor–modified T cells promising (*NEJM* 2014;371:1507)

Prognosis
- Morphologic CR in >80% of adults; but minimal residual disease (MRD) at CR = poor prog.
- Cure achieved in 50–60% if good prog. factors vs. 10–30% w/ poor prog. factors
- Good prognostic factors: younger age, WBC <30,000/μL, T-cell immunophenotype, absence of Ph chromosome or t(4;11), early attainment of CR w/ MRD negative

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 Dx*** (make via karyotyping or FISH; PCR useful but not adequate)
- "Atypical CML" (BCR-ABL ⊖) now considered a separate disease and reclassified as MDS/MPN (qv) w/ many Pts ⊕ for *CSF3R* or *SETBP1* mutations

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

Clinical manifestations
- Triphasic clinical course; 85% present in the chronic phase
- **Chronic phase:** often asymptomatic but common features are fatigue, malaise, weight loss, night sweats, abdominal fullness (**splenomegaly** 50%)
- **Accelerated phase:** refractory leukocytosis, ↓ plt and worsening sx → fever, wt loss, ↑ splenomegaly, bone pain, bleeding, infections, pruritus (basophilia)
- **Blastic phase** = acute leukemia → severe constitutional symptoms, infection, bleeding, and possible **leukostasis** (see "Acute Leukemia")

Diagnostic evaluation
- **Peripheral smear: leukocytosis,** left-shifted with *all stages of myeloid maturation;* anemia, thrombocytosis, **basophilia**
- **Bone marrow:** hypercellular, ↑ myeloid to erythroid ratio, ↓ leuk alkaline phosphatase
- **Chronic:** <10% blasts (peripheral or BM)
- **Accelerated:** 10–19% blasts, ≥20% basos, plts <100k, ↑ spleen size, karyotypic prog.
- **Blastic:** ≥20% blasts (⅔ myeloid, ⅓ lymphoid), may see extramedullary leukemia

Treatment (*Lancet* 2015;385:1447)
- **Tyrosine kinase inhibitor (TKI):** imatinib, dasatinib, nilotinib, bosutinib, & ponatinib are selective inhibitors of BCR-ABL (*JCO* 2010;28:428; *Blood* 2012;120:1390).
  Imatinib, nilotinib, & dasatinib approved as initial Rx.
  Resistance = recurrent dis. 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 & 2013;369:1783).
  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: thrombosis, pancreatitis and CV toxicity
- **Chronic phase:** TKI; continued indefinitely in responders (*Blood* 2012;120:1390)
- **Accelerated phase:** TKI upfront, consider allogeneic HSCT
- **Blastic phase:** TKI vs. TKI + either ALL or AML induction (based on cell type); then HSCT
- **Allogeneic HSCT:** possibility of cure, consider for Pts w/ available donor; Pts who present in accelerated or blastic phase; or Pts with relapsed/refractory disease to TKIs

Goals of TKI Therapy (*Blood* 2013;122:872)

Response	Definition	Optimal time
Hematologic	WBC <10k, plt <450k, no immature cells in blood, basophils <5%, spleen nonpalpable	3 mo
Cytogenetic	Absence of the Ph chromosome in metaphase cells	12 mo
Molecular	<0.1% BCR-ABL = 3-log reduction by quantitative PCR	12 mo

Prognosis (*Cancer* 2013;119:2620)
- 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)
- Accelerated phase CML Rx'd w/ imatinib: ~50% overall survival at 4 y (*Cancer* 2005;103:2099)
- Poor prognostic factors: ↑ age, ↑ platelet count, ↑ spleen size, ↑% of blasts/basophils

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 (<5000/μL, nodes <1.5 cm, nl RBC and Plt counts): 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 (slg); CD5+, CD19+, CD20(dim), CD23+, CD38+ or ZAP70+ a/w unmutated Ig variable heavy chain region & worse prog.
- **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 (JAMA 2014;312:2265)

- Treatment is primarily *palliative* → early stage disease can be followed w/o Rx
- Indications for treatment: Rai stages III/IV, Binet stage C, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections
- Options: combo superior to monoRx (Lancet 2007;370:230), but comorbidities/age important
  purine analogues: fludarabine ("F"), pentostatin ("P")
  alkylating agents: cyclophosphamide ("C"), bendamustine ("B"), CVP, CHOP
  ± **monoclonal Ab** against CD20 (**rituximab,** "R"; ofatumumab) or CD52 (alemtuzumab)
- Healthy/younger (<70y): FCR ↑ survival vs. FC (Lancet 2010;376:1164); FR also acceptable
- Infirm/elderly: many options incl. ibrutinib (NEJM 2015;373:2425); chlorambucil + anti-CD20 [eg, obinutuzumab (NEJM 2014;370:1101) or ofatumumab (Lancet 2015;385:1873)], BR
- Refractory disease: ibrutinib > ofatumumab (NEJM 2014;371:213); acalabrutinib (BTK; NEJM 2016;374:323), idelalisib (PI3K; NEJM 2014;370:997); venetoclax (α-BCL2; NEJM 2016;374:311)
- 17p- or *TP53* mutat.: venetoclax, idelalisib, or ibrutinib ± rituximab (Lancet Oncol 2014;10:1090)
- Consider allo-HSCT in 17p-, *TP53* mutation or refractory CLL (BJH 2012;158:174)
- Supportive care: 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)
- Factors a/w worse prognosis include:
  unfavorable cytogenetics: eg, 17p- or *TP53* mutation (JCO 2010;28:4473)
  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)

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, as can lead to HBV reactivation); consider HIV, HTLV, & EBV serologies and connective tissue diseases autoAbs
- Imaging: PET-CT scans as 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 >⅓ on CXR or >10 cm if in abd; E = involves single contiguous extranodal site; H = hepatic; S = splenic

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HODGKIN LYMPHOMA (HL) (*NEJM* 2010;363:653)

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/ 80% 10-y progression-free survival, 93% overall survival (*JCO* 1997;15:3060)
  Consider rituximab as 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
  Lower intensity regimens comparable efficacy if favorable prognosis (NEJM 2010;363:640)
- **Stages III–IV: ABVD** × 6 cycles or **escalated BEACOPP** (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone)
- Refractory/relapsed disease: salvage chemo + auto HSCT, ± RT
  brentuximab vedotin (CD30 antibody-drug conjugate): salvage (NEJM 2010;363:1812), or post-ASCT consolidation (Lancet 2015;385:1853)
  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, ? role of screening CXR or CT (controversial)
  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	Diffuse large B-cell lymphoma (DLBCL)	*BCL2, MYC, MLL2, CREBBP, etc.*
	Follicular lymphoma	*IGH-BCL2, MLL2*
	CLL/small lymphocytic lymphoma	*IGVH, ZAP70, TP53, SF3B1, etc.*
	Mantle cell	*t(11; 14) BCL1-IgH* → cyclin D1 dysreg
	Marginal zone lymphoma (nodal, extranodal [MALT ✓ *H. pylori*], splenic)	*AP12-MALT1 & BCL-10-Ig enhancer*
	Burkitt's lymphoma	*8q24, c-MYC*
	Hairy cell leukemia (p/w fatigue, ↓ monos, massive splenomegaly; ⊕ TRAP)	*BRAF V600E*
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 2012;380:848)

- Treatment and prognosis determined by histopathologic classification rather than stage
- Rituximab (antibody to CD20; NEJM 2012;366:2008) if CD20+; no role if tumor is CD20–
- **Indolent:** goal is sx mgmt (bulky dis., cytopenias, "B" sx); not curable (except allo HSCT)
  Options include RT for localized disease, rituximab ± chemo (bendamustine, CVP, fludarabine), ibrutinib
  For MALT → treat *H. pylori* if ⊕
  Rituximab maintenance ↑ survival in relapsed disease (JNCI 2009;101:248); growing role for rituximab maintenance in indolent and aggressive disease (Lancet 2011;377:42)
  Hairy cell: cladribine; oral BRAF inhibitor if relapsed/refractory (NEJM 2015;373:1733)
- **Aggressive** (DLBCL, 30–40% of NHL): goal is cure (JCO 2005;23:6387)
  R-CHOP (rituximab, cyclophosphamide, doxorubicin = hydroxydaunorubicin, vincristine = Oncovin, prednisone) (NEJM 2002;346:235 & 2008;359:613)
  10-y progression-free survival = 45%; overall survival = 55% (Blood 2010;116:2040)

? R-ACVBP (rituximab, doxorubicin = Adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone) ↑ 3-y OS vs. R-CHOP, but ↑ adverse events (*Lancet* 2011;378:1858)

+ **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 (*NEJM* 1995;333:1540); allo-HSCT if beyond 2nd relapse (*JCO* 2011;29:1342)

Mantle cell: ibrutinib for relapsed/refractory disease (*Lancet* 2016;387:770)

- **Highly aggressive** (Burkitt, lymphoblastic lymphoma, high-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 and/or BCL6)

Burkitt: intensive short-course chemo (*Blood* 2004;104:3009) + rituximab (*BJH* 2014;165:102)

Low risk defined as nl LDH & single focus of disease <10 cm; all others high risk

Low-risk Rx: CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate ± rituximab) (*Leuk Lymph* 2004;45:761)

High-risk Rx: CODOX-M/IVAC (above w/ ifosfamide, etoposide, high-dose cytarabine), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone)

Dose-adjusted EPOCH-R w/ promise (see below; titrate to ANC) (*NEJM* 2013;369:1915)

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

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%

- Aggressive: ↑ chance of cure, but overall worse prognosis

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 immunosupp. Pts such as s/p solid organ transplant or w/ chronic HBV. Treat with standard CHOP (often CD20–) or consider EPOCH, overall poor prognosis.

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)

- Hyper**C**alcemia due to ↑ osteoclast activity
- **R**enal disease: multiple mechanisms include toxic effect of filtered light chains → *renal failure* (cast nephropathy) or *type II RTA*; amyloidosis or light chain deposition disease → *nephrotic syndrome*; hypercalcemia, urate nephropathy, type I cryoglobulinemia
- **A**nemia (normocytic) due to bone marrow involvement; rarely, may see AIHA
- **B**one pain due to ↑ osteoclast activity → lytic lesions, 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: inhibition of or Ab against clotting factor; Ab-coated platelets
- 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%, no myeloma-defining event or amyloidosis; risk of prog. 10%/y, depends on M protein concen., subtype, FLC ratio
  - 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)
- Gene mutations include *TP53, NRAS, KRAS, BRAF,* & NK-κB pathway (*Nature* 2011;471:467)
- **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*

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* 2011;364:1046; *Am J Hematol* 2012;87:79)

- Decisions generally dictated by *risk stratification* and *transplant eligibility*
- Active drugs incl. **proteasome inhibitors:** bortezomib (V), carfilzomib (Cz), ixazomib (I); **immunomodulators:** lenalidomide (R), thalidomide (T), pomalidomide; **immunotherapy:** daratumumab (anti-CD38), elotuzumab (SLAMF7)
  Other active drugs incl. prednisone (P), dexamethasone (D), melphalan (M), panobinostat, cyclophosphamide (Cy);
  CAR-T cells promising (*NEJM* 2015;373:621&1207; *Lancet* 2016;387:1551)
- Induction Rx regimens w/ best response rate combine proteasome inhib (V, Cz) & immunomod (R). Common induction regimens include doublets (RD, VD) or triplets (RVD, CyBorD), based on comorbidities and risk (*NEJM* 2014;371:906 & 2016;374:1621).
- If *not* transplant eligible: **induction chemo** ↑ survival, not curative; consider maint chemo
- If transplant *eligible:* induction chemo (eg, RVD, VCD, RD; *Lancet* 2010;376:2075) then **high-dose melphalan + auto-HSCT.** Not curative, but ↑ survival c/w chemo (*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. Tandem auto-HSCT & allo-HSCT ↑ survival for some (*NEJM* 2003;349:2495).
- Relapsed/refractory: based on prior response & HSCT eligibility: HSCT (if good prior response, no prior HSCT), RD, CVD, VRD, CzRD, IRD, pomalidoimide+D, daratumumab
- 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;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 population >70 y of age, and 7.5% in population >85 y of age (*NEJM* 2006;354:1362)

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* 2002;346:564)

- ~1%/y or ~25% lifetime risk → MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum free light chain ratio: ↑ risk of progression to MM (*Blood* 2005;105:812)

Waldenström's Macroglobulinemia (WM)

Definition (*Blood* 2009;114:2375)

- B-cell neoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- 91% w/ *MYD88* (NF-κB pathway) L265P mut., may distinguish from MM (*NEJM* 2012;367:826)
- *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:** defined as ratio of viscosity of serum to H_2O (nl ratio 1.8) hyperviscosity syndrome when relative serum viscosity >5–6

Treatment

- Hyperviscosity: **plasmapheresis**
- Sx (eg, prog. anemia): rituximab ± chemo (eg, bendamustine, Cy, etc.); ibrutinib esp. in *MYD88* mut/*CXCR4* wt (*NEJM* 2015;372:1430). 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 (sibling matched at 8/8 major Ag): lowest risk of GVHD; preferred donor
  Mismatched related (eg, 1/8 Ag mismatch) or *haploidentical* (mismatch at 4/8 Ag): easiest to find, but ↑ risk of GVHD, rejection; ∴ need additional immunosuppression
  Matched unrelated: ↑ risk of GVHD; ∴ matching of 10 HLA alleles (*DQ* also) to ↓ risk; chance of match correlates w/ ethnicity (*NEJM* 2014;371:339)
  Umbilical cord blood: HSC processed at birth & stored; ↓ risk of GVHD; tolerate mismatch but much slower immune reconstitution (*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 **higher ablative chemo doses** and then rescues the hematopoietic system (used for lymphoma, multiple myeloma, testicular cancer, neuroblastoma)
  Allo HSCT produces **graft-vs.-tumor** (GVT) effect, in addition to hematopoietic rescue (used for AML, ALL > CML, CLL, MDS, lymphoma)
- **Nonmalignant disease:** allo HSCT replaces abnl lymphohematopoietic system w/ one from nl donor (eg, immunodef., aplastic anemia, hemoglobinopathies, ? autoimmune dis.)

Transplantation procedure

- **Preparative regimen:** *chemotherapy* and/or *immunosuppression* prior to transplantation
  myeloablative conditioning ("MAC"): chemotherapy and/or total body irradiation. Goal is *eradication* of underlying disease for which transplant is being performed.
  reduced intensity conditioning ("RIC" or "mini"): lower dose conditioning → ↓ toxicity to allow Pts w/ comorbidities or ↑ age to tolerate HSCT. Goal = transplant when in remission. Depends mostly on GVT; ↓ transplant-related mortality, but ↑ relapse (*Blood* 2015;126:23). Otherwise eligible candidates should have MAC.
- **Sources of stem cells:**
  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 (*NEJM* 2012;367:1487)
  umbilical cord blood (UCB): less stringent HLA-matching requirements, but fewer cells per donor (∴ 2 donors combined); slower engraftment, delayed immune recovery
  haploidentical: most available; new conditioning makes safer/more common
- **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; *Lancet* 2009;373:1550)
  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 beyond 3 mo posttransplant; *BMT* 2009;43:149)
  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
- **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	**Days 30–90**	**>90 days**
	Mucositis Organ dysfunction Neutropenia	Acute GVHD ↓ cellular immunity	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		
Immune-mediated	Acute GVHD		Chronic GVHD
	Primary graft failure	Secondary graft failure	

*Primarily among persons who are seropositive before transplant.

Prophylaxis/Supportive Medications during HSCT

Medication	Prophylaxis against	Duration
Fluconazole or posaconazole	*Candida*	75 d
Acyclovir	HSV/VZV	365 d
Valganciclovir 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

Pathology and Genetics				
	Pathology	**%**	**Typ locat.**	**Genetic mutations in**
Non-small cell	Adeno-carcinoma (incl. bronchioalveolar)	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 classifiable	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
  bronchioalveolar carcinoma associated with women, nonsmokers, *EGFR* mutations
- Asbestos: when combined with smoking, synergistic ↑ in risk of lung cancer
- Radon: risk to general population unclear

Clinical manifestations

- ~10% are asx at presentation and are detected incidentally by imaging
- **Endobronchial growth** of 1° tumor: **cough, hemoptysis, dyspnea,** 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 or arm swelling (>80%), venous distention of neck & chest wall (~60%), dyspnea/cough (~50%), HA (~10%); Rx = steroids & diuretics, RT ± chemo after tissue dx, SVC stent for severe sx, fibrinolytic + anticoag if thrombus
- **Extrathoracic metastases:** brain, bone, liver, adrenal
- **Paraneoplastic syndromes**
  Endocrine:
  ACTH (SCLC) → **Cushing's syndrome;** ADH (SCLC) → **SIADH**
  PTH-rP (squamous cell) → **hypercalcemia**
  Skeletal: digital clubbing (non–small cell), **hypertrophic pulmonary osteoarthropathy** (adenocarcinoma) = symmetric polyarthritis and proliferative periostitis of long bones
  Neurologic (SCLC): **Eaton-Lambert,** peripheral neuropathy, cerebellar degeneration, limbic encephalitis
  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 in current or former (quit w/in 15 y) smokers, age 55–74 y → 20% ↓ in lung cancer–related mortality (*NEJM* 2011;365:395 & 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.2.2016)

- **Initial imaging:** chest CT (include liver and adrenal glands) w/ contrast if possible
- **Tissue: 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) or sputum cytology (central lesions)
- **Staging**
  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 IA)

- **Genetics:** ✓ *EGFR* mut. & *ALK*, *ROS1* or *RET* rearrang. for stage IV nonsquam NSCLC
- PFTs w/ quantitative V/Q if planned treatment includes surgical resection; need to have 30% of normal, predicted lung fxn *after* resection

TNM Staging System for NSCLC (7th Edition)

	N stage	N0	N1	N2	N3
T/M stage	**Definition**	no ⊕ nodes	ipsilat. hilar	ipsilat. mediast.	contralat. or supraclav.
T1	T ≤2 cm (T1a) or T >2–3 cm (T1b)	IA	IIA		
T2	T ≤5 cm (T2a) or T 5–7 cm (T2b)	IB/IIA	IIA/B		
T3	T >7 cm or invasion of chest wall, diaph., mediast. pleura, pericard.	IIB	IIIA		
T4	Invasion of mediast., heart, great vessels, trachea, esoph, vertebrae; separate tumor nodule ipsilat. lobe			IIIB	
M1a	Nodules contralat lobe; pleural nodules or malignant effusion	IV			
M1b	Distant metastasis				

NSCLC treatment (*NCCN Guidelines* v.2.2016)

- **Stages I & II: surgical resection + adjuvant chemo** (surgery alone for stage IA) (*NEJM* 2004;350:351 & 2005;352:2589)
- **Stage III: chemoradiation** is main treatment modality
  IIIA viewed as potentially resectable (*Lancet* 2009;374:379) and IIIB as unresectable
  neoadjuvant chemoradiation may convert unresectable → resectable
- **Stage IV: chemotherapy** ↑ survival; early palliative care also ↑ survival (*NEJM* 2010;363:733)
  backbone of therapy is platinum-based doublet; cisplatin/pemetrexed better for adenocarcinoma; cisplatin/gemcitabine better for squamous (*JCO* 2008;26:3543)
  PD-1 inhib (eg, nivolumab, pembrolizumab, atezolizumab) if progression on chemo (*NEJM* 2015;373:123; *Lancet* 2016;387:1540 & 1837); immune-related adverse events include pneumonitis, consider Rx w/ high-dose corticosteroids
  bevacizumab (anti-VEGF mAb) + chemo ↑ survival by 2 mo; ↑ bleeding risk, ∴ avoid if untreated, brain mets (*JCO* 2009;27:5255), hemoptysis or squamous (*NEJM* 2006;355:2542)
  if EGFR mut.: EGFR tyrosine kinase inhibitor (TKI, eg, erlotinib) 1st-line Rx; next-gen EGFR TKI for those who develop resistance mutations (*NEJM* 2015;372:1689 & 1700)
  if ALK rearrang.: ALK TKI (crizotinib 1st-line Rx; *NEJM* 2014;371:2167); ceritinib 2nd-line
  TKI toxicities: rash & diarrhea (common); lung & liver injury (rare but potentially serious)
  palliative radiation used to control local sx caused by tumor or metastasis
  solitary brain metastasis: surgical resection + brain radiation may ↑ survival

NSCLC Simplified Staging Schema, Treatment and 5-y Survival

Stage	% at dx	Definition	Treatment	5-y (%)
I	10–20	Isolated lesion	Surgery + chemo	>60
II	10–20	Hilar node spread	Surgery ± radiation ± chemo	40–50
IIIA	15	Mediast. spread but resectable	Chemoradiation ± surgical resection	25–30
IIIB	15	Unresectable	Chemoradiation ± biologic ± surgery (selected cases)	10–20
IV	40	Metastatic	Chemo ± bevacizumab or tyrosine kinase inhibitor and/or supportive care	4

SCLC treatment (*NCCN Guidelines* v.1.2016)

- SCLC usually disseminated at presentation but can be very responsive to chemoradiation
- **Chemotherapy** (platinum + etoposide) is primary treatment modality
- **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 and genetics (risk assessment tool: www.cancer.gov/bcrisktool/)

- In U.S., most common cancer in women; 2nd leading cause of cancer death in women
- Age: incidence rates ↑ with age, with possible ↓ in slope after menopause
- **Genetics** (*Nature* 2012;490:61): mutations in *TP53, PIK3CA,* and *GATA3; HER2* amplified. 15–20% have ⊕ FHx → 2× ↑ risk; ~45% of familial cases a/w known germline mutation
  BRCA1/2: 35–85% lifetime risk of breast cancer & ↑ risk of **ovarian cancer;** ? ↑ colon & prostate cancer; prog not worse than in noncarriers w/ breast cancer (*NEJM* 2007;357:115); BRCA2: a/w ↑ *male* breast cancer & pancreatic cancer. Germline loss-of-function mutations in *PALB2* a/w 35% ↑ risk of 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); *no* ↑ risk shown with OCP use (*NEJM* 2002;346:2025)
- Benign breast conditions: ↑ risk w/ atypia (atypical ductal or lobular hyperplasia; *NEJM* 2015;372:78) & proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; *no* ↑ risk w/ cysts, fibroadenoma, or columnar changes
- ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin lymphoma

Prevention (with selective estrogen receptor modulator or AI; *Annals* 2013;159:698)

- Tamoxifen: ↓ risk contralat. breast CA as adjuvant Rx. Approved for 1° prevent. if ↑ risk: ↓ invasive breast cancer, but ↑ DVT & uterine CA; ? ↑ in mortality (*Lancet* 2002;360:817).
- Raloxifene: ↓ risk of invasive breast cancer & vertebral fx, ↑ risk of stroke & DVT/PE (*NEJM* 2006;355:125); = tamoxifen in prevention of breast cancer w/ ↓ risk of DVT/PE & cataracts, trend toward ↓ uterine cancer (*JAMA* 2006;295:2727)
- AIs in high-risk postmeno ↓ breast cancer by >50% (*NEJM* 2011;364:2381; *Lancet* 2014;383:1041)
- *BRCA 1/2* ⊕: intensified surveillance. Prophylactic bilat. mastectomy → ~90% ↓ risk; 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's** 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* 2016;164:279)

- **Mammography:** ~20–30% ↓ **in breast cancer mortality** (smaller abs. benefit in women <50 y) (*Lancet* 2006;368:2053; *Annals* 2009;151:727); 75% of all abnl findings benign; suspicious: 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/ CBE and mammo (age 25 in *BRCA 1/2* 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 Pts; consider annually if >20% lifetime risk (eg, ⊕⊕ FHx, *BRCA 1/2,* prior chest RT) (*Lancet* 2011;378:1804)
- **Genetic testing** should be considered in women with strong FHx

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: ductal cancer invading nipple epidermis ± associated mass

- **Biomarkers:** ✓ estrogen, progesterone receptor (ER/PR) and *HER2/neu* status
- Oncotype DX 21-gene risk recurrence score has predictive and prognostic value in ER ⊕, HER2 ⊖, and node ⊖ Pts (*NEJM* 2015;373:2005)
- Circulating tumor DNA may serve as biomarker of met tumor burden (*NEJM* 2013;368:1199)

Simplified Staging System for Breast Cancer

Stage	Characteristics	Description	5-y surv.
I	Tumor ≤2 cm	Operable locoregional	90%
IIA	Tumor >2 cm or *mobile* axillary nodes		80%
IIB	Tumor >5 cm		65%
IIIA	Internal mammary or *fixed* axillary nodes	Locally advanced	50%
IIIB	Direct extension to chest wall or skin	Inoperable locoregional	45%
IIIC	Infraclavicular or supraclavicular nodes		40%
IV	Distant metastases	Metastatic	25%

Treatment

- **Local control: surgery and radiation therapy (RT)**
  - *Breast-conserving* usual approach w/ lumpectomy + breast RT + axillary node dissection (ALND), unless multicentric dis., diffuse microCa^{2+}, BRCA1/2 ⊕, prior RT, pregnant, ? tumor >5 cm; cavity shaving ↓ risk of need for re-excision (*NEJM* 2015;373:503)
  - *Sentinel lymph node dissection (SLND)* prior to ALND preferred if w/o palp axillary LNs: T1-2 w/ ⊕ SLND & Rx w/ lumpect./RT/chemo may not need ALND (*JAMA* 2011;305:569)
  - *Radiation therapy* (RT) after mastectomy for ≥4 ⊕ LN, tumor >5 cm, or ⊕ surgical margins → ↓ locoregional recurrence and ↑ survival (*Lancet* 2011;378:1707); regional nodal RT ↓ recurrence and breast cancer mortality (*NEJM* 2015;373:307 & 317)
- **Systemic therapy:** for stage I–III except tumors <1 cm (complex risk assessment needed). http://www.adjuvantonline.com/index.jsp can guide use of chemo and/or hormonal Rx.
  - *Chemotherapy: neoadjuvant* (to ↑ breast conservation; path complete response a/w ↑ disease-free survival; *Lancet* 2014;384:164) or *adjuvant* (anthracycline-based). Addition of taxane (eg, paclitaxel) → small ↑ survival (*NEJM* 2010;362:2053 & 2010;363:2200). Consider platinum in triple ⊖ cancers (*JCO* 2015;33:13).
  - *Anti-HER2 therapy* (growing list of agents) in *HER2* ⊕ tumors (*NEJM* 2012;366:176)
    - **trastuzumab** (anti-*HER2* mAb) ↑ survival (*NEJM* 2011;365:1273); 1 y = 2 yr (*Lancet* 2013;382:1021); after anthracycline or w/ taxane to ↓ cardiotox (*JCO* 2002;20:1215)
    - lapatinib (tyrosine kinase inhib. of *HER2* & *EGFR*) + trastuzumab ↑ survival after failing trastuzumab (*JCO* 2012;30:2585); dual inhib. initial Rx ↑ response (*Lancet* 2012;379:633)
    - pertuzumab (anti-*HER2* mAb, prevents dimerization) ↑ progression-free survival when added to trastuzumab as 1st-line Rx for metastatic dis. (*NEJM* 2015;372:724)
    - trastuzumab emtansine (T-DM1, *HER2* mAb conjugated to microtubule inhibitor) ↑ survival compared to 2nd-line lapatinib + capecitabine (*NEJM* 2012;367:1783)
  - *Bevacizumab* (anti-VEGF): ? in neoadjuvant Rx if *HER2* ⊖ (*NEJM* 2012;366:299 & 310)
  - *Hormonal (in ER/PR ⊕ or unknown status)*
    - **tamoxifen:** 39% ↓ recurrence and 30% ↓ breast cancer mortality in pre- and post-menopausal patients; 10 y of Rx superior to 5 y (*Lancet* 2011; 378:771 & 2013;381:805)
    - **aromatase inhibitors (AI)** (anastrozole, letrozole, exemestane): ~18% ↓ recurrence vs. tamoxifen in *postmenopausal* Pts (*NEJM* 2005;353:2747 & 2016;375:209)
    - 2nd-line: ovarian ablation with LHRH agonists (goserelin) or oophorectomy if *premenopausal*; pure antiestrogens (fulvestrant) if *postmenopausal*
  - *Cell proliferation inhibitors (if postmenopausal & failed hormonal Rx)* palbociclib (CDK 4/6 inhib): ↑ progression-free survival (*NEJM* 2015;373:209) everolimus (mTOR inhib): ↑ progression-free survival (*NEJM* 2012;366:520)

Treatment of Carcinoma *in situ* and Invasive Carcinoma of the Breast

LCIS	Close surveillance ± chemoprevention; ? prophylactic bilat. mastectomy
DCIS	Mastect. or lump. + RT; ALND *not* indic.; + chemoprev (*Lancet* 2016;387:849 & 866)
I **II**	Surgery + RT + Adjuvant chemo if ↑ risk: tumor >1 cm *or* ⊕ LN *or* ER/PR ⊖ (*Lancet* 1998;352:930) + Hormonal therapy if ER/PR ⊕ (or unknown status) (*Lancet* 2009;374:2055) + anti-*HER2* Rx if *HER2* ⊕ and tumor ≥1 cm or ⊕ LN
III	Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + Hormonal therapy for ER/PR ⊕ (or unknown status) tumors + anti-*HER2* Rx if *HER2* ⊕
IV	ER/PR⊕: hormonal Rx (*NEJM* 2012;367:435) or chemo ± everolimus/palbociclib ER/PR⊖: *HER2* ⊕ → chemo + anti-*HER2* therapy; *HER2* ⊖ → chemotherapy Bony mets: bisphosphonates & denosumab ↓ fractures (*Cochrane* 2012;CD003474)

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 (usually asymptomatic at presentation)

- **Obstructive sx** (more common with BPH): hesitancy, ↓ stream, retention, nocturia
- **Irritative sx** (also seen with prostatitis): frequency, dysuria, urgency
- Periprostatic spread: hematuria, hematospermia, new-onset erectile dysfunction
- Metastatic disease: bone pain, spinal cord compression, cytopenias

Screening (*NEJM* 2012;367:e11; *JAMA* 2014;311:1143; *Lancet* 2014;384:2027)

- **Digital rectal exam** (DRE): size, consistency, lesions
- **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)
- ACS rec: ≥50 y (or ≥ 45 y if African-Am or ⊕ FHx) should discuss PSA screening w/ MD; USPSTF rec. against screening in asx males (no ↓ in prostate cancer-related mort.)

Diagnostic and staging evaluation

- **Transrectal ultrasound** (TRUS) **guided biopsy,** with 6–12 core specimens
- **Histology: Gleason grade** (2–10; low grade ≤6) = sum of the differentiation score (1 = best, 5 = worst) of the 2 most prevalent patterns in the bx; correlates with prognosis
- **Imaging:** to evaluate extraprostatic spread
  bone scan: for PSA >10 ng/mL, high Gleason grade or clinically advanced tumor
  abdomen-pelvis CT: inaccurate for detecting extracapsular spread and lymph node mets
  endorectal coil MRI: improves assessment of extracapsular spread

TNM Staging & Treatment of Prostate Cancer (*Lancet* 2015;387:70)

Stage	Tumor	Nodes, Mets	Treatment
I	T1a = non-palp., not visible on imaging	N0, M0, Gleason 2–4	**Surveillance:** consider if life expect. <10 y. Dutasteride ↓ risk of progression (*Lancet* 2012;379:1103). **Radiation** (external or brachy; *NEJM* 2006;355:1583). Short-term androgen deprivation ↓ mort. (*NEJM* 2011;365:107)
II	T1/T2 = w/ in prostate	N0, M0	**Radical prostatectomy** (± RT and/or hormonal Rx if high-risk features): ↓ prostate cancer mortality, espec. if <65 y and not low risk (*NEJM* 2014;370:932)
III	T3 = extends thru capsule	N0, M0	**Radiation** + androgen deprivation (see below) (*Lancet* 2011;378:2104)
IV	T4 = invades adjacent structures	N0, M0	**Radiation** (for M0 disease) **Androgen deprivation Rx (ADT)** (*NEJM* 2009;360:2516) **GnRH analogues** (leuprolide, goserelin) **antiandrogens** (flutamide, bicalutamide) **Docetaxel** added to ADT improves overall survival in metastatic disease (*NEJM* 2015;373:737) **If castrate resistant:** chemo (eg, docetaxel); androgen synthesis inhib. (abiraterone; *NEJM* 2011;364:1995) or receptor signaling inhib. (enzalutamide; *NEJM* 2012;367:1187) ↓ mort.; immuno Rx (*NEJM* 2010;363:411); olaparib (PARP inhib) if BRCA ⊕ (*NEJM* 2015;373:1697) Bone mets: bisphosph or denosumab, latter ↓ bone mets & fx (*NEJM* 2009;361:745; *Lancet* 2011;377:813 & 2012;379:39); radium-223 ↓ mortality by 30% (*NEJM* 2013;369:213)
		N1, M0	
	Any T	Any N, M1	

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
- PSA doubling time, Gleason, & time to biochemical recurrence predict mortality following recurrence. For local recurrence following RP, salvage RT may be beneficial if low PSA.
- Metastatic disease: median survival ~44-57 mo (*NEJM* 2015;373:737); all become castrate resistant (in 15–20% discontinuation of antiandrogens results in paradoxical ↓ in PSA)

Prevention

- Finasteride and dutasteride ↓ prostate cancers detected by bx, but ↑ # of high Gleason grade tumors; no Δ in overall mortality (*NEJM* 2003;349:215; 2010;362:1192; 2013;369:603)

COLORECTAL CANCER (CRC)

Epidemiology and risk factors (*Lancet* 2010;375:1030; *CA Cancer J Clin* 2011;61:212)

- 4th most common cancer in U.S. men & women; 2nd leading cause of all cancer death
- Rare before age 40, w/ 90% of cases occurring after age 50. ~75% are sporadic.
- **Family history:** up to 25% of Pts have ⊕ FHx. Risk depends on # of 1st-degree relatives (w/ CRC *or* polyp) and their age at dx; ~5% have an identifiable germline mutation
  - **Familial adenomatous polyposis (FAP):** mutation in *APC* gene → 1000s of polyps at young age → ~100% lifetime risk; ↑ risk of thyroid, stomach, small bowel cancers
  - **Hereditary nonpolyposis colorectal cancer (HNPCC):** most common hereditary CRC (~3% of all CRC); mutations in DNA mismatch repair genes (eg, *MSH2, MLH1*) → microsatellite instability (MSI) → ↑ tumor progression → ~80% lifetime risk.
    Predom. **right-sided** tumors; ↑ risk of **endometrial,** ovarian, stomach, urothelial, small bowel and pancreatic cancers.
    Amsterdam criteria: ≥3 family members w/ HNPCC-related cancer; one of which is dx before age 50, affecting 2 successive generations.
    MAP (MYH-assoc polyposis): autosomal *recessive*; consider if mult. polyps but ⊖ for FAP
- **Inflammatory bowel disease:** ↑ risk with ↑ extent and duration of disease
- **COX-2:** ↓ risk of adenomas w/ ASA & NSAIDs. ASA a/w ↓ CRC incidence, mets and mort. (*Lancet* 2010;376:1741; 2012;379:1591 & 1602). ASA effect limited to *PIK3CA*-mut CRC (*NEJM* 2012;367:1596). ASA rec for 1° prevention if age 50–59 (69?) y & ≥10% 10-y risk of CRC.

Pathology and genetics (*NEJM* 2009;361:2449; *Nature* 2012;487:330)

- **Adenoma → carcinoma sequence** reflects accumulation of multiple genetic mutations. ↑ risk of malig. w/ large (>2.5 cm), villous, sessile adenomatous polyps. Adenomas typically observed ~10 y prior to onset of cancer (both sporadic & familial).
- Genetic profile in sporadic CRC: *APC* (~80%), *KRAS* (~40%), *TP53* (50–70%), *DCC* or *SMAD4*, or *BRAF* (~15%); chrom instability (majority) or mismatch repair defic (10–15%)
- Upfront genotyping may guide Rx; eg, benefit of anti-EGFR Ab cetuximab greater in *KRAS* wild-type than KRAS mutant (*NEJM* 2008;359:1757). *BRAF* mutation may guide clinical trials. Lack of CDX2 a/w ↑ benefit from chemo (*NEJM* 2016;374:211).

Clinical manifestations

- Distal colon: Δ **bowel habits, obstruction,** colicky abdominal pain, **hematochezia**
- Proximal colon: **iron defic. anemia,** dull vague abd pain; obstruction atypical due to larger lumen, liquid stool and polypoid tumors (*vs.* annular distal tumors)
- Metastases: nodes, **liver,** lung, peritoneum → RUQ tenderness, ascites, supraclavicular LN
- Associated with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis

Screening (*JAMA* 2016;315:2564)

- **Average risk:** colonoscopy starting at age 50 & repeat q10y strongly preferred method
- **↑ risk:** earlier and/or more frequent screening. ⊕ FHx: age 40 or 10 y before index dx, then q5y. IBD: 8–10 y after dx, then q1–2y. Known or suspected familial syndrome: genetic counseling & very early screening (eg, age 20–25 y), then q1–2y.
- **Imaging**
  - **Colonoscopy:** test of choice as examines entire colon; 90% Se for lesions >1 cm. Flex sig less Se vs. colo and CTC (*Gut* 2009;58:241). If polyp found, re ✓ in 3–5 y. Removal of adenomatous polyps associated with lower CRC mortality (*NEJM* 2012;366:687).
  - **Sigmoidoscopy:** 21% ↓ incidence in CRC & 26% ↓ mortality in distal CRC (*NEJM* 2012;366:2345). Benefit may also be seen w/ 1-time flex-sig (*Lancet* 2010;375:9726).
  - **CT colonography (CTC):** c/w colonoscopy. ~90% Se for lesions ≥1 cm but considerably less for smaller lesions (*NEJM* 2008;359:1207). In high-risk Pts, Se only 85% for advanced neoplasia ≥6 mm (*JAMA* 2009;301:2453). At population level, ↑ participation w/ CTC, but ↓ yield vs. colonoscopy; ∴ similar screening overall (*Lancet* 2012;13:55).
- **Biochemical fecal testing**
  - **Occult blood** (FOBT): ↓ mortality (*NEJM* 1993;328:1365 & 2000;343:1603); 3 card home testing more Se (24% vs. 5%) than DRE/FOBT (*Annals* 2005;142:81). Repeat q1y.
  - **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)

Staging (*AJCC Cancer Staging Manual*, 7th ed, 2010)

- TNM staging: Size/depth of primary (T), locoregional nodes (N), distant metastases (M). Staging is complex and based on pathologic correlation with observed survival data.
- **Colonoscopy + biopsy/polypectomy + intraoperative** and **pathologic** staging essential for evaluating extracolonic spread
- CT scans of chest and abdomen/pelvis (inaccurate for depth of invasion & malignant LN)
- Baseline **CEA** in Pt *with known CRC* has prognostic significance and is useful to follow response to therapy and detect recurrence; *not* a screening tool

Treatment Based on TNM and Modified Dukes Staging of Colorectal Cancer				
TNM	**Dukes**	**Path. criteria**	**5-y surv.**	**Treatment**
I	A	Into submucosa or muscularis	94–97%	Surgery alone (resection and analysis of ≥12 LN)
IIA	B	Into serosa	83%	Surgery; no established role for adjuvant chemo for colon cancer[a]
IIB	B	Into peritoneum	74%	Preop RT or 5-FU/RT added for rectal cancer → postop chemo
IIC	B	Direct invasion	56%	
IIIA	C	≤6 ⊕ LNs	86%	Surgery + chemotherapy[b]
IIIB	C	Varying # ⊕ LNs & local invasion	51–77% 15–47%	Preop RT or chemorad added for rectal cancer (*NEJM* 2006;355:1114)
IIIC	C			
IV	D	Distant metastases	5%	Chemotherapy ± surgical resection for isolated mets (~30% 5-y surv) Consider resection of 1° tumor if perf, obstruction or bleeding

NCCN Clinical Practice Guidelines, www.nccn.org 5-y survival data are approx. equivalent for colon and rectal cancers, shown as average, w/ ranges for TNM substaging, adapted from SEER data (*JCO* 2010;28:256 & 264). [a]Consider adjuvant chemo for high-risk stage II (obstruction, perf, adherence to adjacent structures, inadequate nodal sampling, lymphovasc invasion, poorly differentiated). MSI-high CRC benefit less from adjuvant chemo (*NEJM* 2003;349:247). [b]Adjuvant FOLFOX (see below) is standard of care chemo (*NEJM* 2004;350:2343).

- Chemotherapy (*Lancet* 2014;383:1490)
  FOLFOX (**5-FU + leucovorin + oxaliplatin**), FOLFIRI or CapeOx (*NEJM* 2004;350:2343)
  ± Bevacizumab (anti-VEGF, *NEJM* 2004;350:2335) or cetuximab/panitumumab (anti-EGFR mAb, *NEJM* 2004:351:337; benefit limited to Pts w/o *RAS* mutations; *NEJM* 2013;369:1023)
  Consider FOLFOXIRI-bevacizumab particularly if BRAF⊕ mutations or needing response for potentially curative resection (*NEJM* 2014;371:1609)
  Regorafenib (multikinase inhib.) and TAS102 (trifluridine + tipiracil) ↑ survival in progressive metastatic CRC (*Lancet* 2013;381:303; *NEJM* 2015;372:1909)

CHEMOTHERAPY SIDE EFFECTS

Nausea & vomiting common (*NEJM* 2016;374:1356; 375:134 & 177)

Select Adverse Effects from Chemotherapy		
Toxicity	**Common Agents**	**Comments**
Cardiotoxicity (*JCO* 2005;23:7685; *NEJM* 2013;368:1154) *Stop agent if adverse event; ? role for ACEI in prevention* (*Circ* 2006;114:2474).	**Anthracyclines**	Dose-dependent CMP; ✓ EF pre-Rx; via topoisomerase IIb (*Nat Med* 2012;18:1639)
	5-FU	Spasm → ischemia; CCB may prevent
	Trastuz. & PD-1 inhib	CMP, esp. w/ concom anthracycline
	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 w/ steroids
	TKI (esp. dasatinib)	Pulmonary effusion
	Cyclophosphamide (<1%)	Pneumonitis, progressive fibrosis; d/c drug
	Bevacizumab	Pulm hemorrhage (esp. NSCLC)
	Anti-PD1 (eg, nivolumab)	Pneumonitis
	Anti-CTLA-4 (ipilimumab)	Organizing pneumonia, sarcoidosis
Nephrotoxicity/ urologic toxicity	Platinum Rx (**cisplatin**)	Esp. proximal tubule; pretreat w/ IV saline
	Methotrexate	Rx deposition; alkalinize urine, hydration
	Cyclophosphamide	Hemorrhagic cystitis; give Mesna
Neurotoxicity (*Sem Oncol* 2006;33:324)	Platinum Rx (**cisplatin**)	"Stocking-glove;" vit. E Ppx (*JCO* 2003;21:927)
	Cytarabine	Cerebellar toxicity (irreversible 5–10%)
	Methotrexate (esp. intrathecal)	Late leukoenceph, meningitis; reverse w/ intrathecal glucarpidase, leucovorin
	Ifosfamide	Enceph (10–30%); ? Rx w/ methylene blue, thiamine, dexmedetomidine
	Taxanes, vincristine	Sensorimotor long fiber neuropathy
Hepatotoxicity (*Sem Oncol* 2006;33:50)	TKI (eg, imatinib, nilotinib)	↑ LFTs, rarely necrosis; hold Rx, ? steroids
	Gemcitabine	Common ↑ ALT/AST; ↓ dose if ↑ bili
	Methotrexate	↑ ALT/AST, rarely fibrosis
Dermatologic	TKI (eg, imatinib)	Dermatitis, can be severe (eg, SJS)

PANCREATIC TUMORS

Pathology and genetics *(Ann Rev Pathol 2008;3:157; Nature 2012;491:399)*

- Histologic types: adenocarcinoma, acinar cell carcinoma, endocrine tumors, cystic neoplasms (eg, IPMN, see below); rarely, mets to pancreas (eg, lung, breast, renal cell)
- Pancreatic adenocarcinoma accounts for majority of pancreatic cancer (~85%)
- Location: ~60% in head, 15% in body, 5% in tail; in 20% diffuse infiltration of pancreas
- Mutations in adenoca.: *KRAS* (>90%), *p 16* (80–95%), *p53* (50–75%), *SMAD4* (~55%)

Epidemiology and risk factors *(NEJM 2014;371:1039; Lancet 2016;388:73)*

- Pancreatic adenocarcinoma 4th leading cause of cancer death in U.S. men and women
- 80% of pancreatic adenocarcinomas occur in Pts 60–80 y
- Acquired risk factors: **smoking** (RR ~1.5; 20% Pts), obesity, chronic pancreatitis, ? diabetes
- Hereditary risk factors: genetic susceptibility may play a role in 5–10% of cases
  Hereditary chronic pancreatitis: mutation in cationic trypsinogen gene (*PRSS 1*), *SPINK 1*
  Familial cancer syndromes and gene mutations with ↑ risk: familial atypical multiple mole melanoma (*CDKN2A/p 16*), familial breast and ovarian cancer (*BRCA2*), Peutz-Jeghers (*LKB 1*), ataxia-telangiectasia (*ATM*), ? hereditary colorectal cancer (HNPCC and FAP)

Clinical manifestations

- **Painless jaundice** (w/ pancreatic head mass), **pain** radiating to back, ↓ **appetite & wt**
- New-onset atypical diabetes mellitus (25%); unexplained malabsorption or pancreatitis
- Migratory thrombophlebitis (Trousseau's sign), not specific to panc cancer *(JCO 1986;4:509)*
- Exam: abd mass; nontender, palpable gallbladder (Courvoisier's sign, but more often seen w/ biliary tract cancers); hepatomegaly; ascites; left supraclavicular (Virchow's) node & palpable rectal shelf (both nonspecific signs of carcinomatosis)
- Laboratory tests may show ↑ bilirubin, ↑ alk phos, anemia

Diagnostic and staging evaluation *(NCCN Guidelines v.2.2012)*

- **Pancreatic protocol CT scan** (↑ w/ arterial & venous phase imaging) **or MRI**
- If no lesion seen, → EUS, ERCP, MRI/MRCP may reveal mass or malignant ductal strictures
- 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 (nb, also ↑ in benign liver/biliary disease); may be useful to follow dis. postop

Clinical (Radiologic) Staging & Prognosis of Pancreatic Adenocarcinoma

Stage (% at dx)	Criteria	Median Survival
Resectable, 15–20%	No extrapanc. dis. or bulky LAN Patent SMV & portal vein; celiac axis & SMA not involved	10–20 mo (favorable: tumor <3 cm, ⊖ marg., well-differen.) 5-y ~30% node ⊖ vs. ~10% if ⊕
Locally advanced (unresect.), 40%	Extensive PV/SMV, celiac axis or SMA involvement	8–12 mo
Metastatic, 40%	Usually liver & periton.; occ lung	Up to 11 mo w/ FOLFIRINOX

Treatment of pancreatic adenocarcinoma *(NEJM 2014;371:1039; Lancet 2016;388:73)*

- Resectable: surgery ± adjuvant (neoadjuvant or postoperative) therapy
  pancreaticoduodenectomy = **Whipple procedure** = resection of pancreatic head, duodenum, CBD and gallbladder ± partial gastrectomy
  adjuvant therapy: ↑ survival, but choice of regimen controversial (chemo vs. chemo/RT and gemcitabine vs. 5-FU *(J Surg Oncol 2013;107:78; JAMA 2013;310:1473)*
- Locally advanced: optimal strategy controversial. Gemcitabine alone vs. gemcitabine + RT *(JCO 2008;26:2144s; Ann Oncol 2008;19:1592; JCO 2011;29:4105)*.
- Metastatic: **FOLFIRINOX** (5-FU + leucovorin, irinotecan, oxaliplatin) if good perform. status *(NEJM 2011;364:1817)*; **gemcitabine** + nab-paclitaxel *(NEJM 2013;369:1691)* or gemcitabine monotherapy if poor performance status *(JCO 1997;15:2403). Offer clinical trials.*
- Palliative and supportive care:
  obstructive jaundice or gastric outlet obstruction: endoscopic stenting or surgical bypass
  pain: opiates, celiac plexus neurolysis, radiation therapy
  weight loss: pancreatic enzyme replacement, nutrition consult, end-of-life discussions

Cystic lesions of the pancreas *(NEJM 2004;351:1218; Oncologist 2009;14:125)*

- <10% of pancreatic neoplasms. Dx w/ CT, ERCP, MRCP, or EUS.
- **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): neoplasm arising in main pancreatic duct or a branch; a/w ductal dilation w/ extrusion of mucinous material. Uncertain progression to cancer (? 5–20 y). Surgery based on age, size, location, & dysplasia.

FEVER AND NEUTROPENIA (FN)

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 a/w 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
- Infection with atypical organisms and bacterial meningitis is rare

Prevention
- Levofloxacin (500 mg qd) ↓ febrile episodes & bacterial infections in chemo-related high-risk neutropenic patients; no difference in mortality (*NEJM* 2005;353:977 & 988)

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: age <60 y, no symptoms, no major comorbidities, cancer in remission, solid tumor, no h/o fungal infection or recent antifungal Rx
- Exam: temp <39°C, no tachypnea, no hypotension, no Δ MS, no dehydration
- Studies: ANC >100 cells/μL, anticipated duration of neutropenia <10 d, normal CXR

Initial antibiotic therapy (*Clin Infect Dis* 2011;52:e56, *NCCN Guidelines* v.2.2015)
- Empiric regimens including drug w/ **antipseudomonal activity;** consider VRE coverage if colonized; OR 3.8 for VRE if VRE ⊕ (*BBMT* 2010;16:1576)
- PO abx may be used in low-risk Pts (<10 d neutropenia, nl hep/renal fxn, no N/V/D, no active infxn, stable exam): cipro + amoxicillin-clavulanate (*NEJM* 1999;341:305)
- IV antibiotics: no clearly superior regimen; monotherapy or 2-drug regimens can be used
  Monotherapy: ceftazidime, cefepime, imipenem, or meropenem
  2-drug therapy: aminoglycoside + antipseudomonal β-lactam
  PCN-allergic: levofloxacin + aztreonam or aminoglycoside
- **Vancomycin** in select cases (HoTN, PNA, clinically apparent catheter-related or soft-tissue infxn, MRSA colonization, gram ⊕ BCx, h/o quinolone ppx); d/c when cultures ⊖ × 48 h

Modification to initial antibiotic regimen
- Low-risk Pts who become afebrile w/in 3–5 d can be switched to PO antibiotics
- Empiric antibiotics changed for fever >3–5 d or progressive disease (eg, add vancomycin)
- Antifungal therapy is added for neutropenic fever >5 d
  liposomal amphotericin B, caspofungin, micafungin, anidulafungin, voriconazole, & posaconazole are all options (*NEJM* 2002;346:225; 2007;356:348)

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 (*NEJM* 2013;368:1131)
- 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 impact mortality.
- 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 the most common causes, followed by renal cell carcinoma, NHL and myeloma
- **Site of involvement: thoracic** (60%), lumbar (25%), cervical (15%)
- Signs and symptoms: **pain** (>95%, *precedes neuro Δs*), **weakness, autonomic dysfunction** (urinary retention, ↓ anal sphincter tone), **sensory loss**

Diagnostic evaluation

- Always take back pain in Pts with solid tumors very seriously
- Do *not* wait for neurologic signs to develop before initiating evaluation b/c duration & severity of neurologic dysfunction before Rx are best predictors of neurologic outcome
- Urgent **whole-spine MRI** (Se 93%, Sp 97%); CT myelogram if unable to get MRI

Treatment

- **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; *BJH* 2010;149:578)

- Large tumor burden or a rapidly proliferating tumor → spontaneous or chemotherapy-induced release of intracellular electrolytes and nucleic acids
- Most common w/ Rx 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/m² 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
- 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 × 1, repeat as indicated) for ↑↑ UA, esp. in aggressive malig; UA level must be drawn on ice to quench *ex vivo* enzyme activity (*JCO* 2003;21:4402; *Acta Haematol* 2006;115:35). Avoid in G6PD deficiency as results in hemolytic anemia.
- Treat hyperkalemia, hyperphosphatemia and symptomatic hypocalcemia
- Hemodialysis may be necessary; early renal consultation for Pts w/ renal insuffic. or ARF

CANCER OF UNKNOWN PRIMARY SITE

Evaluation of Cancer of Unknown Primary (*Lancet* 2012;379:1428)

Path	Possible sources	Markers	Imaging	Additional path
Adeno.	Colon, upper GI, panc. HCC Breast Ovarian, prostate Lung	CEA, CA19-9 AFP CA15-3 CA125, PSA	Endoscopy/EUS Abd/pelvic CT Mammography Pelvic U/S Chest CT	CDX1, CK7/20 ER/PR, GCDFP CA125, PSAP TTF1, CK7
Squam.	Lung Head & neck Esophageal Cervix, anus	None	Chest CT Laryngoscopy Endoscopy	TTF1, CK7
Poorly Differen.	Germ cell Lymphoma Thyroid GIST, sarcoma Neuroendocrine	hCG, AFP LDH Thyroglob.	Testicular U/S PET Thyroid U/S Abd/pelvic CT	PLAP, isochrom 12p LCA, flow, cytogenetics Thyroglobulin c-KIT, desmin, vimentin NSE, chromogranin *Consider EM for all*

Additional studies for each possible source listed in same row.

- Bony mets: common primary tumors include breast, lung, thyroid, kidney, prostate

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 health care-assoc (HAP/HCAP)	*S. aureus, Pseudo., Klebsiella, E. coli, Enterobacter, Acinetobacter* (HCAP risk factors: hosp or abx w/in 90 d, nursing home, home infusion Rx or dialysis w/in 30 d, home wound care, family member w/ MDR pathogen, immunosupp)
Immunosuppressed	*Above* + PCP, fungi, *Nocardia*, non-TB mycobacteria (NTM), CMV
Aspiration (*NEJM* 2001;334:665; *Curr Opin Pulm Med* 2011;17:148)	*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 (eg, w/ *S. pneumo*): 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 (typically w/ putrid breath)

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
- **CXR** (PA & lateral; see Radiology inserts) → tap effusions if >5 cm or severe PNA
- Other: $\mathbf{S_aO_2}$ 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 for AFB stain and mycobacterial cx (*empiric respiratory isolation while pending*); avoid quinolones if suspect TB; request rapid DNA probe if stain ⊕
  - Induced sputum for PCP if HIV ⊕ or known ↓ cell-mediated immunity
- Viral testing (DFA or PCR) on nasopharyngeal swab or sputum
- Bronchoscopy: consider if immunosupp., critically ill, failing to respond, or chronic pneumonia. Also if 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)

Prevention

- Pneumococcal vaccine (PPSV23): *all* persons >65 y of age. If high-risk comorbidity, give at younger age and consider additional vaccination with PCV13.
- VAP precautions: HOB >30°, chlorhexidine rinse; aspiration precautions in high-risk Pts
- Tdap booster: 1-time dose in adults with uncertain vaccination history (*MMWR* 2012;61:468)

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)

Pneumonia Severity Index, Prognosis, & Recommended Triage (*NEJM* 1997;336:243)

Class	Score	Mortality	Suggested Triage
I & II	≤70	<1%	Outpatient
III	71–90	3%	? Brief inpatient
IV	91–130	8%	Inpatient
V	>130	29%	ICU

Variables	Points
Demograph.	Men (age in y), women (age – 10), nursing home resident (+10)
Coexist. probs	Neoplasm (+30), liver dis. (+20), CHF (+10), CVA (+10), renal dis. (+10)
Exam	Δ MS (+20), RR >30 (+20), SBP <90 (+20), T <35°/>40° (+15), HR >125 (+10)
Laboratory	pH <7.35 (+30), BUN >30 (+20), Na <130 (+20), glc >250 (+10), Hct <30 (+10), P_aO_2 <60 or S_aO_2 <90 (+10), pleural effusion (+10)

Treatment (*CID* 2007;44 Suppl:S27; *JAMA* 2016;315:593)

Scenario	Regimen	Special considerations
CAP (outPt)	Azithro or doxy	Recent abx or multiple comorbidities: respiratory FQ or [azithro + amox/clav]
CAP (ward)	Resp FQ or [3rd-gen ceph + azithro]	Doxy can replace azithro
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	Clindamycin, amox-clav, or β-lactam + metronidazole	

- Consider TMP-SMX if PCP suspected in immunosupp. host. Consider oseltamivir for flu.
- Steroids (pred 50 mg × 7 d or methylpred 0.5 mg/kg q12h × 5 d) *may* speed clinical stabilization and ↓ late resp failure (*Lancet* 2015;385:1511; *JAMA* 2015;313:677; *Annals* 2015;163:519), but not well studied in flu and not widely embraced yet
- Duration: CAP: 5–7 d if stable & afebrile for 48–72 h
  HCAP: 8 d (exception: 15 d for *Pseudomonas* or other nonfermenting GNR)
- When possible, de-escalate abx based on sensitivities

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.
- Seasonal flu: 365,000 hosp, 51,000 deaths per y in U.S.; most >65 y (*NEJM* 2008;359:2579)
- Pandemic 2009 H1N1 (swine): more severe in younger and obese Pts (*JAMA* 2009;302:1896)
- Sporadic 2011 H3N2: adults exposed to swine (also human-to-human) (*MMWR* 2011;60:1615)
- H5N1 influenza (avian): ongoing small outbreaks globally

Diagnosis

- Primarily clinical: **cough, fever, myalgias,** arthralgias, rhinorrhea, pharyngitis (in contrast, viral bronchitis p/w cough ± low-grade temp; usually benign & self-limited)
- Respiratory viral panel on nasal washing or sputum/BAL
- Rapid influenza test on nasal swab: Se ~50–70% (? lower for pandemic flu), Sp >95%
- DFA (Se ~85%), RT-PCR (gold standard) avail. for influenza (PCR distinguishes type)

Treatment (*NEJM* 2008;359:2579; *Lancet* 2015;385:1729)

- Seasonal influenza: treat with neuraminidase inhib. (oseltamivir, zanamivir), which are effective vs. A & B (shortens sx by ~1 d), but resistance emerging. M2 inhib. (amantadine, rimantadine) not recommended due to widespread resistance (*MMWR* 2011;60:1).
- Pandemic H1N1: nearly 100% sens. to **oseltamivir.** H5N1: Uncertain resistance pattern. H7N9: newly emerging in Asia (*NEJM* 2013;368:1888)
- 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.
- Consider inhaled ribavirin for RSV 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

Candida species

- **Microbiology:** normal GI flora; *C. albicans* & nonalbicans spp. (consider azole resistance if h/o Rx or nonalbicans; *C. parapsilosis* ↑ echinocandin resistant). Sensi testing available.
- **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: r/o retinal involvement (ophtho consult in all cases, 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 (*must determine colonization vs. infection*)	Fluconazole or intravesical ampho* if sx, severely immunosupp. or will undergo GU procedure
Candidemia w/o neutropenia	**Echinocandin** or fluconazole or ampho, *remove any intravascular catheters if possible*
Febrile neutropenia	**Echinocandin** or ampho

*See IDSA guidelines for ampho dosing. Liposomal preparation preferred, if available.

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
    - In HIV ⊕ or immunosupp. Pts, CNS Rx has induction (ampho ± flucytosine), 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 in healthy Pts: fluconazole vs. observation, based on clinical setting

Histoplasmosis (*CID* 2007;45:807)

- Hyperendemic 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* 2005;41:1217)

- **Endemic:** 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:** 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 B if severe, disseminated or immunosupp.

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

- **ABPA; hypersensitivity pneumonitis:** see "Interstitial Lung Disease"
- **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 manifestations: 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, **pulmonary** (PNA w/ infarct & necrosis); **cutaneous** (indurated painful cellulitis ± eschar); **GI** (necrotic ulcers).
- **Treatment:** debridement + Rx (ampho, posaconazole, or isavuconazole); high mortality

Fungal diagnostics

- **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 clinically useful for *Coccidio*
- **Antigen detection**
  - **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
  - **1,3-β-D-glucan:** Se for many fungal infxns (*Candida, Aspergillus, Histo, Coccidio, Fusarium, Pneumocystis, Sporothrix*), but not *Crypto, Blasto, Mucor, Rhizopus;* not Sp
  - **Galactomannan:** serum levels Se ~65%, Sp ~90% for invasive aspergillosis. BAL levels in Pts w/ hematologic malignancy ↑ Se, but ↓ Sp (false ⊕ seen w/ colonization)
  - **Blastomyces:** urine > serum Ag, high Se but modest Sp given X-react w/other fungi
- **Biopsy** (ie, histopathology): nb, no grinding of tissue if Zygomycetes suspected

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

- Anatomic
  - **lower:** urethritis, cystitis (superficial infection of bladder)
  - **upper:** pyelonephritis (inflam of renal parenchyma), renal/perinephric abscess, prostatitis
- Clinical
  - **uncomplicated:** cystitis in immunocompetent ♀ w/o underlying structural/neuro disease
  - **complicated:** upper tract infection in women *or* any UTI in men or pregnant women *or* UTI with underlying structural/neuro disease, bladder dysfxn or immunosuppression

Microbiology

- Uncomplicated UTI: ***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*) usually contaminants (*Annals* 2012;156:ITC3).
- Complicated UTI: *E. coli* (30%), enterococci (20%), *PsA* (20%), *S. epi* (15%), other GNR
- Catheter-associated UTI: **yeast** (30%), *E. coli* (25%), other GNR, enterococci, *S. epi*
- Urethritis: *Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Trichomonas vaginalis, Mycoplasma genitalium,* HSV
- *S. aureus:* uncommon primary urinary pathogen in absence of catheter or recent instrumentation; ∴ consider bacteremia w/ hematogenous seeding

Clinical manifestations

- **Cystitis: dysuria, urgency, frequency,** hematuria, suprapubic pain; fever usually *absent.* R/o vaginitis if symptoms of cystitis and urethritis.
- **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 sx
  - Significant bacterial counts: typically $\geq 10^5$ CFU/mL in women, $\geq 10^3$ CFU/mL in men or catheterized Pts. 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
- Blood cultures: obtain in febrile Pts; consider in complicated UTIs
- DNA detection/cx for *C. trachomatis/N. gonorrhoeae* in high-risk Pts or sterile pyuria
- If ♀ prostatitis: 1st void, midstream, 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

Scenario	Empiric treatment guidelines[a]
Cystitis (*JAMA* 2014;16:1677)	Uncomp: nitrofurantoin[b] 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 Asx bacteriuria in pregnancy or prior to urologic surgery → abx × 3 d
Catheterized	Abx as above & **remove catheter.** Exchange if removal impossible.
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* amp/sulbactam *or* aminoglycoside × 14 d (Δ IV → PO when clinically improved & afebrile 24–48 h)
Renal abscess	Drainage + antibiotics as for pyelonephritis

[a]Choice of agent individualized based on h/o allergies and adherance, local practice patterns, community prevalence and uropathogen resistance patterns, availability, cost, and Pt and provider threshold for failure. For empiric outPt Rx, community resistance to abx should be <20% for cystitis or <10% for pyelonephritis. Beta-lactams have less efficacy than other abx for UTI (*CID* 2011;52:e103; *NEJM* 2012;366:1028)

[b]Note risk of pulmonary fibrosis with prolonged or recurrent use.

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 and oral flora (incl anaerobes) + special exposures:

Feature	Microbiology	Clinical
Cat bite	*P. multocida*	Rapid onset
Dog bite	*P. multocida*	Rapid onset
	C. canimorsus	Sepsis w/ symmetric, peripheral gangrene in asplenic/cirrhosis and other immunosupp.
Penetrating injury	*Pseudomonas*	Can be a/w deep tissue abscess
Gardening	*Sporothrix*	Ulcerating nodules, lymphatic spread
Salt H_2O or raw oysters/fish	*V. vulnificus*	Hemorrhagic bullae & sepsis (esp. in cirrhotics). If suspected, Rx w/ doxy + ceftaz.
	Erysipelothrix	Rapid onset, endocarditis can develop
Fresh H_2O	*Aeromonas*	Myonecrosis/rhabdo can occur. If suspected, Rx w/ doxy + cipro.

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)

Purulent	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
Yes	*S. aureus* (incl. MRSA) >> β-hemolytic *Strep.*	Mild	I&D only
		Mod	TMP-SMX or doxy; some data for clinda (NEJM 2015;372:1093), but MRSA sensitivity variable
		Severe	Vanc, dapto, linezolid, ceftaroline, or telavancin

Mild: no systemic signs of infection; moderate: systemic signs; severe: SIRS or immunocompromised
Narrow abx per Cx data. Dalbavancin & oritavancin being studied (NEJM 2014;370:2169 & 2180).

- **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)

NECROTIZING FASCIITIS

Definition

- Infection and necrosis of superficial fascia, subcutaneous fat and deep fascia (necrosis of arteries and nerves in subcutaneous fat → gangrene)
- Fournier's gangrene: necrotizing fasciitis of the male genitalia or female perineum

Epidemiology

- Affects healthy individuals but ↑ risk: DM, PVD, EtOH abuse, IVDU, immunosupp., cirrhosis

Microbiology

- Type I (after abd/perineal surgery or trauma; in DM, PVD): polymicrobial (w/ anaerobes)
- Type II (usually extremities): *Strep pyogenes* ± MRSA, often healthy w/o obvious portal of entry; up to ½ have toxic shock syndrome (TSS)

Clinical manifestations
- Need *high degree of clinical suspicion* because of nonspecific physical exam
- Most common sites: extremities, abdominal wall, and perineum, but can occur anywhere
- **Cellulitic skin** Δs with poorly defined margins + **rapid spread** + **systemic toxicity**
- **Pain out of proportion** to apparent cellulitis; skin hyperesthetic and later anesthetic
- **Bullae, darkening of skin to bluish-gray ± crepitus** or radiographically visible gas

Diagnostic signs
- Clinical dx sufficient to initiate **urgent surgical exploration**
- Aspiration of necrotic center; BCx; Gram stain; ✓ CK for tissue necrosis
- Imaging: **noncontrast CT,** but do not delay therapy (*Arch Surg* 2010;145:452)
- Microbiologic dx from Gram stain and culture of surgical specimens

Treatment
- Definitive treatment is **surgical débridement** of necrotic tissue and fasciotomy
- Type I: empiric Tx w/vanc + pip-tazo
- Type II: PCN + clinda. If ↑ risk of CA-MRSA, + vanco. If concern for strep, IVIG.

Prognosis
- Generally fatal if untreated; reported mortality 20–50%

Clostridial Myonecrosis (Gas Gangrene)

Definition
- Life-threatening, fulminant clostridial infection of skeletal muscle
- **Wound contamination** w/ clostridial spores after **trauma** (penetrating or crush injury)
- Most commonly *C. perfringens; C. septicum* assoc w/ cancer (GI, heme), even w/o trauma

Clinical manifestations
- Incubation period 6 h to 2–3 d
- Sense of heaviness/pain, often at site of trauma; rapid worsening; marked systemic toxicity
- Bronze skin discoloration, tense bullae, serosanguineous or dark fluid and necrotic areas
- **Crepitus** present but not prominent (gas is in muscle), may be obscured by edema

Diagnostic studies
- Gram stain: **large, Gram ⊕ rod w/ blunt ends** *(can be Gram-variable)*, few polys
- Bacteremia in ~15%
- Plain radiographs: gas dissecting into muscle

Treatment
- **Surgical exploration with débridement,** fasciotomies and amputation if necessary
- **Antibiotics:** high-dose **penicillin G** 24 MU IV divided q2–3h + **clinda** 900 mg IV q8h

Neuropathic Foot Ulcer

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

Microbiology
- **Mild** (superficial, no bone or joint involvement): usually *S. aureus* or aerobic streptococci
- **Limb- or life-threatening** = deep, bone/joint involvement, systemic tox., limb ischemia
- Mono- or polymicrobial with aerobes + anaerobes
  aerobes = *S. aureus*, strep, enterococci and GNR (including *Pseudomonas*)
  anaerobes = anaerobic streptococci, *Bacteroides, Clostridium* (rare)

Clinical manifestations
- Clinical dx: ≥2 classic s/s of inflammation (erythema, warmth, tenderness [may be absent in neuropathy], pain or induration) or purulent secretions ± crepitus (indicating gas and ∴ mixed infection w/ GNR & anaerobes or *Clostridium*)
- Complications: osteomyelitis, systemic toxicity (fever, chills, leukocytosis, hyperglycemia)

Diagnostic studies
- Avoid superficial swabs (*only* helpful if ⊕ for *S. aureus* and suspect infxn); **wound cx** (eg, deep tissue sample or curettage at ulcer base after débridement) has ↑ Se
- Blood cx should be obtained in all Pts, ⊕ in 10–15%
- **Osteomyelitis should always be ruled out:** probe to bone test for all open wounds in a diabetic foot (high Sp but low Se); imaging (see below); **bone biopsy** best

Treatment (*CID* 2012;54:e132)

Severity of Infxn	Empiric Antibiotics
Mild	PCNase-resistant PCN *or* 1st-gen. ceph. (TMP-SMX if ? MRSA)
Chronic, previously treated or serious	(FQ *or* ceftriaxone + clinda) *or* amp-sulbactam *or* ticar-clav *or* ertapenem. If MRSA, add vanco *or* TMP-SMX *or* linezolid *or* telavancin *or* dapto *or* ceftaroline.
Limb or life-threatening	Vanco + anti-*Pseudomonal* agent: imipenem *or* pip-tazo *or* (aztreonam + metronidazole)

- Elevation, non–weight-bearing status, **wound care,** glycemic control
- Evaluation and treatment for venous insufficiency and arterial ischemia
- **Many require surgery:** early, aggressive and repeated débridement; revascularization or amputation may be necessary
- Management by multidisciplinary team improves outcomes

Osteomyelitis

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

Microbiology (*NEJM* 1997;336:999; *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)

Diagnostic studies (*JAMA* 2008;299:806)

- Identification of the causative organism is key
- **Tissue cx** (aspiration bx Se 30–74%) unless ⊕ blood Cx. Do not rely on swabs of ulcers or fistulae drainage.
- High suspicion in diabetic foot (see above) if can probe ulcer to bone or ulcer >2 cm^2
- **Blood cultures** (more often ⊕ with acute hematogenous osteomyelitis)
- **ESR** >70 greatly increases 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).
- **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 (⅔): 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 débridement) 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)

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) **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 (*Lancet* 2012;380:1684)

- **Blood cultures** ×**2** ***before abx***
- **WBC count:** >10,000 in >90% of bacterial meningitis in healthy hosts
- *Consider* **head CT** to r/o mass effect before LP *if* ≥ 1 high-risk feature (age >60 y, immunosupp., h/o CNS disease, new-onset seizure, Δ MS, focal neuro findings, papilledema); absence of all these has NPV 97%; however, in Pts w/ mass effect, herniation may occur w/o LP and may not occur even w/ LP (*NEJM* 2001;345:1727)
- **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

Typical CSF Findings in Meningitis					
Type	**Appearance**	**Pressure (cm H_2O)**	**WBC/mm³** *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

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), 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

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** (~9%): all ages/seasons; MRI: temporal lobe lesions/edema; EEG: temporal focus
- **VZV** (~9%): 1° or reactivation; ± vesicular rash; all ages (favors elderly), all seasons
- **Arboviruses** (~9%): Eastern/Western equine, St. Louis, Japanese, Powassan, W. Nile (*NEJM* 2005;353:287): fever, HA, **flaccid paralysis,** rash. Risk factors for severe dis: 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
- Nonviral mimics: autoimmune/paraneoplastic (anti-NMDAR, anti-Hu, anti-Ma2, anti-CRMP5), bacterial endocarditis, brain abscess, toxoplasmosis, TB, toxins, vasculitis, Whipple's disease, subdural hematoma, encephalomyelitis (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 MRI unavailable); HSV w/temporal lobe involvement, W. Nile w/ thalamic hyperintensity
- EEG to r/o seizure; findings in encephalitis are nonspecific

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

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

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: vaccine approved for Pts >50 y (↓ lifetime risk from 20% to 10%, also ↓ PHN)

BACTERIAL ENDOCARDITIS

Definition

- Infection of endothelium of heart (including but not limited to the valves)
- Acute (ABE): infxn of normal valves w/ virulent organism (eg, *S. aureus*, β-hemolytic strep, *Strep pneumo*)
- Subacute (SBE): more indolent infxn w/ less virulent organism (eg, *S. viridans*, *Enterococcus*); often abnl valves

Predisposing conditions

- **Abnormal valve**
  - *High risk:* prior endocarditis, rheumatic heart disease, AoV disease (incl. bicuspid), complex cyanotic lesions, prosthesis (annual risk 0.3–1%)
  - *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 endocarditis (NVE)		Prosthetic valve endocarditis (PVE)	
Etiology	**Non-IVDA**	**IVDU**	**Early** (≤60 d post)	**Late** (>60 d post)
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:** systemic emboli (eg, to periphery, CNS, kidneys, spleen, or joints; *JACC* 2013;62:1384), stroke, PE (if right-sided), mycotic aneurysm, MI (coronary artery embolism)
- **Immune complex phenomena:** arthritis, glomerulonephritis, ⊕ RF, ↑ ESR
- **SBE:** can p/w fatigue, nonspecific sx in Pts w/o risk factors; ∴ need high index of suspicion

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.
- Abdomen: tender splenomegaly; musculoskeletal: arthritis, vertebral tenderness
- Extremities (*typically seen in SBE, not ABE*)
  - **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
- Neuro: Δ MS or focal deficits
- Devices: erythema, tenderness or drainage at catheter site, PM/ICD pocket tenderness

Diagnostic studies (*EHJ* 2015;36:3075)

- **Blood cultures** (*before abx*): at least 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 ⊖.
- CBC w/ diff (↑ WBC common in ABE; anemia in 90% SBE), ESR, RF, BUN/Cr, U/A, & UCx
- **ECG** (on admission and at regular intervals) to assess for new conduction abnormalities
- **Echocardiogram:** obtain TTE if low clinical suspicion, expect good image quality; TEE if (i) mod-to-high suspicion, (ii) high-risk Pt (prosthetic valve, prior IE, congenital heart dis), (iii) TTE nondx, (iv) TTE ⊖ but high-risk endocarditis, or (v) suspect progressive or invasive infection (eg, persistent bacteremia or fever, new conduction abnl, etc.) (*Circ* 2015;132:1435)

Method	Sensitivity		
	NVE	PVE	Abscess
Transthoracic (TTE)	50–65%	36–69%	28–36%
Transesophageal (TEE)	>90%	~90%	80–87%

(*EHJ* 1999;20:232; *J Am Soc Echo* 2003;16:67; *Heart* 2004;90:614)

- ^{18}F-FDG PET/CT may have utility in assessing PVE (*JACC* 2013;61:2374)
- Brain MRI may be useful to detect silent cerebral emboli (*Circ* 2009;120:585)
- **Cx ⊖ endocarditis:** may be due to abx prior to BCx. PCR, bacterial 16S ribosomal RNA, serologies may be helpful. Detailed hx: animal exposure, travel, unpasteurized dairy, etc. Seek ID eval (*NEJM* 2007;356:715; *CID* 2010;51:131).

Treatment (*Circ* 2015;132:1435; *EHJ* 2015;36:3075)

- **Obtain culture data first**
  ABE → abx should start promptly after cx data obtained
  SBE → if hemodynamically stable, may defer abx until BCx properly obtained
- **Suggested empiric therapy**
  NVE: vanco ± nafcillin (or cefazolin)
  PVE: *early* (≤60 d): **vanco + cefepime + gent;** *intermediate* (60–365 d): **vanco + gent;** *late* (>1 y): **vanco + CTX + gent**
- **Adjust abx regimen & duration** based on valve (NVE vs. PVE)
  if possible, de-escalate abx to organism-directed Rx guided by *in vitro* sensi's or local patterns of Rx-resist
  add rifampin for PVE due to staph spp. (usually after BCx ⊖ to ↓ risk resistance develops)
  combination therapy for *Enterococcus* (amp + gent or amp + CTX)
- Repeat BCx q24-48h until Pt defervesces and BCx ⊖; usually 2–3 d
- Fever may persist even >1 wk after appropriate abx. *Consider metastatic infxn if >1 wk.*
- Systemic anticoagulation relatively *contraindicated* given risk of hemorrhage in cerebral embolic strokes; w/o stroke, can continue short-acting anticoag for pre-existing indication
- 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.** With NVE & sx <3 mo → 4 wk of abx; sx >3 mo → ≥6 wk. Uncomplicated right-sided NVE or PCN-S strep spp → 2 wk may be comparable.
- Posthospitalization outPt IV abx monitoring; future endocarditis Ppx

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
- **Uncontrolled infxn** (urgent surgery w/in days): periannular abscess (10–40% NVE, 60–100% PVE), fistula, worsening conduction, PVE w/ dehiscence, ↑ veg. size or persistent sepsis (eg, ⊕ BCx after ~1 wk of appropriate IV abx and no drainable metastatic focus or other identifiable cause)
- **Organism:** consider surgery for *S. aureus*, fungal or multiRx-resistant organisms
- **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 hemorrhage (then ideally wait 1 mo) or severe stroke (*Stroke* 2006;37:2094)
- **PVE:** esp. w/ valve dysfxn or dehiscence or *S. aureus* or GNR infection. Seek ID eval.

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
- Aortic valve worse prognosis than mitral valve

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

BACTEREMIA (JAMA 2014;312:1330)

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

- 1° infxn/indwelling catheters (ICHE 2008;29:996): coag-neg staph (incl *S. epi* and others) 34%, *S. aureus* 10%, enterococci 16%, *Candida* spp. 12%, *Klebsiella* spp. 5%
- 2° infxn: dependent on source

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

- **Pt:** fever, rigors, SIRS (96% sens.), IVDU, comorbidities, immunosupp, indwelling lines
- **Organism**
  more likely pathogenic: *S. aureus*, β-hemolytic strep, enterococci, GNR, *S. pneuma, 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 the 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 *S. aureus*, **obtain TEE** (TTE only if nosocomial, no intracardiac device, no e/o IE, no HD)

Treatment

- **1° infxn:** 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: if uncomplicated (*all* of followng: ⊖ echo, no prosthetic material, no signs of metastatic infxn, after starting abx defervesce w/in 2–3 d and BCx ⊖ w/in 2–4 d) then 2 wks of abx, o/w 4 wks min. (depends on site of infxn, see individual sections)

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 echo ⊖ *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

- **2° infxn:** assess for primary source of infection and treat. Source control essential for cure and to prevent recurrence.
- **Persistently ⊕ BCx:** d/c indwelling catheters, consider metastatic infxn, infected thrombosis or infected prosthetic material (joint, abscess, vascular graft, PPM, etc.)

TUBERCULOSIS

Epidemiology

- U.S.: 10–15 million infected (10× ↑ risk if foreign-born or minority); worldwide: ~2 billion
- After resurgence in U.S. 1984–1992, rates have declined
- Multidrug resistant (**MDR**) **TB:** resistant to isoniazid (INH) and rifampin (RIF). Can occur as primary infxn if exposed in former Soviet Republics, China
- Extensively drug resistant **(XDR) TB** resistant to INH, RIF, FQ and injectables
- **Pts more likely to develop TB disease** (*NEJM* 2011;364:1441)
  - *High-prevalence populations* (more likely to be exposed & infected): immigrant from high-prevalence area, homeless, IVDU or medically underserved, resident or worker in jail or long-term facility, HCW at facility w/ TB, close contact to Pt w/ active TB
  - *High-risk populations* (infected & likely to progress to active disease): HIV ⊕, immunosupp. incl. biologics, uncontrolled DM & smoking, close contact w/ active TB Pt, underweight, CKD, organ Tx, IVU, EtOH, malnourished, cancer, gastrectomy

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 infection

- **Whom to screen:** high-prevalence and high-risk populations (HIV ⊕ Pts should have PPD testing as part of initial evaluation and annually thereafter)
- **How to screen:** Mantoux tuberculin test (ie, purified protein derivative or PPD) inject 5-TU (0.1 mL) intermed. strength PPD *intradermally* → wheal; examine 48–72 h
- **How to interpret a PPD:** determine max. diameter of *induration* by palpation

Size of reaction	Persons considered to have ⊕ test
>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.

(*NEJM* 2002;347:1860)

- **IFN-γ release assays (IGRA):** (Ag-stimulated IFN-γ release from Pt's T-cells): can use to screen when PPD could be used (*MMWR* 2010;59:1); ↑ Sp, esp. in BCG Rx'd Pts (*Annals* 2008;149:177). Does not distinguish active vs. latent or past infxn. Relies on host immune fxn; Se limited in immunosupp. (*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 INH 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

Preventive therapy (prevent progression to active disease)

- Prophylaxis reduces incidence of active disease by 65–75%
- Treat Pts who are ⊕ based on guidelines (*NEJM* 2015;372:2127; *Eur Respir J* 2015;46:1563) or any exposed HIV ⊕ or immunocompromised Pt
- **R/o active disease** in any Pt w/ suggestive s/s before starting INH. If HIV ⊕, routinely ask if cough, fever or night sweats; if yes → ✓ sputum smear, CXR, CD4

Scenario	Prophylaxis Regimen
Likely INH sensitive	INH 300 mg PO qd + pyridoxine 25 mg PO qd × 6–9 mo *or* 12-wk observed combo Rx (INH + rifapentine) (*NEJM* 2011;365:2155)
HIV ⊕	INH 300 mg PO qd + pyridoxine 25 mg PO qd × 9 mo
Contact case INH resistant	RIF × 4 mo
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 (risk ↑ w/ age; *Chest* 2005;128:116): if 5× ULN or sx → stop TB meds & re-eval

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

- Isolate Pt per infection control if hospitalized, modified isolation per Dept of Health if outPt
- Use multiple drugs (see below) to which organism susceptible; consult ID before empiric Rx if possible MDR-TB (suspect if prior TB Rx, from or travel to area w/ ↑ rates of MDR, exposure to person w/ likely MDR-TB, poor Rx adherence) or if INH resistance in community ≥4% (includes most of U.S.), extrapulm. TB or HIV ⊕ (*NEJM* 2008;359:636)
- Screen for HIV in Pts starting TB Rx; if HIV ⊕, consult ID re: timing of concurrent HIV Rx
- Promote adherence to Rx; directly observed Rx cost-effective if high risk for nonadherence
- Obtain monthly smears/cx on treatment until 2 consecutive are ⊖ for TB
- Monthly clinical evaluation to monitor for Rx response and adverse drug rxns
- "Paradoxical *worsening*" of sx can occur after starting Rx. More common w/ extrapulm. TB (eg, tuberculoma, LAN) likely due to hypersensitivity response to killing of bacilli. 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

- AIDS: HIV + CD4 <200/mm^3 *or* AIDS-defining opportunistic infection (OI) *or* malignancy

Epidemiology

- ~1 million Americans living w/ HIV; ~36 million worldwide
- 13% in U.S. unaware of infxn, many dx w/ late disease. CDC rec testing all people for HIV.
- Routes: sexual (risk is 0.3% for male-to-male, 0.2% for male-to-female, 0.1% for female-to-male transmission), IVDU, transfusions, needlesticks (0.3%), vertical (15–40% w/o ARV)

Prophylaxis (*JAMA* 2014;312:390)

- Postexposure (PEP): risk infxn ~0.3%; Rx: 2 NRTIs + II × 4 wks
- Preexposure (PrEP): TDF/FTC qd or on-demand effective (44-86% ↓) & safe in high-risk, adherent populations w/o renal insufficiency (*NEJM* 2010;363:2587 & 2015;373:2237; *Lancet* 2016;387:53). Monitor renal fxn, STDs, preg, & HIV status.

Acute retroviral syndrome

- Occurs in ~40–90% of Pts ~2–6 wk after infxn; ± ELISA ⊕, ⊕ viral load (2 wk after infxn); early ART may be beneficial (*NEJM* 2013;368:207 & 218)
- Mono-like syndrome (↑ mucocut. & neuro manifestations compared to EBV or CMV)

Diagnostic studies

- **ELISA** for HIV-1 Ab/Ag: ⊕ 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)
- **Rapid tests:** Ab tests; use saliva, plasma, blood or serum; 99% Se & 96–99% Sp (*Annals* 2008;149:153); PPV in low prev populations is low; needs confirmation
- **PCR (viral load):** detects HIV-1 RNA 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
- **At least 1-time HIV screening recommended for all adults** (*Annals* 2013;159:51)
- **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 (*Lancet* 2014;384:258)

- **Document HIV infection;** counseling re: treatment options, adherence, & disclosure
- **H&P** (including focus on h/o OIs, STDs); **review all current meds**
- **Lab evaluation:** CD4 count, PCR, HIV genotype, CBC w/ diff., Cr, lytes, LFTs, A1c, & fasting lipids; PPD or IGRA, syphilis & toxo screen & CMV IgG; HAV, HBV, & HCV serologies; *Chlamydia* & gonorrhea screen; baseline CXR; Pap smear/anal pap in ♀/♂

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
EI FI	enfuvirtide (T20; Fuzeon)	injection site reaction
EI	maraviroc (MVC; Selzentry)	dizziness, hepatotoxicity; ✓ CCR5 tropism assay
II	dolutegravir (DTG; Tivicay) elvitegravir (EVG; Vitekta) raltegravir (RAL; Isentress)	Class: diarrhea & other GI intol; ↑ CPK DTG + metformin requires glc monitoring
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

- ***ARVs should be given in consultation w/ HIV specialist*** (*JAMA* 2016;316:191)
- Counseling re: strict adherence to ARVs is essential; genotype prior to ART-initiation
- All HIV ⊕ Pts should be treated w/ ARVs (*NEJM* 2015;373:795; http://aidsinfo.nih.gov); especially those w/ AIDS-defining illness, preg, HIV-assoc. nephropathy, HCV/HBV co-infxn
- Rec regimens include: 2 NRTI (eg, TAF + FTC) + *either* II *or* boosted PI (eg, DRV/r)

- Initiation of ARVs may *transiently worsen* existing OIs for several wks due to immune reconstitution inflammatory syndrome (IRIS)

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)

OI	Indication	1° Prophylaxis
Tuberculosis	⊕ PPD (≥5 mm)/IGRA or high-risk exposure	INH + vit B_6 × 9 mo
***Pneumocystis jiroveci* (PCP)**	CD4 <200/mm³ *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/mm³ *and* ⊕ *Toxo* IgG	TMP-SMX DS qd *or* dapsone 50 mg qd + pyrimethamine 50 mg qwk + leucovorin 25 qwk
MAC	CD4 <50/mm³	azithro 1200 mg qwk *or* clarithro 500 mg bid
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
<500	Constitutional sx; noninfectious disease (CVD, bone, oncologic) Mucocutaneous: Kaposi's sarcoma; seborrheic dermatitis; oral hairy leukoplakia; lymphoma; candidiasis; HSV; VZV Recurrent bacterial infections, TB (pulm and extrapulm); neurosyphilis
<200	*PCP, Toxo, Bartonella, Crypto, Histo, Coccidio*
<50–100	CMV, MAC, CNS lymphoma, PML, death (<50 is medical emergency) Invasive aspergillosis, bacillary angiomatosis (disseminated *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 or antigenemia
  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
  abnormal LFTs → abd CT, liver bx for path & cx 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 eruptions
- Dermatophyte infx: prox subungual onychomycosis (at nail bed); pathognomonic for HIV
- **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 (at any CD4 count) 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

Cardiac & vascular (*JACC* 2013;61:511)

- Dilated CMP (10–20%); PHT; CAD); 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).
  Alternative Rx if sulfa-allergy or renal insufficiency.

Gastrointestinal & hepatobiliary

- **Esophagitis:** *Candida*, CMV, HSV, 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
- **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-associated** nephropathy (collapsing FSGS); nephrotoxic drugs (incl TDF)

Hematologic/oncologic (*Lancet* 2007;370:59; *CID* 2007;45:103)

- **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 ↑ as CD4 ↓, usu. MSM
  Mucocut. (violacious lesions); *pulmonary* (nodules, infiltrates, LAN); GI (bleed, obstruct.)
- **Cervical/anal CA** (HPV); ↑ rates of liver (a/w HBV/HCV), gastric, & lung CA

Neurologic

- **Meningitis:** *Crypto* (p/w HA, Δ MS, CN palsy ± meningeal s/s; dx w/ CSF; serum CrAg 90% Se), bact (inc. *Listeria*), viral (HSV, CMV, 1° HIV), TB, histo, *Coccidio,* lymphoma
- **Neurosyphilis:** meningitis, cranial nerve palsies, dementia, otic or ophtho s/s
- **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 ↓)
- **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: clarithromycin + ethambutol ± rifabutin.

Cytomegalovirus (CMV)

- Usually reactivation with ↓ CD4. Retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis. 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/ *Ehrlichia, 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) 3-30d after bite	Pathogenesis: local effects of spirochete. *General:* **flu-like illness** *Derm* (~80%): **erythema migrans** (EM) = erythematous patches w/ central clearing, often popliteal, axilla, or inguinal; 6–38 cm in size
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 y after bite	Pathogenesis: immune response *Derm:* **acrodermatitis chronica atrophicans,** panniculitis *Rheum* (~60%): **recurrent mono- or oligoarthritis of large joints** (classically knee), synovitis *Neurologic:* subacute encephalomyelitis, polyneuropathy, dementia

(*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 (ie, clinical dx)
- *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 New England, mid-Atl, MN, WI)
  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
- Antibiotics: *if* clin. manifestations *and* ⊕ serology in endemic area
  Stage 1 or stage 2 w/o meningitis, arthritis, or carditis: **doxy** 100 mg PO bid × 2–3 wk; alternative (eg, preg, doxy allergy): amox 500 mg PO tid or cefuroxime 500 mg PO bid
  Meningitis, arthritis, carditis: CTX 2 g IV qd × 2–4 wk; alternative (eg, severe β-lactam allergy): doxy 100–200 mg PO bid × 2–4 wk
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias

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)*

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 US
- 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

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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; clinda & quinine if severe (more toxic)
- Duration depends on host; immunosupp Pts often need longer Rx
- Exchange transfusion if parasitemia >10%, severe hemolysis or SIRS

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** (consider holding antipyretics); less likely to mount fever if: chronic renal or liver dis., extremes of age, protein calorie malnutrition, immunosupp., 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 ↑ Alk ϕ): 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 ½, *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)

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 & S. Korea	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* 2002;347:505; *CID* 2007;44:1560; *Curr Opin Infect Dis* 2007;20:449)

- Pts visiting friends and relatives abroad are most likely to contract illness during travel
- Geography influences Ddx in returned travelers: http://www.nccdc.gov/travel/notices
- 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 hospitalization and empiric Rx.** One ⊖ smear does *not* r/o malaria.
- 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.

Hypopituitary Syndromes

Panhypopituitarism (*Lancet* 2016;epub)

- 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)
  - **Secondary** (hypothalamic dysfunction or stalk interruption): tumors (including craniopharyngioma), infection, infiltration, radiation, surgery, trauma
- Clinical manifestations
  - **Hormonal:** acute → weakness, easy fatigability, hypotension, polyuria and polydipsia; chronic → bradycardia, sexual dysfxn, loss of axillary & pubic hair, wt loss, amenorrhea
  - **Mass effect:** headache, visual field Δs, cranial nerve palsies, galactorrhea
  - **Apoplexy** (pituitary hemorrhage or infarction, usually w/ underlying pituitary adenoma): sudden headache, N/V, visual field Δs, cranial nerve palsies, meningismus, Δ MS, hypoglycemia, hypotension
- Diagnostic studies
  - **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**
- 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

↓ ACTH

- Sx similar to 1° adrenal insufficiency (see "Adrenal Disorders") *except:*
  - no salt cravings or hypokalemia (b/c aldo preserved)
  - no hyperpigmentation (b/c ACTH/MSH is not ↑)

↓ 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*

↓ PRL

- Inability to lactate

↓ GH

- ↑ chronic risk for osteoporosis, fatigue, weight gain
- Dx with failure to ↑ GH w/ appropriate stimulus (eg, insulin tolerance test, glucagon stimulation)
- GH replacement in adults controversial (*Annals* 2003;35:419)

↓ 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

↓ ADH (hypothalamic or stalk disease): diabetes insipidus

- 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"

Hyperpituitary Syndromes

Pituitary tumors

- 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, hormone levels, ± visual field testing
  - if <10 mm, no mass effect, no hormonal effects, can f/up q3–6mo

Hyperprolactinemia (*NEJM* 2010;362:1219 and *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** to evaluate for tumor
- 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:** usually non-fxn, presents as *hypopituitarism* b/c of 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

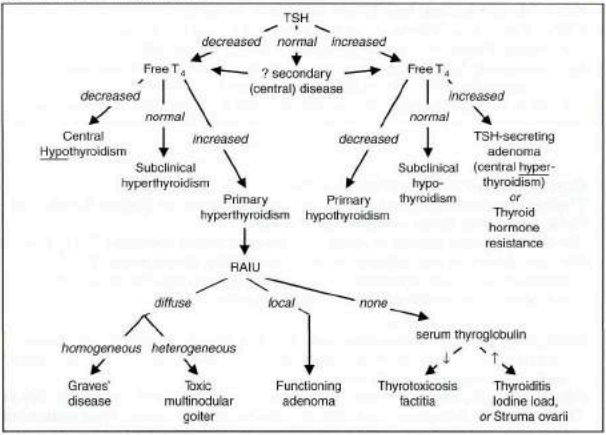
Autoimmune Polyglandular Syndromes (APS)	
Type	**Features**
I (children)	Mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency
II (adults)	Adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1

Diagnostic Studies in Thyroid Disorders

Test	Comments
Thyroid-stimulating hormone (TSH)	*Most sensitive test* to detect 1° hypo- and hyperthyroidism May be inappropriately normal in central etiologies ↓'d by dopamine, glucocorticoids, severe illness
Free T_4 (FT_4)	Unbound T_4, not influenced by TBG
Total T_3 and T_4	*Total* serum concentrations (∴ influenced by TBG)
Thyroxine-binding globulin (TBG)	↑ TBG (∴ ↑ T_4): estrogen (OCP, pregnancy), hepatitis, opioids, hereditary ↓ TBG (∴ ↓ T_4): androgens, glucocorticoids, nephritic syndrome, cirrhosis, acromegaly, antiepileptics, hereditary
Reverse T_3	Inactive, ↑'d in sick euthyroid syndrome
Thyroid antibodies	Antithyroid peroxidase (TPO) seen in Hashimoto's (high titer), painless thyroiditis and Graves' disease (low titer) Thyroid-stimulating Ig (TSI) and thyrotropin-binding inhibitory immunoglobulin (TBII) seen in Graves' disease
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
Radioactive iodine uptake (**RAIU**) scan	Useful to differentiate causes of hyperthyroidism **↑ uptake** homogeneous = Graves' disease heterogeneous = multinodular goiter 1 focus of uptake w/ suppression of rest of gland = hot nodule **no uptake** = subacute painful (de Quervain's) or silent thyroiditis, exogenous thyroid hormone, recent iodine load, struma ovarii or antithyroid drugs

(*Lancet* 2001;357:619 & *Thyroid* 2003;13:19)

Figure 7-1 Approach to thyroid disorders



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:JTC61)
- **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
- ↓ **FT_4**; ↑ **TSH** in primary 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: 1^{st} = 0.1–2.5 mIU/L, 2^{nd} = 0.2–3.0 mIU/L, 3^{rd} = 0.3–3.0 mIU/L (*Thyroid* 2011;21:1081)
- Myxedema coma: 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

Subclinical hypothyroidism (*Lancet* 2012;379:1142)
- Mild ↑ TSH and **normal free T_4** with only subtle or no sx
- If TSH <7 or ⊖ anti-TPO Ab, ~½ euthyroid after 2 y (*JCEM* 2012;97:1962)
  if ↑ titers of antithyroid Abs, progression to overt hypothyroidism is ~4%/y
- Rx controversial: follow expectantly or treat to improve mild sx or dyslipidemia
  most initiate Rx if TSH >10 mU/L, goiter, pregnancy or infertility
  if TSH 5–10 mU/L Rx if age ≤60 y (usually don't Rx if ≥60 b/c ↑ risk CV complications)

Hyperthyroidism

Etiologies (*Lancet* 2016;epub)
- **Graves' disease** (60–80% of thyrotoxicosis)
- **Thyroiditis:** thyrotoxic phase of subacute (granulomatous) or painless (lymphocytic)
- **Toxic adenomas** (single or multinodular goiter)
- TSH-secreting pituitary tumor or pituitary resistance 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 of hyperthyroidism
- 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
- **Thyroid storm** (extremely rare): delirium, fever, tachycardia, systolic hypertension but wide pulse pressure and ↓ MAP, GI symptoms; 20–50% mortality

Laboratory testing
- ↑ **FT_4** and **FT_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

Graves' disease (*NEJM* 2008;358:2594)

- ♀:♂ 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 selected Pts w/ CV disease or elderly w/ antithyroid drugs 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)
- Thyroid storm: β-blocker, PTU or methimazole, iopanoic acid or iodide (for Wolff-Chaikoff effect) >1 h after PTU, ± steroids (↓ $T_4 \rightarrow T_3$)

Subclinical hyperthyroidism (*Lancet* 2012;379:1142)

- Mild ↓ TSH and **normal free T_4** with only subtle or no sx
- ~15% → overt hyperthyroidism in 2 y; ↑ risk of AF, CHD (*Archives* 2012;172:799), fracture (*JAMA* 2015;313:2055)
- Rx controversial: consider if TSH <0.1 mU/L and ↑ risk for CV disease or osteopenic

Nonthyroidal Illness (Sick Euthyroid Syndrome)

(*Thyroid* 1997;7:125 and *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, FT_4, & T_3
- Mild illness: ↓ $T_4 \rightarrow T_3$ conversion, ↑ $rT_3 \Rightarrow$ ↓ T_3; in severe illness: ↓ TBG & albumin, ↑↑ rT_3 ⇒ ↓↓ T_3, ↑ degradation of T_4, central ↓ TSH ⇒ ↓↓ **T_3**, ↓↓ **T_4**, ↓ **FT_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 (*Annals* 1997;126:63 & *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

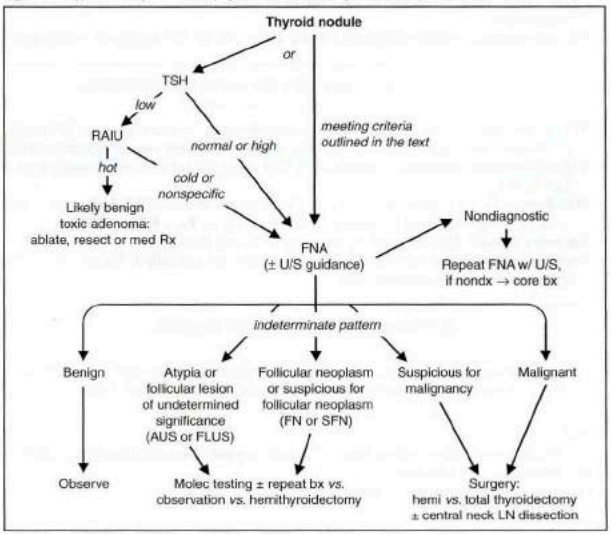
Hyperthyroidism (3% of Pts on amio; ~10–20% of Pts *in iodine-deficient areas*)

- 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 → 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 Nodules (*NEJM* 2015;373:2347 & *Thyroid* 2016;26:1)

- Prevalence 5–10% (50–60% if screen with U/S), ♀ > ♂, ~7–15% malignant
- Features associated w/ ↑ risk of malig: age <20 or >70 y, ♂, h/o neck XRT, hard & immobile mass, cervical LAN, dysphonia
- Worrisome U/S findings: hypoechoic, solid, irregular borders, microcalcifications, height > width, >20 mm (*JAMA IM* 2013;173:1788)
- Features associated w/ benign dx: cystic nodules, "spongiform" sonographic pattern
- Screening U/S recommended for those with FHx of MEN2 or medullary thyroid cancer, personal h/o neck XRT, palpable nodules or multinodular goiter
- Any evidence of tracheal deviation or compression → consider ✓ PFTs & refer to surgery
- >10-mm nodule: FNA if hypoechoic solid or solid component of cystic; ↑ suspicion of malig if irregular margins, microcalcifications, rim Ca^{2+}, height > width, or extrathyroidal extension
- >15-mm nodule: FNA if solid isoechoic, or partially cystic with mural solid component
- >20-mm nodule: FNA if spongiform/other benign solid pattern (no FNA if purely cystic)
- Molecular testing if indeterminate pattern on FNA (occurs in ~15–30%)
- Suppressive Rx w/ high-dose levothyroxine *no longer recommended* for benign nodules in iodine-sufficient regions
- Cancer very rare in asx nodules diagnosed as benign (*JCEM* 2014;99:510 & *JAMA* 2015;313:926)
- After complete surgical resection of thyroid cancer, RAI in medium- and high-risk Pts (*Lancet* 2013;381:1046 & 1058)

Figure 7-2 Approach to thyroid nodules (*NEJM* 2015;373:2347 & *Thyroid* 2016;26:1)



CUSHING'S SYNDROME (HYPERCORTISOLISM)

Definitions (*Lancet* 2015;386:913)

- Cushing's syndrome = cortisol excess
- Cushing's disease = Cushing's syndrome 2° to pituitary ACTH hypersecretion

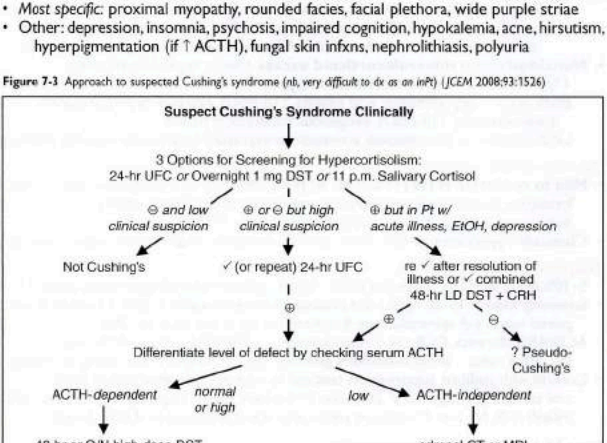
Etiologies of hypercortisolism

- 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

Figure 7-1 Approach to suspected Cushing's syndrome (*nb, very difficult to dx as an inPt*) (*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:peripheral 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
- If transsphenoidal surgery (TSS) not successful → repeat TSS. Can do pituitary XRT, but XRT not effective immediately, ∴ initiate medical Rx w/ mitotane, ketoconazole, or metyrapone to ↓ cortisol, and/or mifepristone to block cortisol action at glucocorticoid receptor, or bilat surgical adrenalectomy if med Rx fails or is contraindicated.
- 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 (glycyrrhizinic acid inhibits 11β-HSD), extreme hypercortisolism (overwhelming 11β-HSD), exogenous mineralocorticoids
  - Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

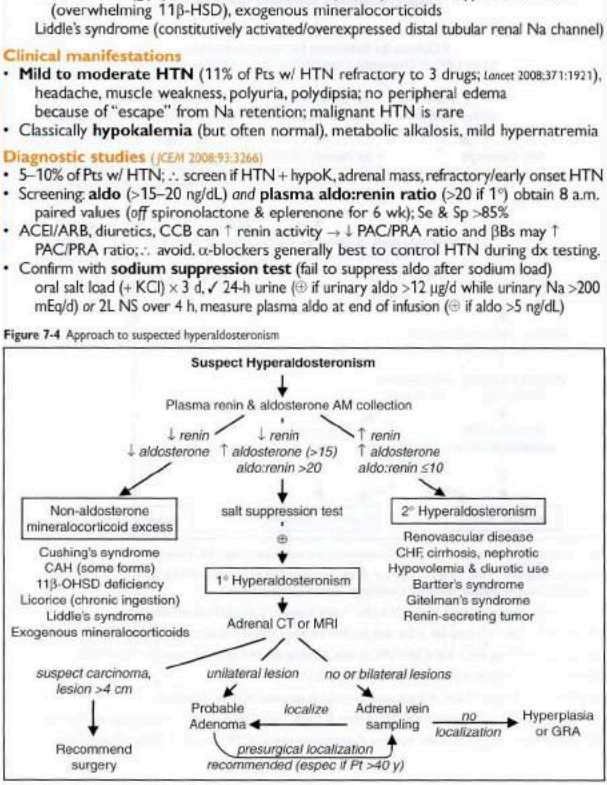
Clinical manifestations

- **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)

- 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



(Adapted from *JCEM* 2008;93:3266 and *Surg Clin N Am* 2014;94:643)

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: <5 μg/dL virtually diagnostic; ≥18 μg/dL rules it out (except in severe septic shock—see below)
- 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)
- 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)

Adrenal insufficiency & critical illness (*NEJM* 2003;348:727; *JAMA* 2009;301:2362)

- ↑ circulating cortisol despite ↓ ACTH due to ↓ clearance and possibly stimulation by cytokines; low cortisol binding proteins; ∴ dx of adrenal insufficiency problematic (*NEJM* 2013;368:1477)
- Nonetheless, reasonable to perform ACTH stim ASAP in hypotensive Pt suspected to have absolute adrenal insufficiency
- Reasonable to perform 250-μg ACTH stim and initiate glucocorticoid replacement if ↑ in cortisol <9 μg/dL or absolute cortisol level <10 μg/dL, but decision to Rx should be based on clinical assessment; unlikely to require Rx if spot or post-ACTH cortisol >18 μg/dL
- Initiate corticosteroids early: use hydrocortisone 50–100 mg IV q6–8h; prior to ACTH stim test, use dexamethasone 2–4 mg IV q6h + fludrocortisone 50 μg daily
- Rx of *relative adrenal insufficiency* controversial (see "Sepsis")

Treatment

- *Acute* insufficiency: volume resuscitation w/ normal saline + **hydrocortisone IV** as above
- *Chronic* insufficiency
  prednisone ~5 mg PO qam, or hydrocortisone: 15–25 mg PO qd (⅔ a.m., ⅓ early p.m.)
  fludrocortisone (*not* needed in 2° adrenal insufficiency): 0.05–0.1 mg PO qam
  backup dexamethasone 4-mg IM prefilled syringe given to Pt for emergency situations

Pheochromocytoma & Paraganglioma

Clinical manifestations (five Ps) (*Lancet* 2005;366:665)

- **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)
- "Rule of 10": 10% extra-adrenal (known as paraganglioma), 10% in children, 10% multiple or bilateral, 10% recur (↑ in paraganglioma), 10% malignant (↑ in paraganglioma), 10% familial, 10% incidentaloma
- Paroxysms can be triggered by meds (eg, β-blockers) abdominal manipulation
- Associated with MEN2A/2B, von Hippel Lindau, neurofibromatosis type 1, familial paraganglioma (mutations in succinate dehydrogenase gene B, C and D)

Diagnostic studies (*JCEM* 2014;99:1915)

- 24° urinary fractionated metanephrines: 85–97% Se, 69–95% Sp. Screening test of choice if low-risk (as 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. Draw blood in supine position after Pt 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; *JCEM* 2010;95:4106)

- **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:* size <4 cm; smooth margins, homogenous and hypodense appearance; unenhanced CT <10 Hounsfield units or CT contrast-medium washout >50% at 10 min. 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) as 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 mos 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 2011;365:2389)*	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 q1–2y

Calciphylaxis (calcific uremic arteriopathy)

- 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* 2008;359:391)	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 *n*l 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, Rx of severe vit D deficiency or 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, ↑ ICP, 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 gtt or PO to follow as effect of IV bolus typically lasts only a few hours
- Chronic: oral Ca (1–3 g/d; Ca citrate better absorbed than Ca carbonate, esp. if achlorhydria or on PPI) and typically calcitriol (0.25-2 mcg/d), and replete vitamin D deficiency. Consider thiazide to ↓ urinary Ca or recombinant PTH 1-84.
- Chronic renal failure: phosphate binder(s), oral Ca, calcitriol or analogue

DIABETES MELLITUS

Definition (*Diabetes Care* 2016;39:513)

- 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* 2014;383:69): 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** (*Annals* 2015;162:ITC1): insulin resistance + relative insulin ↓; prevalence 8%; 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)
- **M**ature-**O**nset **D**iabetes of the **Y**oung (**MODY**): autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*NEJM* 2001;345:971)
- **Secondary causes of diabetes:** exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), B 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	
Diet	Type 1: carb counting; Type 2: wt reduction diet + exercise
Metformin (biguanide) *First-line pharmacoRx for all T2D*	↓ hepatic gluconeogenesis. ↓ Hb_{A1C} ~1.5%. Wt neutral, N/V & diarrhea, rare lactic acidosis Contraindic. in renal (eg, Cr >1.5) or liver failure
Sulfonylureas (SU)	↑ insulin secretion, ↓ Hb_{A1C} ~1.5%. Hypoglycemia, wt gain.
Thiazolidinediones (TZD) (PPARγ agonists)	↑ insulin sens. in adipose & muscle. ↓ Hb_{A1C} ~1%. Wt gain, hepatotoxicity, fluid retention & CHF, bone fractures ? ↑ MI w/ rosiglitazone; not pioglitazone (*BMJ* 2011;342:d1309) Contraindic. in liver disease and NYHA III–IV, monitor LFTs
GLP-1 agonists	↑ glc-depend insulin secretion, ↓ Hb_{A1C} ~0.5%. ↓ **CV events** (*NEJM* 2016;375:311). *Wt loss*, N/V & diarrhea (30–45%).
DPP-4 inhibitors	Block degrad. of GLP-1 & GIP → ↑ insulin. ↓ Hb_{A1C} –0.5%. ? ↑ risk of CHF with some (*NEJM* 2013;369:1317 & 2015;373:232)
SGLT-2 inhibitors (block renal tubular glc uptake)	↑ glucosuria. ↓ Hb_{A1C} –0.6–1%. Wt loss, ↓ **CV death & HF, slows progression of kidney disease** (*NEJM* 2016;373:2117 & *NEJM* 2016;375:323). ↑ risk of normoglycemic DKA (*Diabetes Care* 2016;39:532), fungal GU infxn & UTIs, hypovolemia, ↑ LDL.
Glinides (nonsulfonylurea insulin secretagogues)	↑ insulin secretion, ↓ Hb_{A1C} ~1.5% Hypoglycemia (but less than w/ SU), wt gain
α-glucosidase inhibitors	↓ intestinal CHO absorption, ↓ Hb_{A1C} 0.5–0.8%. GI distress (gas).
Pramlintide	Delays gastric emptying & ↓ glucagon, ↓ Hb_{A1C} 0.5%. GI sx. To be used as adjunctive Rx w/ insulin in T1D or T2D
Insulin (Additional T1D options: insulin pump, pancreatic or islet cell transplant)	Hypoglycemia, wt gain. T1D: generally combine intermed./long-acting (NPH or glargine) & short-/rapid-acting (regular or lispro) insulin. T2D: consider if mono oral Rx not adequate (esp. if Hb_{A1c} high) and start if combo oral Rx not adequate.
Gastric bypass	Can cure DM & prevent complications (*NEJM* 2014;370:2002)

(*Lancet* 2014;383:1068; *JAMA* 2015;314:1052; *Diabetes Care* 2016;39:552; *Endocr Pract* 2016;22:84)

Insulin Preparations (*JAMA* 2014;311:2315)

Preparation	Onset	Peak	Duration	Side effects/Comments
Lispro, aspart	5–15 min	60–90 min	2–4 h	Give immediately before meal
Regular	30–60 min	2–4 h	5–8 h	Give ~30 min before meal
NPH	1–2 h	4–8 h	12–18 h	Can cause protamine Ab prod
Glargine	2 h	No peak	20–24 h	Once daily (a.m. or p.m.)
Detemir	1–3 h	No peak	18–26 h	Once daily

Complications (*NEJM* 2004;351:48; 2007;356:820; 2012;366:1227)

- **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), 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* 2015;38:549)

- ✓ Hb_{A1C} q3–6mo, goal <7% for most Pts. Can use goal Hb_{A1C} ≤7.5–8% if h/o severe hypoglycemia or other comorbidities. Microvascular & macrovascular complications ↓ 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
- **BP** ≤140/90 (*JAMA* 2015;313:603); ≤130/80 in young or select high-risk; benefit of ACE-I
- **Lipids:** statin initiation in all diabetics age 40–75 if LDL-C >70 (see Lipids section)
- **ASA** if age >50 (♂) or 60 (♀) or other cardiac risk factors (*Circ* 2010;121:2694)
- Dilated retinal exam and comprehensive foot exam yearly

Management of hyperglycemia in inpatients (for ICU Pts: see "Sepsis")

- Identify reversible causes/exacerbaters (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)
- Modification of outPt treatment regimen: In T1D, do not stop basal insulin (can → DKA).
  In 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)
- InPt insulin: can use outPt regimen as guide; if insulin naïve:
  total daily insulin = wt (kg) ÷ 2, to start; adjust as needed
  give ½ of total daily insulin as basal insulin in long-acting form to target fasting glc
  give other ½ as short-acting boluses (standing premeal & sliding scale corrective 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;39:599)

- 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 (*Diabetes Care* 2009;32:1335)	
Rule out 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 (*Diabetes Care* 2003;26:533)
- 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* 2016;39:599)
- 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 (r/o possible precipitants; ~15% mortality due to precipitating factors)
- **Aggressive hydration:** initially NS, then ½ NS, average fluid loss up to 8–10 L
- **Insulin** (eg, 10 U IV followed by 0.05–0.1 U/kg/h)

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
- If IV access available, give 25–50 g of D_{50} (50% dextrose)
- If no IV, can give 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 hypercholest.* (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
Ezetimibe	15–20%	—	—	Well tolerated
Fibrates	5–15%	5–15%	35–50%	Myopathy risk ↑ w/ statin. ↑ Cr; ✓ renal fxn q6mo.
Niacin	10–25%	~30%	40%	Flushing (ASA preRx may ↓), ↑ glc & UA. No benefit if on statin w/ low LDL-C (*NEJM* 2014;371:203).
Resins	20%	3–5%	↑	Bloating, binds other meds
Ω-3 FA	5% ↑	3%	25–50%	Dyspepsia, diarrhea, skin Δs, bleeding; ? effective (*JAMA* 2012;308:1024), definitive trials underway
PCSK9i	40–65%	5–10%	15–25%	mAb inj SC q2w or q4w (*JACC* 2015;65:2638)

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 on top of statin, as monoRx, and in FH (*EHJ* 2014;35:2249); prelim data w/ encouraging ↓ CV outcomes (*NEJM* 2015;372:1500), definitive trials ongoing

Treatment of other lipid fractions (*Lancet* 2014;384:618 & 626)

- **HDL-C:** low levels a/w ↑ risk of MI, but no clinical yet benefit 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)
- **Lp(a):** consider ↓ to <50 mg/dL w/ niacin in intermed- to high-risk Pts (*EHJ* 2010;31:2844)

2013 ACC/AHA Guideline & 2016 Expert Consensus Decision Pathway

Population	10-y CV risk	Statin Recommendation
Clinical ASCVD	n/a	High intensity (? moderate if age >75 y)
LDL-C ≥190 mg/dL	n/a	High intensity
DM, age 40–75 y	n/a	High intensity (? moderate if risk <7.5%)
Age 40–75 y (and none of the above)	≥7.5%	High or moderate intensity
	5–<7.5%	Reasonable to offer moderate intensity
	<5%	Consider statin if additional risk factor
Consider EZE or PCKS9i if LDL-C ≥70 & h/o ACS, athero event while on statin, DM, or FH		

Circ 2014;129(Suppl 2):S1 & *JACC* 2016;68:92. ASCVD incl h/o ACS, stable angina, art. revasc, stroke, TIA, PAD. 10-y CV Risk Score: http://my.americanheart.org/cvriskcalculator. Additional risk factors to consider: LDL-C ≥160 mg/dL, genetic hyperlipid., FHx premature ASCVD, hsCRP >2 mg/L, CAC score ≥300 or ≥75th %ile, ABI <0.9

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

Doses are in mg. Simva 80 mg has ↑ myopathy risk and should not be used unless dose already tolerated >12 mo.

Approach to patient with joint pain

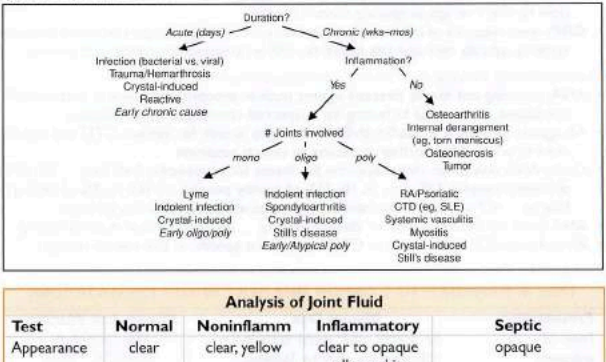
- **Articular** vs. **periarticular** (bursitis, tendinitis) source of pain: typically active ROM more painful than passive ROM in periarticular process
- **Inflammatory** vs. **noninflammatory** pain: *features of inflammatory pain* include swelling, warmth or redness in specific joint, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise
- Physical exam (see table): localize complaint and identify objective signs of inflammation
- 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[a])*
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Intracellular Crystals	⊖	⊖	⊕ in some (eg, gout)	⊖

[a]WBC count of aspirated fluid in septic bursitis often < WBC count in septic arthritis.

Radiologic features of major arthritides

- **OA:** plain films: **osteophytes,** asym joint space narrowing (JSN), subchondral sclerosis & cysts. MRI may show early disease not seen on plain films; U/S ≈ MRI for structural damage.
- **RA:** plain films: early = periarticular **osteopenia;** late = **erosions,** symmetric JSN MRI & U/S able to 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 used for detection of microtophi (double contour sign); MRI ≈ U/S for erosions.
- **Spondyloarthritis** (sacroiliac joint): plain films: pseudo-widening of joint space (early), sclerosis, erosions, **ankylosis.** MRI most Se for early Δ; U/S ≈ MRI to detect enthesitis.

Comparison of Major Arthritides

Feature	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
Lab data	normal	often ⊕ RF & anti-CCP	↑ UA (may be nl during flare)	± HLA-B27

Inflammatory Marker & Autoantibody Testing

Inflammatory markers *(Med Rheumatol 2009;19:469)*

- **ESR:** *indirect* measure of inflammation (↑ RBC aggregation due to acute-phase proteins); slow to rise; ↑ w/ age, pregnancy, anemia, obesity
- **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: *screening test* for Ab directed against nuclear proteins and found in autoimmune conditions, most useful in testing for suspected connective tissue diseases
- Ab against dsDNA & Ro/La/Smith/RNP are *highly specific* for various CTD and can be used to w/u ⊕ ANA further in setting of clinical suspicion
- Order ANA only when *clinical suspicion for disease* b/c nonspecific: 1:40 (low ⊕, 25–30% of healthy people); 1:80 (low ⊕, 10–15% of healthy people); ≥1:160 (⊕, 5% of healthy). May be ⊕ in Pts prior to clin manifest *(NEJM 2003;349:1526; Arthritis Res Ther 2011;13:1)*.
- ANA does *not* correlate well w/ disease activity. ∴ no clinical value in serial testing
- RF and anti-CCP can be seen in CTD but are not specific in this clinical setting

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 ⊕ vasc, 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, Ro/La, RF/anti-CCP, ANCA, ± myositis panel
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	SLE (GN or nephrotic), ANCA ⊕ vasc (GN), scleroderma renal crisis (diffuse), Sjögren's (RTA/TIN), PAN (infarct), HSP, Goodpasture's (GN), cryo	ANA, Ro/La (RTA/TIN) dsDNA, C3/C4, RNA Pol III (SRC), Scl-70 (SRC), ANCA, GBM, cryos
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* 2010;376:1094; *NEJM* 2011;365:2205; *Ann Rheum Dis* 2010;69:70)

- 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), 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; 5% of ♀ >70 y; ♀ to ♂ ratio = 3:1; peak incidence 50–75 y

Clinical manifestations (*Medicine* 2010;38:167)

- Usually insidious onset **pain, swelling** and impaired function of joints (typically PIPs, MCPs, wrists, knees, ankles, MTPs and cervical spine) with **morning stiffness** for ≥1 h
- Typically polyarticular (60% small joints, 30% large joints, 10% both), may be monoarticular (knee, shoulder, wrist) early in course; nb, rheumatoid joints can become *infected*
- 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, pleuritis, effusions (low glc), nodules, airway disease, PHT 20% of the time precedes joint manifestations
CV	Pericarditis (effusions in ⅓ of sero ⊕), myocarditis, accelerated athero/MI, AF, coronary/systemic vasculitis. ↑ risk CV death (*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 synd (2° amyloidosis) NSAIDs and MTX may also cause renal damage
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 (*Annals* 2007;146:797)

- **RF** (IgM/IgA/IgG anti-IgGAb) in ~70% of Pts; also seen in other rheumatic diseases (SLE, Sjögren's), infection (SBE, hepatitis, TB), types II & III cryo, 5% of healthy population
- **Anti-CCP** (Ab to cyclic citrullinated peptide): in ~80% of Pts, similar Se (~70%), 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, ⊕ (espec. high titer) RA or anti-CCP, ANA, ↑ ESR or CRP, and duration ≥6 wk

Management (*Ann Rheum Dis* 2014;73:516)

- Early dx and Rx (esp. DMARD) w/ *frequent* follow-up and escalation of Rx as needed 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 **D**isease-**M**odifying **A**nti-**R**heumatic **D**rug **(DMARD)** (typically take 1–3 mo to have max effect)

- Rapid-acting drugs:
  NSAIDs or COX-2 inhibitors (↑ CV, GI adverse events), consider starting with PPI; **glucocorticoids** [low-dose (<20 mg/d oral) or joint injection]; or
  NSAIDs + glucocorticoids: ↑ GI adverse events, minimize long-term concurrent use
- **DMARDs**
  MTX (1st line unless CKD, hepatitis, EtOH or lung disease), SAS or leflunomide; consider HCQ if seronegative and mild disease;
  If inadequate response after 3 mo (despite DMARD dose escalation):
  combination Rx w/ other DMARDs (eg, "triple therapy" w/ MTX, SAS and HCQ) *or*
  biologic (anti-TNF typically 1st line unless contraindication)
  MTX/SAS/HCQ non-inferior to etanercept/MTX (*NEJM* 2013;369:307)
  JAK inhibitor if fail biologics, although also promising data as initial DMARD (*NEJM* 2014;370:2377 & 2016;374:1243)
- 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)	GI distress (esp. nausea), myelosuppression, ILD, hepatotoxicity ✓ *G6PD prior to SAS* Supplement MTX & SAS w/ folate
Biologic DMARDs (all anti-TNF have similar efficacy)	Anti-TNF: etanercept, infliximab, adalimumab, certolizumab, golimumab CTLA4-Ig: abatacept IL-6R Ab: tocilizumab (studied as mono-Rx w/o MTX) Anti-CD20: rituximab IL-1R Ab: anakinra	↑ risk bacterial/fungal/viral infxn (esp. TB, zoster, hepatitis, and w/ stnd or high-dose; *Lancet* 2015;386:258); ∴ ✓ *for TB, Hep B/C prior to starting* ? CHF & demyelinating CNS disease for anti-TNF ***Never use 2 biologics together***
Other	Hydroxychloroquine (HCQ) JAK inhib: tofacitinib (TF), baricitinib Rarely: cyclosporine, azathioprine, gold	HCQ: retinopathy, rash JAK inhib: infxn, ↑ Cr, ↑ LFTs, HTN CsA: nephrotox, HTN, gum hyperplasia

(*Lancet* 2008;371:987; 2013;381:451,918, & 1541; *NEJM* 2012;367:495 & 508, & 369:307)

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

Comparison of Gout and Pseudogout

	Gout (NEJM 2011;364:443)	Pseudogout (Rheum 2009;48:711)
Acute clinical	Sudden onset painful *monoarticular* arthritis (classically **podagra** [MTP of great toe]) or bursitis; freq. nocturnal *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; Hypomagnesemia; Hemochromatosis
Crystal	Monosodium urate	Calcium pyrophosphate dihydrate
Polarized microscopy*	Needle-shaped, **negatively birefringent**	Rhomboid-shaped, weakly **positively birefringent** crystals
Radiographic findings	Erosions w/ overhanging edge (late); "double contour sign" on MSK US	**Chondrocalcinosis:** punctate, linear densities in articular cartilage, menisci, fibrocartilage of wrist, hands, symphysis pubis
Other	a/w uric acid stones; urate nephropathy	✓ Ca, Mg, Fe, ferritin, TIBC, UA, PTH in young or severe cases

**Crystals should be intracellular; Infection can coexist with acute attacks, ∴ always ✓ Gram stain & Cx*

GOUT

Definition & epidemiology (Lancet 2010;375:318; Nat Rev Rheumatol 2015;11:649)

- Humans lack enzyme to metabolize urate (end-product of purine metabolism)
- Monosodium urate (MSU) crystal deposition in joints promotes inflammation
- ♂ > ♀ (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)

- **UA underexcretion (85–90%):** meds (eg, diuretics); idiopathic; ↓ renal function; obesity
- Uric acid (UA) 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

- ↑ UA is not diagnostic: 25% of measurements nl during flare; ± ↑ WBC & ESR
- Arthrocentesis is gold standard: negatively birefringent needles (see table above)
- 2015 ACR/EULAR Classification Criteria (Ann Rheum Dis 2015;74:1789) used 1° in research

Acute treatment (Arthritis Care Res 2012;64:1447; Am Fam Physician 2014;90:831)

- 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

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 (Annals 2016;164:464)
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 (*Lancet* 2011;377:165; *Am Fam Physician* 2014;90:831)

- **Approach:** if ≥2 attacks/y, ≥1 tophus, joint erosions or urolithiasis → start urate lowering Rx & pharmacologic prophylaxis to ↓ risk of acute attacks
- **Pharmacologic prophylaxis:** continue for at least 6 mos 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)
- **Urate-lowering Rx:** goal UA <6 mg/dL; *do NOT discontinue during acute attack or acute kidney injury (unless allopurinol hypersensitivity syndrome)*
- **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 inhib	1st line; adjust starting dose in CKD; titrate ↑ q2–5wk a/w rash, hypersensitivity syndrome (see below), diarrhea, dyspepsia, BM suppression, hepatitis; monitor CBC & LFTs; *not nephrotoxic* max dose = 800 mg/d
Febuxostat (PO)	Nonpurine xanthine oxidase inhib	2nd line; use if allopurinol intolerant a/w LFT Δ, rash, arthralgias, nausea 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)
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 UA <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

Classification system (NEJM 2016;374:2563)

- 5 subtypes: ankylosing spondylitis (most common), reactive arthritis, psoriatic arthritis, IBD-associated arthritis and undifferentiated
- Can also distinguish axial-predominant from peripheral-predominant joint involvement
- All subtypes share common clinical manifestations: inflammatory spine disease, peripheral arthritis, enthesitis and extra-articular manifestations (primarily ocular and skin disease)

Epidemiology & pathogenesis (Nat Rev Rheumatol 2015;10:110)

- ↑ prevalence of HLA-B27; HLA-B27 accounts for ~30% of attributable genetic risk
- Environmental factors likely critical for disease, esp. reactive arthritis (eg, infection)
- Prevalence of 0.5–2% of population, worldwide

Spondyloarthritis (SpA) Epidemiology and Key Presentation Features

Disease	Epidemiology	Other
Ankylosing spondylitis	♂:♀ = 3:1; onset in teens to mid-20s (rare after 40 y)	Progressive limitation of spine motion; "bamboo spine"
Psoriatic arthritis	♂ = ♀; peak incidence 45–54 y; seen in 20–30% of Pts w/ psoriasis (*Ann Rheum Dis 2005;64:ii14*)	In 13–17%, arthritis precedes psoriasis by yrs. Does not correlate with psoriasis activity. A/w HIV.
Reactive arthritis	♂ >> ♀; 20–40 y; 10–30 d s/p post-GI or GU infxn* in genetically susceptible host	Previously "Reiter's syndrome": arthritis, urethritis and conjunctivitis. Most resolve w/in 12 mo.
IBD-associated	♂ = ♀; seen in 20% of IBD Pts; Crohn's > UC	Type I <5 joints: correlates w/ IBD Type II >5 joints or axial disease: does not correlate w/ IBD

*GU: *Chlamydia, Ureaplasma urealyticum*; GI: *Shigella, Salmonella, Yersinia, Campylobacter, C. diff.*

Major clinical manifestations (Lancet 2011;377:2127)

- **Inflammatory back pain:** SI joints (**sacroiliitis**), apophyseal joints of spine characterized by **IPAIN** (**I**nsidious onset, **P**ain at night, **A**ge of onset <40 y, **I**mproves w/ exercise/hot water, **N**o improvement w/ rest), a.m. stiffness, *responsive to NSAIDs*
- **Peripheral arthritis:** typically asymmetric, oligoarticular, large joints, lower > upper limb; however, can be symmetric & polyarticular (thus, mimic RA), esp. in psoriatic arthritis
- **Enthesitis:** inflammation at site of tendon/ligament insertion into bone, esp. Achilles, pre-patellar, elbow epicondyles, plantar fascia
- **Rigidity of spine:** bamboo spine by X-ray, ankylosis due to progressive growth of bony spurs which bridge intervertebral disc
- **Dactylitis** ("sausage digit"): inflammation of entire digit (joint + tenosynovial inflamm)
- **Uveitis:** anterior uveitis *most common extra-articular manifestation*; p/w pain, red eye, blurry vision, photophobia, usually unilateral

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
Periph distrib.	Lower > Upper	Upper > Lower (see below)	Lower > Upper	Lower > Upper
HLA-B27	80–90%	20%	50–80%	5–30%
Enthesitis	Frequent	Frequent	Frequent	Rare
Dactylitis	Uncommon	Common	Common	Uncommon
Ocular	Uveitis in 25–40%	Conjunctivitis, uveitis, episcleritis,	**Conjunctivitis** (noninfectious), uveitis, keratitis	Uveitis
Skin	None	**Psoriasis;** nail pitting and onycholysis	Circinate balanitis, keratoderma blennorrhagica	*E. nodosum*, pyoderma-gangrenosum
Imaging	Bamboo spine (symm syndes.)	"Pencil-in-cup" DIP deformity	*Asymmetric* syndesmophytes	Periph dis. rarely erosive
Other	↑ CAD; aortitis, AI, conduction defects	↑ CAD	**Urethritis,** AI, conduction defects	

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 due to panniculitis, typically on shins; Ddx incl. idiopathic, infxn, sarcoid, drugs, vasculitis, IBD, lymphoma
- **Pyoderma gangrenosum:** neutrophilic dermatosis → painful ulcers w/ violaceous border; Ddx incl. idiopathic, IBD, RA, myelogenous leukemia

Psoriatic arthritis subtypes (*Lancet* 2011;377:2127)

- **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

Clinical assessment (*Nat Rev Rheumatol* 2012;8:253)

- **Axial disease assessment**
  - Nb: following 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)
- **Seronegative:** notable for *absence* of rheumatoid factor or autoantibodies; ± ↑ESR/CRP
- **HLA-B27:** nonspecific, as 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
- **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")
- **Infectious evaluation for reactive arthritis** (⊖ studies do not r/o)
  - U/A, PCR of urine and/or genital swab for *Chlamydia*; urethritis usually due to *Chlamydia* infxn preceding arthritis, but also can see sterile urethritis post dysentery
  - ✓ stool Cx, *C. diff* toxin. Consider HIV in workup of reactive or psoriatic arthritis.

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 (*Ann Rheum Dis* 2006;65:423) and may slow progression of structural changes (*Curr Rheumatol Rep* 2012;14:422); adalimumab or infliximab preferred if inflammatory eye disease
- **Apremilast** (PO PDE-4 inhibitor): approved for use in PsA (*Ann Rheum Dis* 2014;73:1020); associated with GI side effects and significant wt loss
- **Ustekinumab** (SC IL-12/23 inhibitor): approved for use in PsA (*Ann Rheum Dis* 2014;73:990)
- **Secukinumab** (IL-17A inhibitor): improves signs & symptoms of PsA & ankylosing spondylitis (*NEJM* 2015;373:1329 & 2534; *Lancet* 2015;386:1137)
- **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

Etiologies & Diagnosis of Infectious Arthritis

Etiologies *(Curr Rheumatol Rep 2013;15:332)*

- **Bacterial** (nongonococcal): early diagnosis required
- **Gonococcal** (*N. gonorrhea*): consider in sexually active young adults
- Viral: parvovirus, HCV, HBV, acute HIV; typically 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 (unpast. dairy)

Diagnosis *(JAMA 2007;297:1478)*

- H&P w/ poor sensitivity and specificity for septic arthritis; ∴ **arthrocentesis** should be performed as soon as suspected and prior to starting antibiotics if possible
- *Take care not to tap through an infected area, thus introducing infxn into joint space*
- ✓ Synovial fluid cell count w/ differential, Gram stain, bacterial culture, crystals
  WBC >50k w/ poly predom 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 secondary to IVDU, endocarditis or skin infection
  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 inc. 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
- Conventional radiographs should be obtained but usually normal until after ~2 wk of infection when bony erosions, joint space narrowing, osteomyelitis, periostitis can be seen
- **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, immunosupp.

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 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.
- Prognosis: *10–50% mortality* depending on virulence of organism, 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, endocervix, urethra 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;** purulent arthritis rare
    acute onset of tenosynovitis (60%) in wrists, fingers, ankles, toes
    rash (>50%): 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 or cefotaxime** × **7 d w/ empiric doxycycline** for *Chlamydia*
  (fluoroquinolones no longer recommended due to resistance)
- Joint arthroscopy/lavage may be required if 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
- *Take care not to tap through infected skin, thus 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 tx 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; SSc, systemic sclerosis. (*Primer on the Rheumatic Diseases*, 12th ed., 2001; *Lancet* 2013;382:797).

- Auto-Ab testing directed by clinical findings, as 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: immune damage to endothelial cells and reactive O_2 species production → persistent oxidative stress → perivascular inflammation → fibroblast activation and fibrosis. Cytokines, growth factors, genetics, environmental factors and autoantibodies (against PDGF receptor, endothelial cells and 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, PAH 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 ≠ scleroderma), toxin, hypothyroidism, nephrogenic systemic fibrosis, eosinophilic fasciitis, amyloidosis, GVHD

Diagnostic studies & monitoring (*Semin Arthritis Rheum* 2005;35:35)

- Autoantibodies: >95% Pts w/ auto-Ab; generally mutually-exclusive
  ⊕ **anti-Scl-70** (antitopoisomerase 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 compared to general population, therefore must be vigilant
- Frequent (eg, daily) BP ✓ to monitor for HTN suggestive of scleroderma renal crisis

Clinical Manifestations of Systemic Sclerosis	
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 increase in Pt BP as compared with baseline BP*), MAHA urine sediment typically bland; path w/ "onion-skin" hypertrophy of capillaries; affects 5–10% of Pts, 66% w/in 1st year (*Rheum* 2009;48:iii32) ↑ risk w/ >15 mg/d of prednisone (*Arthritis Rheum* 1998;41:1613) 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
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	PBC	
Renal	SRC later in disease course	SRC earlier & more common
Cardiac		Restrictive cardiomyopathy
Other	**CREST syndrome** = **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias	Raynaud's
Antibodies	Centromere (10–40%)	Scl 70, RNA-Pol III (40%)
Prognosis	Survival >70% at 10 y	Survival 40–60% at 10 y

Treatment (*Ann Rheum Dis* 2009;68:620)

- *Minimize steroid exposure to reduce risk of renal crisis*
- Pulmonary fibrosis: **cyclophosphamide** (*NEJM* 2006;354:2655; *Arth Rheum* 2006;54:3692), MMF under investigation; improvement may be minimal (*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 or steroids for pericarditis
- Arthritis: acetaminophen, NSAIDs, hydroxychloroquine, MTX
- Myositis: MTX, AZA, steroids
- Skin: PUVA for morphea. For pruritus: emollients, topical or oral steroids (↓ dose). MTX or MMF effectiveness for skin fibrosis debated (*Ann Rheum Dis* 2011;70:1104).

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%) & DM (24%)
- **Necrotizing autoimmune myositis** (NM): usually in adults; occurs after viral infections, statin exposure (⊕ anti-HMGCR)
- **Inclusion body myositis** (IBM): onset after age 50; ♂ > ♀; often *misdiagnosed as PM*

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*

- **Dermatologic:** may precede myositis by mos to yrs (uncommon for converse)
  erythematous rash on sun-exposed skin: neck & shoulders (shawl sign), face, chest
  heliotrope rash (purplish discoloration) over upper eyelids ± periorbital edema
  Gottron's papules (in >80% & *pathognomonic*): violaceous often scaly areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli subungual erythema, "mechanic's hands" (skin cracks on digits), pruritus
  DM sine myositis (amyopathic DM): dermatologic features w/o myositis, in 10–20%
- Polyarthralgias or polyarthritis: usually early; nonerosive; small joints > large joints
- Raynaud's (30%, DM and overlap CTD) w/ dilatation & dropout of nail bed capillaries
- **Visceral involvement** (*J Rheumatol* 2009;36:2711)
  pulmonary: acute alveolitis; ILD; respiratory muscle weakness; aspiration
  cardiac (33%): often asx; conduction abnl; myo/pericarditis; HF uncommon; ↑ CK-MB/Tn
  GI: dysphagia, aspiration
- **Antisynthetase syndrome** (PM > DM): fever, ILD, Raynaud's, mechanic's hands, arthritis
- DDx: drug-induced 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

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 esoph 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

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): lymphoplasmacytic infiltration

Classification criteria (2 of 3 have 93% Se & 95% Sp; *Arthritis Care Res* 2012;64:475)

1. ⊕ anti-Ro or anti-La or RF + ANA >1:320
2. Labial salivary gland bx w/ lymphocytic sialadenitis and score >1 focus/4 mm^2
3. Keratoconjunctivitis sicca w/ ocular staining score ≥3

Treatment (*Arth Rheum* 2005;52:27 & 2007;57:310; *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: NSAIDs, steroids, DMARDs, rituximab (RCTs are needed)

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 and often evolve to a dominant phenotype of SLE or systemic sclerosis
- Different from undifferentiated CTD (UCTD): 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%); **anti-U1-RNP** in all but *not* specific (seen in ~50% SLE)

Treatment: As per specific rheumatic diseases detailed above

Raynaud's Phenomenon

Clinical manifestations (*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 PVD, tissue injury, or systemic sx*	**Tissue ischemia & injury** (eg, digital ulcers); can be assoc w/ systemic sx
Auto Ab	⊖	Depends on above etiology, often ⊕
Nailfold	Normal	Dropout and/or 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, drugs, caffeine & trauma
- 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
- Others: fish oil (1° RP only; *Am J Med* 1989;86:158), abx for infected ulceration

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/mm³) *or* **lymphopenia** (<1000/mm³) **11. Thrombocytopenia** (<100,000/mm³)	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** **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 cutan.	
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
- Lytes, BUN, Cr, U/A, urine sed, spot microalb:Cr ratio or 24-h urine for CrCl and protein
- CBC, APLA (⊕ in 20–40%; ACL, B2GP1, lupus anticoagulant), total complement, C3 & C4
- 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 as ↓ 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
	Immunosuppressive agents	
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, hepatotoxicity, pneumonitis, alopecia, stomatitis, 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	Allergic rxn; serum sickness; PML

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 Maint.: 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
- Idiosyncratic onset; generally mild disease with arthritis, serositis, skin disease
- ⊕ Anti-histone (95%) (may be ⊖ in anti-TNF); ⊖ anti-ds-DNA (often ⊕ in anti-TNF 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** → occlusion, stenosis, irregularity and aneurysms; carotid U/S Doppler studies; PET-CT; MRA; **pathology** → focal panarteritis, cellular infiltrate with *granulomas* and giant cells (bx not required for dx)
- Treatment: **steroids** ± MTX or AZA; anti-TNF (2nd line, *Autoimmun Rev* 2012;11:678), 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, PMR sx (see below)
  temporal artery (TA) → **headache, tender TAs** and scalp; absent TA pulse
  ophthalmic artery (20%) → optic neuritis, diplopia, amaurosis fugax, blindness
  facial arteries → **jaw claudication**
  large vessel vasculitis → intermittent claudication of extremities; thoracic Ao aneurysm ~50% of Pts w/ GCA ultimately also diagnosed w/ PMR
- Dx studies: ↑ **ESR** (Se 84%, Sp 30%), ↑ CRP (Se 86%, Sp 30%), anemia
  (ESR related to fibrinogen & Ig in blood; Ddx for >100: malignancy esp. multiple myeloma, lymphoma; GCA or other vasculitis; ESRD; endocarditis, TB, osteomyelitis)
  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 Ig vessel involvement (BP Δ or bruits) → MRI/MRA or PET-CT

- **Polymyalgia rheumatica** (*Lancet* 2013;381:63; *JAMA* 2016;315:2442)
  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: **steroids** (*do not await bx/path results* to begin steroids, have at least 2 wk to bx)
  GCA: 40–60 mg/d w/ *slow* taper, ASA daily; consider IV pulse if vision threatened. Adding tocilizumab to steroid may be beneficial (*Lancet* 2016;387:1921); await phase III results.
  PMR: 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, DAH), not a/w ANCA
- Epidemiology: ♂ > ♀; average age of onset ~50 y; primary or **HBV-associated** (~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
  if lung involvement, suspect other vasculitis
- Dx studies: ↑ ESR/CRP, ⊖ ANCA; ✓ HBs Ag; ↓ 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*
- Treatment: **steroids** ± CYC (if severe or failure to induce remission); 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):** granulomatosis w/ polyangiitis, eosinophilic granulomatosis and polyangiitis, microscopic polyangiitis (rarely)
- **anti-MPO (p-ANCA):** microscopic polyangiitis, eosinophilic granulomatosis and polyangiitis, granulomatosis w/ polyangiitis, drug-induced vasculitis, nonvasculitic rheumatic diseases
- **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
  respiratory (90%): *upper:* sinusitis, rhinitis, oral/nasal ulcers, saddle-nose deformity, otitis, hearing loss, subglottic stenosis; *lower:* pulmonary infiltrates, nodules, pulmonary 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 **corticosteroids** + cyclophosphamide (if severe)

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, angiography, EMG; ↓ 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
  - 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 **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)

- **Proteins** due to chronic immune stimulation and/or lymphoproliferation that **precipitate on exposure to cold and redissolve on rewarming,** characterized by their composition
- **Cryoglobulins** = proteins that precipitate from *serum and plasma* when cooled
- 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
$A\beta_2M$	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, $A\beta_2M$
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, $A\beta_2M$
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 thickening w/ *granular sparkling* appearance; ↑ wall w/o ↑ volt 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. Eprodisate promising for renal disease (*NEJM* 2007;356:2349) ? Biologics (anakinra, tocilizumab) for rheum associated disease (*Arth Rheum* 2003;48:2019; *Clin Exp Rheumatol* 2015;33:46)
ATTR	Liver Tx prevents further protein deposition (*Muscle Nerve* 2013;47:157) Small interfering RNA under study (*NEJM* 2013;369:819; *JACC* 2015;66:2451)

- 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 mos 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)

- Spectrum from awake/alert → drowsy → stupor → coma. Vague terms, thus most useful to simply describe response to increasing stimulation (eg, voice → noxious stimuli).
- **Coma:** lack of response to external stimuli. Degree formalized in Glasgow Coma Scale. Caused by focal lesions in upper brainstem (eg, reticular activating system, thalami) or diffuse dysfxn of cerebral hemispheres bilaterally. Mimics: locked-in synd., catatonia.
- Nb, quality of thought can be disturbed w/o affecting level of consciousness (eg, disorient.)
- **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 beyond baseline, develops over mos to yrs, often affecting memory, language, and executive function

Etiologies of Decreased Responsiveness

1° neurologic *(usually with focal signs)*	**Systemic** *(esp. in elderly or prior CNS injury)*
Vasc: ischemic stroke, ICH, ven. thromb	Cardiac: global ischemia, CHF, HTN enceph
Seizure: postictal, status, nonconvulsive	Pulmonary: ↓ P_aO_2, ↑ P_aCO_2
Infxn: meningitis, encephalitis, abscess	GI: liver failure, ↑ NH_3
Traumatic brain injury/concussion	Renal: uremia, dialysis, ↓ or ↑ Na
↑ intracranial pressure: mass, hydrocephalus, herniation	Endo: ↓ glc, DKA/HHNS, hypothyr., Addisonian
Transient global amnesia	ID: pneumonia, UTI, sepsis
Autoimmune/paraneoplastic encephalitis	Hypothermia & hyperthermia
Neurodeg: late-stage (eg, Alzheimer's); or rapidly progressive (eg, CJD) dementia	Intoxication or withdrawal: EtOH, sedatives, opiates, carbon monoxide, anticholinergic
	Psychiatric: catatonia

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, nuchal rigidity* (may be present in meningitis or SAH, *do not test* if possible trauma/cervical spine fx), breathing pattern (eg, Cheyne-Stokes), ecchymoses, rash, signs of head trauma (eg, Battle's, raccoon eyes, hemotympanum, CSF rhinorrhea), asterixis, liver disease stigmata, embolic phenomena/endocarditis, signs of drug use
- **Neuro exam** (see below): perform off sedatives/paralytics if possible, look for deficits that suggest structural cause (eg, stroke, herniation syndrome), 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 enceph, hern., 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 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
- Immobilization of C-spine if concern for cervical trauma
- Thiamine 100 mg IV → dextrose 50 g IVP (order to prevent exacerbation of Wernicke's)
- If opiates suspected: naloxone 0.01 mg/kg; supportive care important in nearly all tox cases
- 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 (*Continuum* 2011;17:967)
- All patients: check CBC, electrolytes, BUN/Cr, tox screen, tox screen, U/A
- *Based on clinical suspicion:*
  labs: NH_3, TSH, am cortisol, B_{12}, ABG, ESR, ANA, TPO, thyroglobulin, BCx
  imaging: head CT, then MRI; 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 (*Annals* 2011;154:746)
- Treat underlying acute illness, eliminate precipitating factors, & provide supportive care
- Address sensory & cognitive impairments (frequent reorientation, 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; avoid benzos except for alcohol withdrawal or seizures

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

Temperature management (*Circulation* 2015;132:2448)
- Indications: comatose (eg, no meaningful response to verbal stimuli) <6 h following cardiac arrest (not isolated resp. arrest). Fully studied only in VT/VF, but consider after asystole or PEA arrest or 6–12 h after cardiac arrest.
- Exclusion: preg, CV instability despite pressors/assist devices, other cause of coma, persistent ↓ O_2
- Relative contraindications: major head trauma, coagulopathy/bleeding, major surgery <14 d, systemic infection/sepsis
- Target temp: 32–36°C × ≥24 h. 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: can use cold saline infusions; ice packs to head, neck & torso; cooling blankets; cooling vest or endovascular catheter if available. Goal to achieve target temp <6 h (but no benefit to prehosp cooling; *JAMA* 2014;311:45). Start rewarming 24 h after cooling is initiated (rewarm ≤0.5°C per h).
- Complications
  dysrhythmias (brady most common): if signif or hemodynamic instability, rewarm
  coagulopathy (can receive lytics, GP IIb/IIIa inhibitors, etc.); ✓ PT and PTT.
  infection: ✓ 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. Pt needs to be off sedation for an adequate time to evaluate (depends on doses used, duration of Rx, metabolic processes in the individual Pt).
- 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)
- For inPt arrest, ~20% survive, ~70% of Pts who survive have good long-term prognosis
- Prior to cooling era, uniformly poor prognosis could be predicted at 72 h only in Pts who have absent pupillary and corneal reflexes, and no motor response to pain; or with absent SSEPs at 48 h. With cooling, it is less clear if the prior measures are as reliable.
- Otherwise, prognosis requires multifactorial approach considering exam, age, comorbid diseases, ancillary data (NSE, EEG, SSEP; imaging is less reliable for poor outcome)
- When in doubt, err on giving more time (esp. if younger or induced hypothermia)

SEIZURES

Definitions (*Epilepsia* 2014;55:475)

- **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 yr (see below for prognostication)
- **Generalized seizures** (involves brain diffusely)
  - *Tonic-clonic* (grand mal): tonic phase (10–20 sec) with contraction of muscles (causing expiratory moan, cyanosis, pooling of secretions, tongue biting) → clonic phase (~30 sec) with intermittent relaxing and tensing of muscles
  - *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, implies a structural lesion)
  - *w/o impaired consciousness:* focal motor/autonomic sx (formerly "simple partial seizure") or focal sensory/psychic symptoms (eg, aura)
  - *w/ impaired consciousness:* 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, diffuse shaking w/o LOC, crying/talking during event
- 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, tramadol, MNZ, meperidine, CsA, antidepressants); 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, focal cortical dysplasia

Clinical manifestations

- **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): tonic and/or clonic movements of head, eyes, trunk or extrem.
- **Postictal period** (mins to h): slowly resolving period of confusion, disorientation, and lethargy. May be accompanied by focal neurologic deficits (Todd's paralysis).

Clinical evaluation

- *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
- PMH: prior seizures or ⊕ FHx, prior meningitis/encephalitis, prior stroke or head trauma
- 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, med levels (if on valproic acid, phenytoin; consider for other AEDs but may take days; levetiracetam level rarely useful unless? noncompliance)

- Routine EEG (~30 min): useful in workup of 1st-time unprovoked seizure, as may determine risk of seizure recurrence. Caveat: interictal EEG nl in 50% of Pts w/ epilepsy, and interictal epileptiform activity (spikes or sharp waves) may be seen in up to 2% of nl population; sleep deprivation and repeated studies ↑ dx yield of EEG.
- Long-term EEG monitoring (hrs to days): useful for differentiating epileptic from non-epileptic spells; 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 meningitis (eg, fever, ↑ WBC, nuchal rigidity) or 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 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 (*Neurocrit Care* 2012;17:3)

- 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	0.1 mg/kg IV	Successive 2–4 mg IV pushes
	Midazolam or	0.2 mg/kg IM	Up to 10 mg IM
	Diazepam*	0.2 mg/kg PR	
<10	**Phenytoin** or	20 mg/kg	1.0–1.5 g IV over 20 min
	Fosphenytoin	20 mg PE/kg	1.0–1.5 g PE IV over 5–10 min
	or **Valproate** or	20–30 mg/kg	1.0–1.5 g IV over 5–10 min
	Levetiracetam	1000 mg	IV 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

Pathophysiology

- Alcohol is a CNS depressant
- Chronic use → insensitivity to inhibitory neurotransmitter γ-aminobutyric acid (GABA)
- Abrupt alcohol cessation → CNS overactivity

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, ⅓ → 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

Clinical Institute Withdrawal Assessment scale 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

CIWA-Ar Scale

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 halluc.	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

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)
  - Route: start IV, transition to PO
  - 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

Ischemic Stroke

Etiologies

- Embolic (~75%): artery → artery, cardioembolic, paradoxical, cryptogenic (AF found in ~12%)
- Thrombotic (~25%): large vessel (atherosclerosis) vs. small vessel ("lacunar," lipohyalinosis of small arteries, often related to HTN, hyperlipidemia, & DM)
- Other: dissection, vasculitis, vasospasm, prothrombotic states, hypoperfusion, genetic

Clinical Manifestations

- Timing: embolic → sudden onset; thrombotic → 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, 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;** sx resolve <24 h (most <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 **ABCD²:** **A**ge ≥60 y (+1); **B**P ≥140/90 (+1); **C**lin features: unilat. weak. (+2), speech impair. w/o weakness (+1); **D**uration ≥60 (+2) or 10–59 min (+1); **D**M (+1)

Physical exam

- General: murmurs, carotid & subclavian bruits, peripheral emboli, endocarditis sequelae
- 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 ≈ MRI, faster, more widely available)
  early signs: hyperdense artery, loss of gray-white differentiation, edema, insular ribbon
  CT can be nl in 1st hrs after sx onset, not Se for small strokes & brainstem strokes
  obtain CT-angio head & neck if endovascular intervention indicated

Acute treatment of ischemic stroke (*JAMA* 2015;313:1451 & 314:1832)

- **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)
  0.6 mg/kg (tested 1° in Asians): ? slightly ↓ efficacy but ½ ICH rate (*NEJM* 2016;374:2313)
- 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: often occurs 1–5 d post large MCA or cerebellar strokes, ↑ risk in young. Temporize: elevate HOB >30°; mannitol ± 23% NaCl. Hemicraniectomy ↓ mortality (*Lancet Neurol* 2007;6:215). Neurosurgery consult in select MCA and all large cerebellar strokes.
- **Endovascular thrombectomy** (*JACC Intv* 2016;9:307): if anterior circulation prox cutoff (mostly MCA) and w/in ~6 h of sx onset, addition of thrombectomy to IV tPA ↑ odds of fxnal independence by 71%, w/ no Δ in ICH or mortality (*NEJM* 2015;372:11, 1009, 1019, 2285 & 2296; *Lancet* 2016;387:1723)

Workup to assess for etiology/modifiable risk factors

- Cardiac: Holter to assess for AF (found in ~12%; *NEJM* 2014;370:2467 & 2478;374:2065); echo to r/o thrombus/vegetation, w/ bubble study to r/o PFO/atrial septal aneurysm if suspect embolic
- Vessel imaging: carotid U/S and Doppler (if no vessel imaging obtained in acute eval)
- 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)
  ticagrelor: trend toward 13% ↓ ischemic stroke vs. ASA (*NEJM* 2016;375:35)
  clopidogrel + ASA (vs. ASA alone): × 90 d in minor strokes/TIA → 32% ↓ risk of stroke, no Δ ICH (*NEJM* 2013;369:11); extended Rx not more effective & ↑ ICH (*Lancet* 2004;364:331)
- **Anticoagulation (AC):** consider only if: AF (qv), cardiac/paradoxical emboli (except bacterial endocarditis); long segment extra-dural dissections; hypercoag state; bridge to CEA in sx carotid stenosis w/ongoing TIAs.
  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)
- Statin: ↓ recurrent stroke w/ atorvastatin 80 mg, LDL goal <70 (*NEJM* 2006;355:549)
- Fluoxetine: ? improved motor recovery after 3 mo (*Lancet Neurol* 2011;10:123)
- Pioglitazone: 24% ↓ risk of stroke in Pts w/ stroke/TIA + insulin resist. (*NEJM* 2016;374:1321)
- **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* 2004;363:1491 & 2010;376:1074)
  stenting: c/w CEA, periprocedural risk of stroke ↑ (esp. in elderly) & MI ↓ (but many asx), subsequent rates of stroke similar (*NEJM* 2016;374:1011 & 1021; *Lancet* 2016;387:1305)

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. No sig benefit shown for PFO closure so far, albeit studies small & w/ favorable trends (*NEJM* 2012;366:991; 2013:1083 & 1092).

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 Neurol* 2005;4:662; *BMJ* 2010;341:c5204)

- ↓ 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;doi: 10.1111/acem.12984)

- 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

- Reverse coagulopathies (qv), goal INR <1.4. Plt goal >100k. No benefit to plt transfusion if on antiplt Rx (*Lancet* 2016;387:2605), but ? consider if expanding ICH; DDAVP if uremic.
- Strict BP control w/ art line, use nicardipine or labetalol gtt. SBP goal ~160 (*NEJM* 2013:368:2355 & ATACH-2, *NEJM* 2016;doi: 10.1056/NEJMoa1603460).
- 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

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 ↓
Babinski	Present	Absent	Absent	Absent

Peripheral Neuropathies

Etiologies based on presentation

- **Mononeuropathy** (1 nerve): if *acute* → trauma; if *chronic* → entrapment, compression, DM, Lyme. Commonly seen: median n. (carpal tunnel synd.); ulnar n. (at elbow or wrist); common peroneal n. (at knee w/ habitual leg crossing); lat femoral cutan. n. (at inguinal lig).
- **Mononeuropathy multiplex** (axonal loss of multiple, separate, noncontig. nerves): vasculitic synd. (eg, PAN, Churg–Strauss, Wegener's, cryo, SLE, RA, Sjögren's), DM, Lyme, leprosy, HIV, hereditary neuropathy w/ pressure palsies; sarcoid, lymphoma, leukemia
- **Polyneuropathy** (multiple symmetric nerves, generally length dependent). 50% idiopathic.
  W/ autonomic features: DM, EtOH, paraneoplastic, B_{12} def, amyloid, chemo, 1° dysauto.
  Painful (small fiber neuropathies): DM, EtOH, amyloid, chemo, heavy metals, porphyria
  Demyelinating. Acute: acute inflam demyelinating polyneuropathy (AIDP) = Guillain-Barré
  Subacute: meds (taxanes), paraneoplastic
  Chronic: idiopathic, DM, CIDP, hypothyroidism, toxins, paraproteinemia, hereditary
  Axonal. Acute: acute motor axonal neuropathy (AMAN), porphyria, vasculitis, uremia
  Subacute: DM, meds (cisplatin, paclitaxel, vincristine, INH, ddI), EtOH, sepsis, paraneo.
  Chronic: DM, uremia, lead, arsenic, HIV, paraproteinemia, B_{12} defic

Clinical manifestations

- Weakness, fasciculations, numbness, dysesthesias (burning/tingling), allodynia
- ± Autonomic dysfxn (orthostasis, bowel/bladder retention/incontinence, impotence)
- 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 titers, RPR, UA, UPEP+IF, ACE, ANCA, genetic testing, heavy metal screen, LP (AIDP, CIDP), cryo, paraneoplastic panel
- Autonomic testing/skin bx (small fiber), nerve bx (mononeuropathy multiplex)
- MRI if possible radiculopathy or plexopathy (after EMG)

Pharmacologic treatment of neuropathic pain (*Lancet Neurol* 2015;14:162)

- Pregabalin, gabapentin, TCAs (nortriptyline, amitriptyline), SNRIs (duloxetine, venlafaxine)
- 2nd line: tramadol, topicals (lidocaine, capsaicin); 3rd line: opiates, 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%; w/o sensory loss; a/w anti-GM1, GD1a Ab); 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 (CMV, EBV, HIV), 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 sym 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: ↓ nerve conduction velocity, conduction block; can be nl in 1st 2 wks
- FVC & NIF: to assess for risk of resp. failure (cannot rely on P_aO_2 or S_aO_2).

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)
- Most recover near baseline in 1 y; 3–5% mortality. Residual deficits: pain, fatigue.

Myasthenia Gravis

Definition & epidemiology (*Lancet Neurol* 2015;14:1023)
- 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). Often later progresses to generalized weakness.
- Limb weakness proximal > distal; DTRs preserved; minimal/no atrophy
- MusK MG (F >> M): mostly cranial/bulbar, neck, and resp weakness.
- LRP4 MG: mostly ocular and limb weakness. Resp failure rare.
- Exacerbations triggered by stressors such as URI, surgery, pregnancy or postpartum, meds (eg, aminoglycosides, macrolides, fluoroquinolones, procainamide, phenytoin, D-penicillamine). Prednisone can *worsen* sx acutely.
- Myasthenic crisis = exacerbation → need for respiratory assistance
- 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; may lead to improvement in up to 85% Pts w/o thymoma
- Cholinesterase inhib (eg, pyridostigmine) 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) + AZA (benefit in 6–15 mo). If no response: mycophenolate, rituximab, MTZ, CsA.
- Myasthenic crisis: treat precipitant; consider d/c cholinesterase inhib. if suspect cholinergic crisis. IVIg or plasmapheresis; if no response, high-dose glucocorticoids (in monitored setting as 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 (incl. critical illness myopathy), zidovudine, alcohol, cocaine, antimalarials, colchicine, penicillamine
- Infectious: HIV, HTLV-1, trichinosis, toxoplasmosis
- Inflammatory (see "Rheumatology"): polymyositis, dermatomyositis, inclusion body myositis

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 (anti-Jo1, antisynthetase, anti-Mi-2, anti-SRP, ANA, RF)
- EMG/NCS: low-amp, polyphasic units w/ early recruitment, ± fibrillation potentials
- Muscle biopsy, molecular genetic testing (where indicated)

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. Rx: NSAIDs, acetaminophen (risk of med overuse HA) if episodic; TCAs if chronic.
- **Cluster HA** and other trigeminal autonomic cephalalgias (TACs) (*Continuum* 2015;21:1041)
  Characterized by unilateral rhinorrhea, red/tearing eye, miosis/ptosis, lid edema, sweating, pain is orbital or temporal, differentiated by timing
  Cluster: ♂ > ♀, unilateral eye pain, restlessness, attacks 15 min–3 h, worsened by EtOH. Ppx: CCB (verapamil). Rx: high-flow O_2 via non-rebreather; sumatriptan IN/SC.
  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: postconcussion, 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 causes: 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 causes: hypoxia, hypercapnia, dialysis HA, HTN, hypoglycemia, ↓TSH
- 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)
- General and neurologic exam (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)
  abnl neuro exam (struct. lesion, poss. in migraine); ↓ *consciousness* (± fever): infxn, ICH
  age >50 y; immunosuppression (CNS infections, PRES)
- LP if ? SAH (✓ for xanthochromia), idiopathic intracranial HTN (✓opening press); image first!

MIGRAINE

Epidemiology: affects 15% of women and 6% of men; onset usually by 30 y

Definition & clinical manifestations

- **Migraine w/o aura** (most common): ≥5 attacks lasting 4–72 h and with both (a) N/V *or* photophobia & phonophobia, and (b) ≥2 of following: unilat., pulsating, mod–severe intensity, 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 hemiplegic migraine:** aura of fully reversible motor weakness lasting up to 24 hr, also w/visual and sensory aura + typical migraine HA
- Precipitants: stress, hunger, foods (cheese, chocolate) and food additives (MSG), fatigue, alcohol, menstruation, exercise

Treatment (*Cephalalgia* 2015;35:271)

- Abortive Rx: 5-HT_1 agonists ("triptans") effective if given early in migraine attack, contraindic if motor aura, CAD, prior stroke. Also consider acetaminophen, caffeine, NSAIDs, steroids; IV options include Mg, metoclopramide, prochlorperazine, valproate, dihydroergotamine (caution if CAD, recent triptan use). *Avoid butalbital, opioids.*
- Prophylaxis: valproic acid, topiramate, ββ, TCAs, butterbur, NSAIDs, magnesium, riboflavin (*Neurology* 2012;78:1337 & 1346)

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 (also see ID section): osteomyelitis, epidural abscess, zoster, Lyme, CMV, HIV
- **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

- **History:** location, radiation, trauma, wt loss, cancer hx, fever, immunocompromised, neurologic symptoms, saddle anesthesia, incontinence, urinary retention, IV drug use
- **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) 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).
- **Laboratory** (depending on suspicion): CBC, ESR, Ca, PO_4, CSF
- **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 manifestations

- Acute: flaccid paraparesis and absent reflexes ("spinal shock")
- Subacute–chronic: spastic paraparesis and hyperactive reflexes
- Posterior column dysfunction in legs (loss of vibratory sense or proprioception)
- Sensory loss below level of lesion
- ⊕ Babinski responses ± ankle clonus

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
- 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 manifestations

- 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.

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 dorsiflexion, 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, steroid injections (ESI) Surgery (if other Rx fails)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. (*NEJM* 2007;356:1241 & 2008;358:818)

Treatment of nerve root compression (*NEJM* 2016;374:1763)

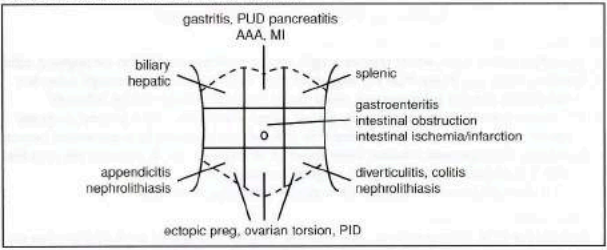
- Conservative: avoid bending/lifting; soft cervical collar (cervical radiculopathy); NSAIDs; muscle relaxants; Rx neuropathic pain (see "Peripheral Neuropathies"); physical therapy.
- Spinal epidural steroid injections (ESI): limited short-term relief of refractory radicular pain (*Pain* 2013;154:2249)
- Surgery: cord compression or cauda equina syndrome; progressive motor dysfunction; bowel/bladder dysfunction; failure to respond to conservative Rx after 3 mo (*NEJM* 2007;356:2245)

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 viscous → peritonitis (perforated ulcer, complicated diverticulitis, trauma)
- Intraperitoneal bleed
- Bowel obstruction (adhesions from previous surgeries, malignancies, hernias)
- 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, type, & screen
- Imaging: KUB (upright) or if stable, CT abomen/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)
- 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

- Evaluation: detailed vascular exam; CT angiography or arteriography
- Initial management: anticoag for embolism/thrombosis; 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
- Securely anchor to skin to prevent inadvertent removal
- 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
- Surgical consultation for debridement of ulcers with necrotic or infected tissue, may require plastic surgical reconstruction for advanced ulcers once clean
- Wound vac (negative pressure vacuum dressing) therapy may accelerate healing

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

Vaginal Bleeding

Abnormal bleeding from lower (vulva, vagina, cervix) or upper genital tract (uterus)

Etiologies

- Premenopausal
  - Not pregnant: menses, dysfunctional uterine bleeding (menorrhagia), leiomyoma, polyp, trauma, cervical dysplasia/cancer (rare), endometrial hyperplasia/cancer (rare)
  - Pregnant
    - 1st trimester: threatened abortion, spont. abortion (missed, incomplete or complete), ectopic pregnancy, molar pregnancy (partial or complete hydatidiform mole)
    - 2nd or 3rd trimester: preterm labor, placenta previa, placental abruption
- Postmenopausal: atrophy, polyp, leiomyoma, endometrial hyperplasia/cancer, cervical dysplasia/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 and LMP to assess timing of menstrual cycle
- Past Ob/Gyn hx (any structural abnl, STD, and contraception)
- Health maint. (Pap smear, HPV screening); domestic violence; anticoag or antiplt meds
- General physical & abdominal exam (incl. tenderness, masses)
- Pelvic exam: external (quantity of bleeding seen on vulva, any lesions, any trauma); also, w/ assistance from Ob/Gyn, speculum exam (quantity of bleeding; cervical os open or close and if open, dilation; any polyps), & bimanual exam (uterine size and tenderness, adnexal mass and tenderness)

Laboratory evaluation & imaging

- Urine (rapid test) & serum pregnancy test (beta-hCG); Hct/hemoglobin
- Pelvic U/S: visualize intrauterine preg to r/o ectopic; if preg, intrauterine not seen, & βHCG > discrim. zone → ? ectopic; if βHCG < discrim. zone → follow βHCG; nl placental position to r/o placenta previa and likely severe abruption
- *Ectopic pregnancy is life-threatening dx, ∴ must rule out if Pt pregnant* (*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 or 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 STD and contraception usage (condoms ↓ STD 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 pregnancy test

Treatment

- Bacterial vaginosis: oral or vaginal metronidazole or clindamycin
- Candida vulvovaginitis: oral or 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 (follicular and corpus luteum) or 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; associated 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 pregnancy); CA-125 if postmenopausal
- Pelvic U/S (even if mass 1st identified on CT, as U/S is best modality); U/S appearance of mass most important factor used to determine risk of malignancy

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 & 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); 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).

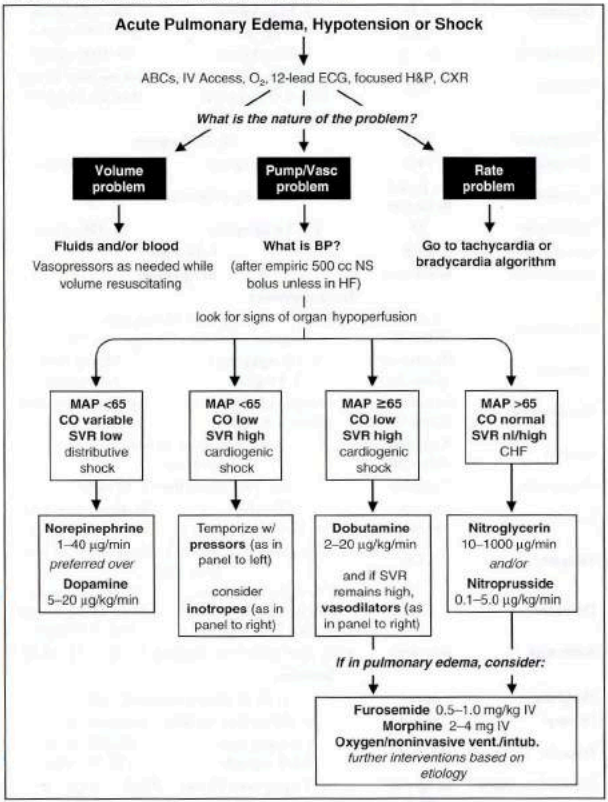
Ocular Emergencies

- **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 antibiotics, NPO, surgical prep

Drug	Class	Dose	
		per kg	average
Pressors, Inotropes and Chronotropes			
Phenylephrine	α_1	10–300 μg/min	
Norepinephrine	$\alpha_1 > \beta_1$	1–40 μg/min	
Vasopressin	V_1	0.01–0.1 U/min (usually <0.04)	
Epinephrine	α_1, α_2, β_1, β_2	2–20 μg/min	
Isoproterenol	β_1, β_2	0.1–10 μg/min	
Dopamine	D β, D α, β, D	0.5–2 μg/kg/min 2–10 μg/kg/min >10 μg/kg/min	50–200 μg/min 200–500 μg/min 500–1000 μg/min
Dobutamine	$\beta_1 > \beta_2$	2–20 μg/kg/min	50–1000 μg/min
Milrinone	PDE	± 50 μg/kg over 10 min then 0.25–0.75 μg/kg/min	3–4 mg over 10 min then 20–50 μg/min
Vasodilators			
Nitroglycerin	NO	10–1000 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	1–16 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 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	

Drug	Class	Dose	
		per kg	average
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, most anaerobes (except *Bacteroides*)	Group A streptococci 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, H. influenzae Salmonella, Shigella Enterococci, Listeria*
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 ⊕ & ⊖, including 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)	Inhibit plasma-mediated β-lactamases	Adds staph, *B. fragilis* & some GNR (*H. flu, M. cat,* some *Klebs*); intrinsic activity against *Acinetobacter* (sulbactam only)

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: Respiratory: *H. influenzae & M. catarrhalis* GI/GU: ↑ activity vs. *B. fragilis*	PNA/COPD flare Abdominal infxns
3rd (eg, ceftriaxone)	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.

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	
Quinupristin/ Dalfopristin	
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, PCP, *Nocardia, Toxoplasma,* most community-acquired MRSA
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (incl. *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*. Approved for abdominal or skin/soft tissue infections. Check susceptibility if organism isolated.

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%)

$$\therefore \textbf{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dL)} \times 13.6\ (S_aO_2 - S_vO_2)}$$

Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein } O_2 \text{ sat} - \text{Pulm. artery } O_2 \text{ sat}}$$ (if no R → L shunt, PV O_2 sat = S_aO_2)

$$Q_s = \frac{\text{Oxygen consumption}}{S_aO_2 - \text{mixed venous } O_2 \text{ sat}}$$ (MVO_2 drawn proximal to potential L → R shunt)

$$\frac{Q_p}{Q_s} = \frac{S_aO_2 - MV\ O_2\ sat}{PV\ O_2\ sat - PA\ O_2\ sat} \approx \frac{S_aO_2 - MV\ O_2\ sat}{S_aO_2 - PA\ O_2\ sat}$$ (if only L → R and no R → L shunt)

Valve equations

Simplified Bernoulli: Pressure gradient (ΔP) = $4 \times v^2$ (where v = peak flow velocity)
Continuity (conservation of flow): $Area_1 \times Velocity_1 = A_2 \times V_2$ (where 1 & 2 different points)

$$\text{or AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{LVOT}}{V_{AoV}}\right)$$ (all of which can be measured on echo)

$$\text{Gorlin equation: Valve area} = \frac{CO/(DEP \text{ or } SEP) \times HR}{44.3 \times \text{constant} \times \sqrt{\Delta P}}$$ (constant = 1 for AS, 0.85 for MS)

$$\text{Hakki equation: Valve area} \approx \frac{CO}{\sqrt{\Delta P}}$$

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 (BOOP, eosinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoid)
Ground glass (CT easier than CXR)	Interstitial thickening or partial filling of alveoli (but vessels visible)	*Acute:* pulm edema, infxn (PCP, viral, resolving bact. PNA) *Chronic:* ILD w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF
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, BOOP
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	BOOP, 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 $\left(\frac{V_D}{V_T}\right) = \frac{P_aCO_2 - P_{expired}CO_2}{P_aCO_2}$

$$\mathbf{P_aCO_2} = k = \times \frac{CO_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

Nephrology

Anion gap (AG) = Na − (Cl + HCO_3) (normal = [alb] × 2.5; typically 12 ± 2 mEq)
Delta-delta (ΔΔ) = [Δ AG (ie, calc. AG − expected) / Δ HCO_3 (ie, 24 − measured HCO_3)]
Urine anion gap (UAG) = (U_{Na} + U_K) − U_{Cl}

Calculated osmoles = $(2 \times Na) + \left(\frac{glc}{18}\right) + \left(\frac{BUN}{2.8}\right) + \left(\frac{EtOH}{4.6}\right)$

Osmolal gap (OG) = measured osmoles − calculated osmoles (normal <10)

Estimated creatinine clearance = $\frac{[140 - age\ (yes)] \times wt\ (kg)}{serum\ Cr\ (mg/dL) \times 72}$ (× 0.85 in women)

Fractional excretion of Na (FE_{Na}, %) = $\left[\frac{\frac{U_{Na}(mEq/L)}{P_{Na}(mEq/L)} \times 100\%}{\frac{U_{Cr}(mg/mL)}{P_{Cr}(mg/dL)} \times 100\ (mL/dL)}\right] = \frac{U_{Na}/P_{Na}}{U_{Cr}/P_{Cr}}$

Corrected Na in hyperglycemia

estimate in all Pts: corrected Na = measured Na + $\left[2.4 \times \frac{(measured\ glc - 100)}{100}\right]$

however, Δ in Na depends on glc (*Am J Med* 1999;106:399)
Δ is 1.6 mEq per each 100 mg/dL ↑ in glc ranging from 100–440
Δ is 4 mEq per each 100 mg/dL ↑ in glc beyond 440

Total body water (TBW) = 0.60 × IBW (× 0.85 if female and × 0.85 if elderly)

Free H_2O deficit = TBW × $\left(\frac{[Na]_{serum} - 140}{140}\right) = \left(\frac{[Na]_{serum} - 140}{3}\right)$ (in 70-kg Pt)

Trans-tubular potassium gradient (TTKG) = $\frac{U_K/P_K}{U_{Osm}/P_{Osm}}$

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

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** = $\frac{\text{true negatives}}{\text{all negatives}} = \frac{d}{c+d}$

ABBREVIATIONS

5′-NT	5′-nucleotidase
6-MP	6-mercaptopurine
a/w	associated with
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
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	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
AZA	azathioprine
Aϕ	alkaline phosphatase
βB	beta-blocker
b/c	because
BAL	bronchoalveolar lavage
BBB	bundle branch block
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
BOOP	bronchiolitis obliterans with organizing pneumonia
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
c/s	consult
c/w	compared with consistent with
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
CCl_4	carbon tetrachloride
CCP	cyclic citrullinated peptide
CCS	Canadian Cardiovascular Society
CCY	cholecystectomy
CD	Crohn's disease
CEA	carcinoembryonic antigen
	carotid endarterectomy
ceph.	cephalosporin
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
CsA	cyclosporine A
CSF	cerebrospinal fluid
CSM	carotid sinus massage
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
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
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
D_LCO	diffusion capacity of the lung
DLE	drug-induced lupus
DM	dermatomyositis diabetes mellitus
DMARD	disease-modifying anti-rheumatic drug
DOE	dyspnea on exertion
DRE	digital rectal exam
DRESS	drug reaction w/ eosinophilia & systemic symptoms
DSE	dobutamine stress echo
DST	dexamethasone suppression test
DTRs	deep tendon reflexes
DU	duodenal ulcer
DVT	deep vein thrombosis
dx	diagnosis
EAD	extreme axis deviation
EAV	effective arterial volume
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EDP	end-diastolic pressure
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EGFR	epidermal growth factor receptor
EGPA	eosinophilic granulomatosis with polyangiitis
EI	entry inhibitor
EIA	enzyme-linked immunoassay
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EMB	ethambutol
ENT	ears, nose, & throat
EOM	extraocular movement/muscles
EP	electrophysiology
Epo	erythropoietin
EPS	electrophysiology study
ERCP	endoscopic retrograde cholangiopancreatography
ERV	expiratory reserve volume
ESP	end-systolic pressure
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ESV	end-systolic volume
ET	endotracheal tube essential thrombocythemia
EtOH	alcohol
ETT	endotracheal tube exercise tolerance test
EUS	endoscopic ultrasound
EVAR	endovascular aneurysm repair
FDP	fibrin degradation product
FEV_1	forced expir. vol in 1 sec
FFP	fresh frozen plasma
FHx	family history
FI	fusion inhibitor
FMD	fibromuscular dysplasia
FMF	familial Mediterranean fever
FNA	fine-needle aspiration
FOB	fecal occult blood
FOBT	fecal occult blood testing
FQ	fluoroquinolone
FRC	functional residual capacity
FSGS	focal segmental glomerulosclerosis
FSH	follicle stimulating hormone
FTI	free thyroxine index
FUO	fever of unknown origin
f/up	follow-up
FVC	forced vital capacity
G6PD	glc-6-phosphate dehydrogenase
GB	gallbladder
GBM	glomerular basement membrane

GBS	Guillain-Barré syndrome
GCA	giant cell arteritis
GCS	Glasgow coma scale
G-CSF	granulocyte colony stimulating factor
GE	gastroesophageal
gen.	generation
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GIB	gastrointestinal bleed
GIST	gastrointestinal stromal tumor
glc	glucose
GMCSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis
GNR	gram-negative rods
GnRH	gonadotropin-releasing hormone
GPA	granulomatosis w/ polyangiitis
GPC	gram-positive cocci
GPI	glycoprotein IIb/IIIa inhibitor
GRA	glucocorticoid-remediable aldosteronism
GU	gastric ulcer
GVHD	graft-versus-host disease
h	hour
H2RA	H2-receptor antagonist
HA	headache
HACA	human antichimeric antibody
HAV	hepatitis A virus
Hb	hemoglobin
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCMP	hypertrophic cardiomyopathy
Hct	hematocrit
HCV	hepatitis C virus
HCW	health care worker
HD	hemodialysis
HDL	high-density lipoprotein
HDV	hepatitis D virus
HELLP	hemolysis, abnl LFTs, low plts
HEV	hepatitis E virus
HF	heart failure
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HHS	hyperosmolar hyperglycemic state
HIT	heparin-induced thrombocytopenia
HK	hypokinesis
HL	Hodgkin lymphoma
h/o	history of
HOB	head of bed
HoTN	hypotension
hpf	high-power field
HPT	hyperparathyroidism
HR	heart rate
HRT	hormone replacement therapy
HS	hereditary spherocytosis
HSCT	hematopoietic stem cell transplantation
HSM	hepatosplenomegaly
HSP	Henoch-Schönlein purpura
HSV	herpes simplex virus
HTN	hypertension
HUS	hemolytic uremic syndrome
hx	history
I&D	incision & drainage
IABP	intra-aortic balloon pump
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity
iCa	ionized calcium
ICD	implantable cardiac defibrillator
ICH	intracranial hemorrhage
ICP	intracranial pressure
ICU	intensive care unit
IE	infective endocarditis
IGF	insulin-like growth factor
IGRA	interferon-γ release assay
II	integrase inhibitor
IIP	idiopathic interstitial PNA
ILD	interstitial lung disease
IMI	inferior myocardial infarction
infxn	infection
inh	inhaled
INH	isoniazid
INR	international normalized ratio
IPAA	ileal pouch-anal anastomosis
IPF	idiopathic pulmonary fibrosis
ITP	idiopathic thrombocytopenic purpura
IVB	intravenous bolus
IVC	inferior vena cava
IVDU	intravenous drug use(r)
IVF	intravenous fluids
IVIg	intravenous immunoglobulin
JVD	jugular venous distention
JVP	jugular venous pulse
KS	Kaposi's sarcoma
KUB	kidney-ureter-bladder (radiography)
LA	left atrium long-acting lupus anticoagulant
LABA	long-acting β_2-agonist
LAD	left anterior descending coronary artery left axis deviation
LAE	left atrial enlargement
LAN	lymphadenopathy
LAP	left atrial pressure leukocyte alkaline phosphatase
LBBB	left bundle branch block
LCA	left coronary artery
LCIS	lobular carcinoma *in situ*
LCx	left circumflex cor. art.
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LE	lower extremity
LES	lower esophageal sphincter
LFTs	liver function tests
LGIB	lower gastrointestinal bleed
LH	luteinizing hormone
LLQ	left lower quadrant
LM	left main coronary artery
LMWH	low-molecular-weight heparin
LN	lymph node
LOC	loss of consciousness
LOS	length of stay
LP	lumbar puncture
lpf	low-power field
LQTS	long QT syndrome
LR	lactated Ringer's
LUSB	left upper sternal border
LV	left ventricle
LVAD	LV assist device
LVEDP	LV end-diastolic pressure
LVEDV	LV end-diastolic volume
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
LVSD	LV systolic dimension
mAb	monoclonal antibody
MAC	mitral annular calcification *Mycobacterium avium* complex

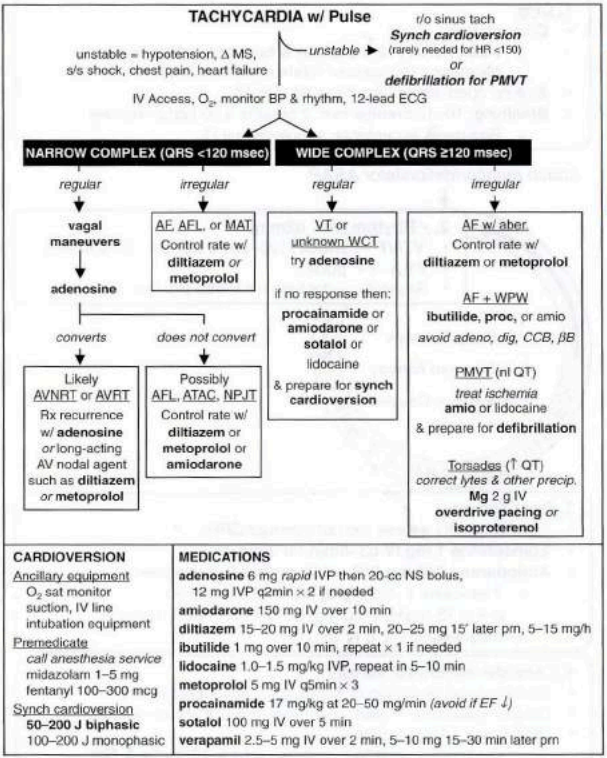
MAHA	microangiopathic hemolytic anemia
MALT	mucosa-assoc. lymphoid tissue
MAO	monoamine oxidase
MAP	mean arterial pressure
MAT	multifocal atrial tachycardia
MCD	minimal change disease
MCP	metacarpal phalangeal (joint)
MCS	mechanical circulatory support
MCTD	mixed connective tissue dis.
MCV	mean corpuscular volume
MDI	metered dose inhaler
MDMA	3,4-methylenedioxymethamphetamine (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
NIDCM	non-ischemic dilated CMP
NIF	negative inspiratory force
NJ	nasojejunal
nl	normal
NM	neuromuscular
NMJ	neuromuscular junction
NNRTI	non-nucleoside reverse transcriptase inhibitor
NNT	number needed to treat
NO	nitric oxide
NPJT	nonparoxysmal junctional tachycardia
NPO	nothing by mouth
NPPV	noninvasive positive pressure ventilation
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NS	normal saline
NSAID	nonsteroidal anti-inflam. drug
NSCLC	non-small cell lung cancer
NSF	nephrogenic systemic fibrosis
NTG	nitroglycerin
N/V	nausea and/or vomiting
NVE	native valve endocarditis
NYHA	New York Heart Association
O/D	overdose
o/w	otherwise
O&P	ova & parasites
OA	osteoarthritis
OCP	oral contraceptive pill
OG	osmolal gap
OGT	orogastric tube
OGTT	oral glucose tolerance test
OI	opportunistic infection
OM	obtuse marginal cor. art.
OSA	obstructive sleep apnea
OTC	over-the-counter
p/w	present(s) with
PA	pulmonary artery
PAC	pulmonary artery catheter
PAD	peripheral artery disease
PAN	polyarteritis nodosa
PASP	PA systolic pressure
PAV	percutaneous aortic valvuloplasty
pb	problem
PBC	primary biliary cholangitis
PCI	percutaneous coronary intervention
PCN	penicillin
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PCT	porphyria cutanea tarda
PCWP	pulmonary capillary wedge pressure
PD	Parkinson's disease peritoneal dialysis
PDA	patent ductus arteriosus posterior descending cor. art.
PE	pulmonary embolism
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PEF	peak expiratory flow
PET	positron emission tomography
PEx	physical examination
PFO	patent foramen ovale
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-1-pyrophosphate
PRWP	poor R wave progression
PS	pressure support pulmonic stenosis
PSA	prostate specific antigen
PsA	*Pseudomonas aeruginosa*
PSC	primary sclerosing cholangitis
PSGN	post streptococcal glomerulonephritis
PSHx	past surgical history
PSV	pressure support ventilation
Pt	patient
PT	prothrombin time
PTA	percutaneous transluminal angioplasty
PTH	parathyroid hormone
PTH-rP	PTH-related peptide
PTT	partial thromboplastin time
PTU	propylthiouracil
PTX	pneumothorax
PUD	peptic ulcer disease
PUVA	psoralen + ultraviolet A
PV	polycythemia vera portal vein
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis
PVR	pulmonary vascular resistance
PZA	pyrazinamide
qac	before every meal
qhs	every bedtime
QoL	quality of life
Qw	Q wave
r/i	rule in
r/o	rule out
RA	refractory anemia rheumatoid arthritis right atrium
RAA	renin-angiotensin-aldosterone
RAD	right axis deviation
RAE	right atrial enlargement
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RAS	renal artery stenosis
RAST	radioallergosorbent test
RBBB	right bundle branch block
RBC	red blood cell
RBF	renal blood flow
RBV	ribavirin
RCA	right coronary artery
RCMP	restrictive cardiomyopathy
RCT	randomized controlled trial
RDW	red cell distribution width
RE	reticuloendothelial
RF	rheumatoid factor risk factor
RHD	rheumatic heart disease
RI	reticulocyte index
RIBA	recombinant immunoblot assay
RMSF	Rocky Mountain spotted fever
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
SBP	spontaneous bacterial peritonitis systolic blood pressure
SBT	spontaneous breathing trial
SC	subcutaneous
SCD	sudden cardiac death
SCID	severe combined immunodefic.
SCLC	small-cell lung cancer
s/e	side effect
Se	sensitivity
sec	second
SERM	selective estrogen receptor modulator
sev.	severe
SHBG	steroid hormone binding globulin
SIADH	synd. of inappropriate ADH
SIBO	small intestine bacterial overgrowth
SIEP	serum immunoelectrophoresis
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	sexually transmitted disease
	ST-segment depression

STE	ST-segment elevation
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
sx	symptom(s) or symptomatic
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
T_3RU	T_3 resin uptake
TAA	thoracic aortic aneurysm
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 uric acid
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
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
V_T	tidal volume
VT	ventricular tachycardia
VTE	venous thromboembolus
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZV	varicella zoster virus
w/	with
WBC	white blood cell (count)
WCT	wide-complex tachycardia
WHO	World Health Organization
wk	week
WM	Waldenström's macroglobulinemia
WMA	wall motion abnormality
w/o	without
WPW	Wolff-Parkinson-White syndrome
w/u	workup
XRT	radiation therapy

INDEX

Figure ACLS-1 ACLS Tachycardia Algorithm



CARDIOVERSION

Ancillary equipment
O_2 sat monitor
suction, IV line
intubation equipment

Premedicate
call anesthesia service
midazolam 1–5 mg
fentanyl 100–300 mcg

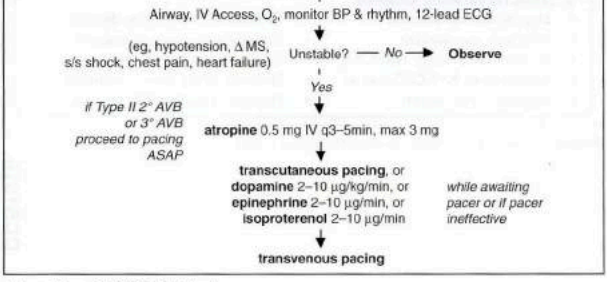
Synch cardioversion
50–200 J biphasic
100–200 J monophasic

MEDICATIONS

adenosine 6 mg *rapid* IVP then 20-cc NS bolus, 12 mg IVP q2min × 2 if needed
amiodarone 150 mg IV over 10 min
diltiazem 15–20 mg IV over 2 min, 20–25 mg 15' later prn, 5–15 mg/h
ibutilide 1 mg over 10 min, repeat × 1 if needed
lidocaine 1.0–1.5 mg/kg IVP, repeat in 5–10 min
metoprolol 5 mg IV q5min × 3
procainamide 17 mg/kg at 20–50 mg/min *(avoid if EF ↓)*
sotalol 100 mg IV over 5 min
verapamil 2.5–5 mg IV over 2 min, 5–10 mg 15–30 min later prn

(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

PULSELESS ARREST

1. CPR

- **C**ompressions
  - **Push hard (2–2.4 inches) & fast (100–120/min)**
  - Minimize interruptions; rotate compressor q2min
- **A**irway: open airway (eg, head tilt-chin lift)
- **B**reathing: 10–12 breaths/min; 2 breaths q 30 compressions
  - Bag-mask acceptable; supplemental O_2

Attach monitor/defibrillator ASAP

2. ✓Rhythm (re✓ q2min)

- **VT/VF → shock** (120–200 J biphas; 360 J mono)
- PEA → ✓ pulse
- Asystole → confirm in ≥1 lead (r/o fine VF)

3. Drug Therapy

4. Advanced Airway

5. Treat Rev Causes

Continuous CPR x 2 min

3. Drug Therapy

- Establish IV/IO access *(do not interrupt CPR)*
- **Epinephrine 1 mg IV q3–5min** (or 2 mg via ETT)
- **Amiodarone 300 mg IVB** ± 150 mg IVB 3–5 min later
  - ? lidocaine 1–1.5 mg/kg IVB (~100 mg) then 0.5–0.75 mg/kg (~50 mg) q5–10min, max 3 mg/kg
  - magnesium 1–2 g IV for TdP

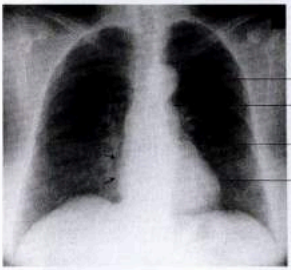
4. Consider Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Clinical assessment: bilat. chest expansion & breath sounds
- Device to ✓ tube placement
  - Continuous waveform capnography (~100% Se & Sp)
  - Colorimetric exhaled CO_2 detection (≈ clinical assess.); false neg w/ ineffective CPR, PE, pulm edema, etc.
- 10 breaths/min w/ continuous compressions

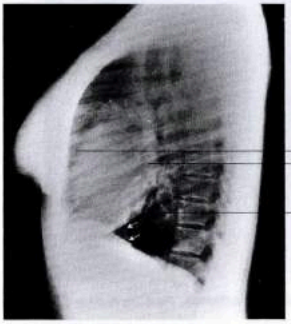
5. Treat Reversible Causes

- Hypovolemia: volume
- Hypoxia: oxygenate
- H^+ ions (acidosis): $NaHCO_3$
- Hypo/hyper K: KCl/Ca et al.
- Hypothermia: warm
- Tension PTX: needle decomp.
- Tamponade: pericardiocent.
- Toxins: med-specific
- Thromb. (PE): lysis, thrombect.
- Thromb. (ACS): PCI or lysis

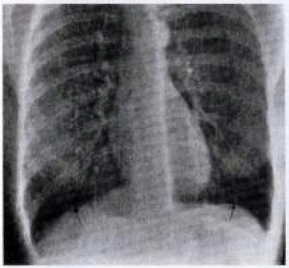
(Adapted from ACLS 2015 *Guidelines & Circ* 2015;132(Suppl 2):S444)



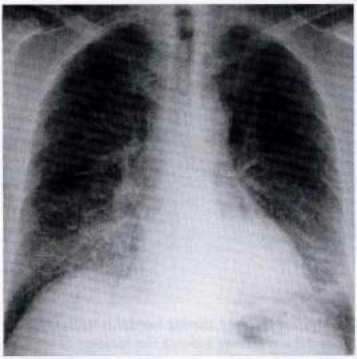
1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicate the location of the superior vena cava. The left cardiac and great vessels border what might be considered as 4 skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (*Radiology 101*, 3rd ed, 2009.)



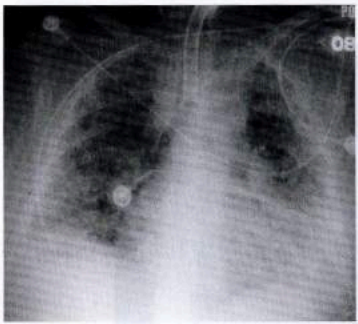
2 Normal lateral CXR. (*Radiology 101*, 3rd ed, 2009.)



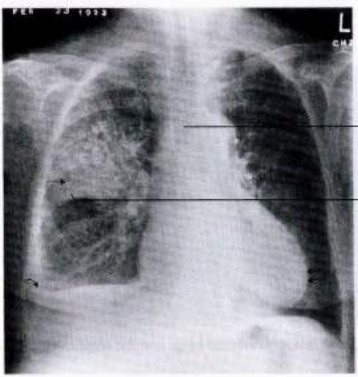
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology 101*, 3rd ed, 2009.)



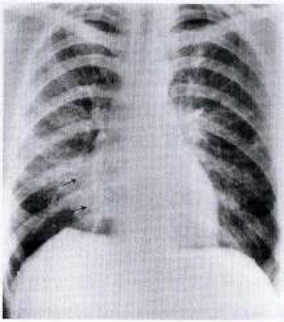
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology* 3rd ed, 2006.)



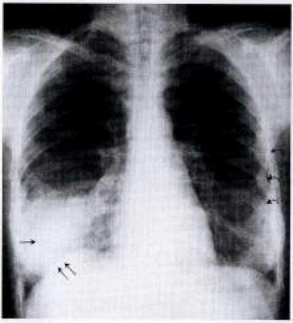
5 Alveolar pulmonary edema. (*Fund. Diag. Radiology* 3rd ed, 2006.)



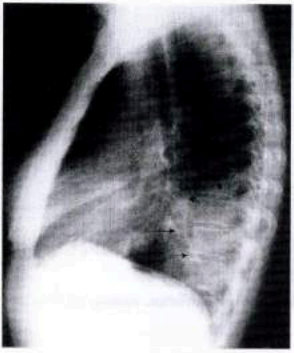
6 Right upper lobe pneumonia. (*Radiology 101*, 3rd ed, 2009.)



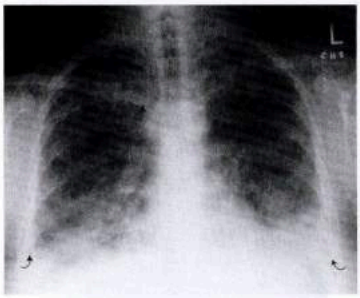
7 Right middle lobe pneumonia. (*Radiology 101*, 3rd ed, 2009.)



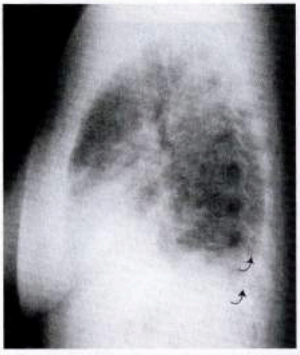
8 Right lower lobe pneumonia (PA). (*Radiology 101*, 3rd ed, 2009.)



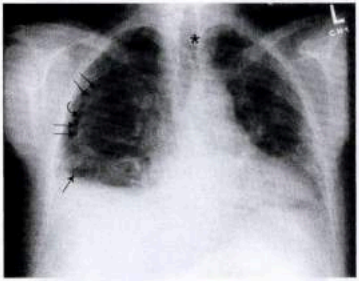
9 Right lower lobe pneumonia (lateral). (*Radiology 101*, 3rd ed, 2009.)



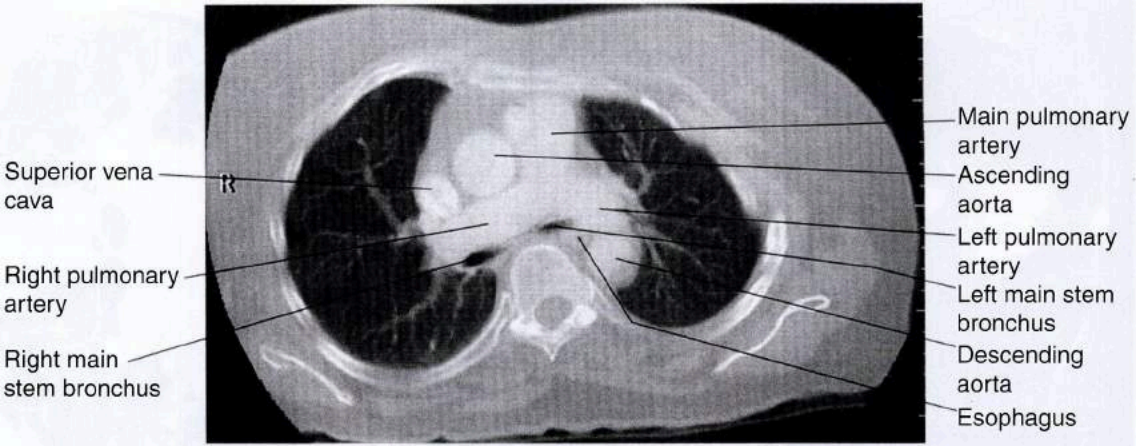
10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow) (PA). (*Radiology 101*, 3rd ed, 2009.)



11 Bilateral pleural effusions (curved arrows) (lateral). (*Radiology 101*, 3rd ed, 2009.)

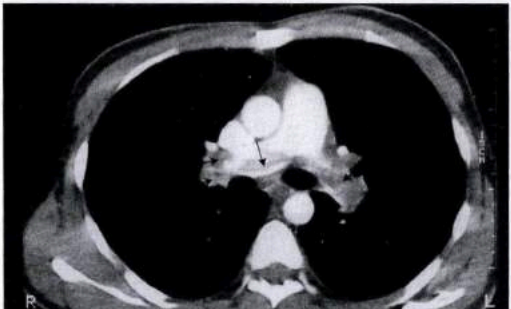


12 Pneumothorax. (*Radiology 101*, 3rd ed, 2009.)

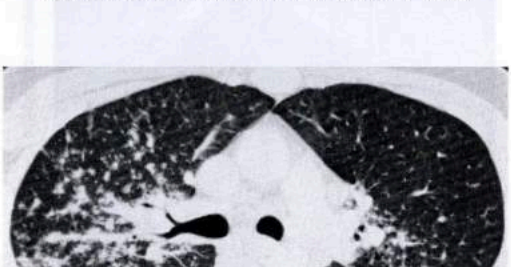


13 Normal chest CT at level of pulmonary arteries (parenchymal windows).
(*Radiology 101*, 3rd ed, 2009.)

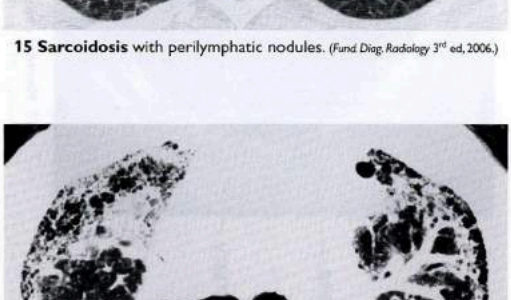
PHOTO INSERT P.5



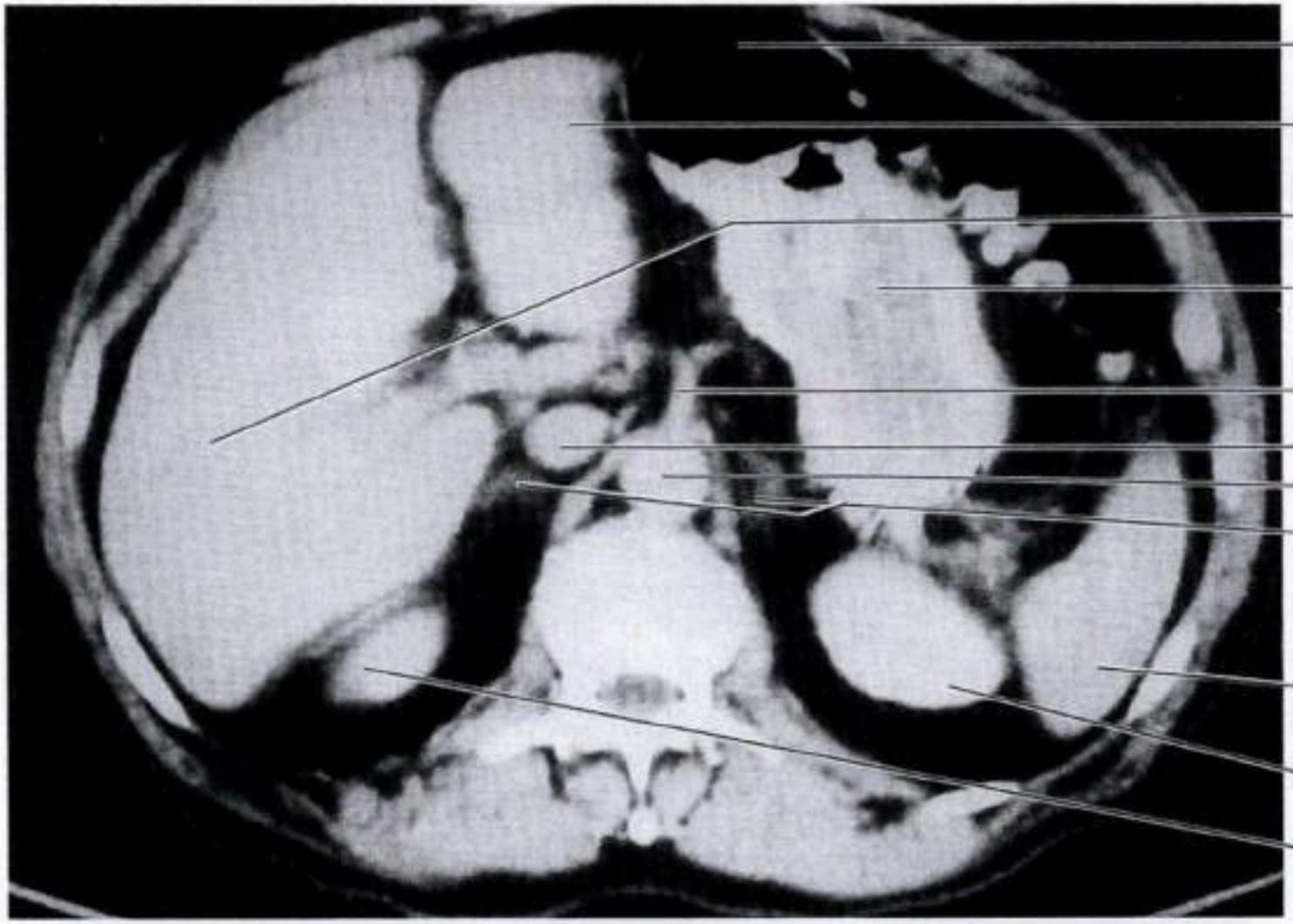
14 Bilateral PE (mediastinal windows). (*Radiology 101*, 3rd ed, 2009.)



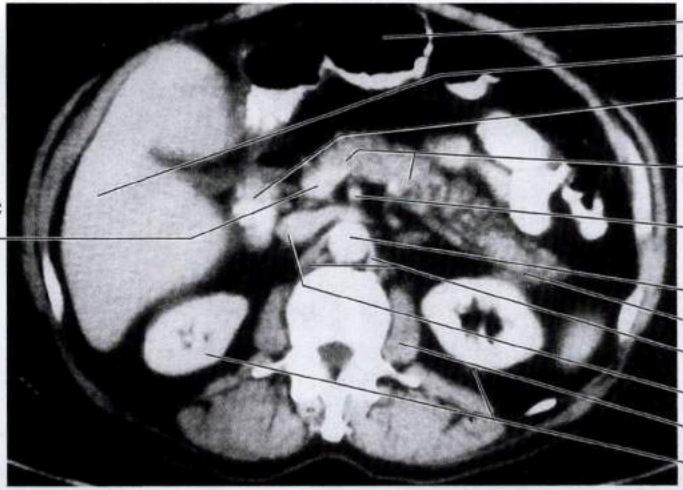
15 Sarcoidosis with perilymphatic nodules. (*Fund. Diag. Radiology* 3rd ed, 2006.)



16 Idiopathic pulmonary fibrosis. (*Fund. Diag. Radiology* 3rd ed, 2006.)

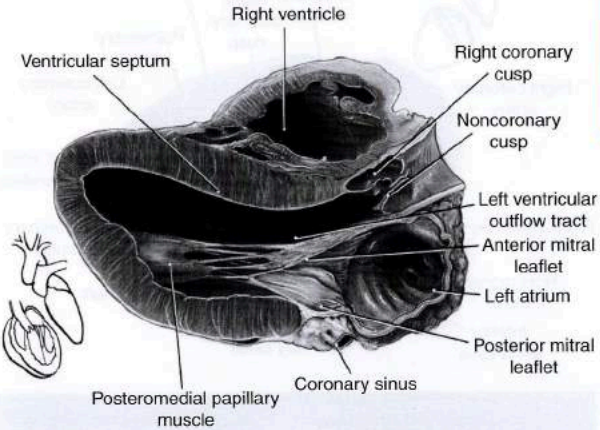


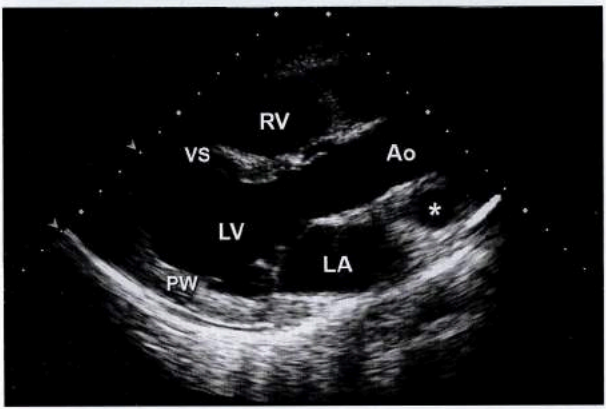
17 Normal abdomen CT at level of liver & spleen. (*Radiology 101*, 3rd ed, 2009.)



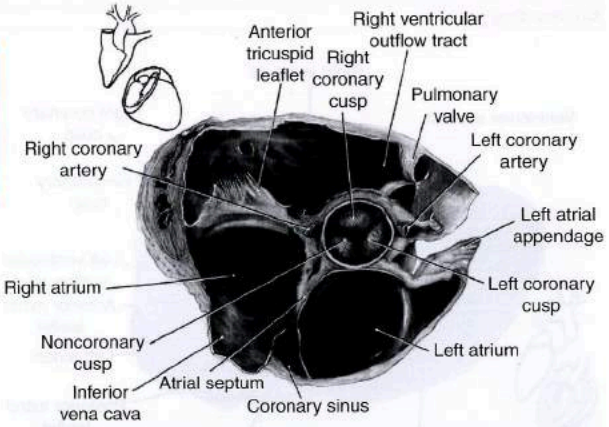
18 Normal abdomen CT at level of pancreas. (*Radiology 101*, 3rd ed, 2009.)

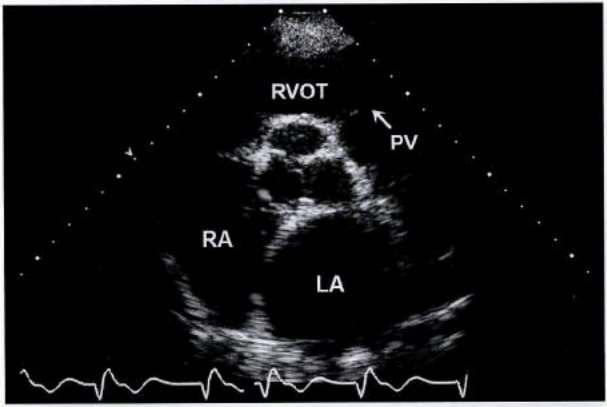
Photo Insert P-9



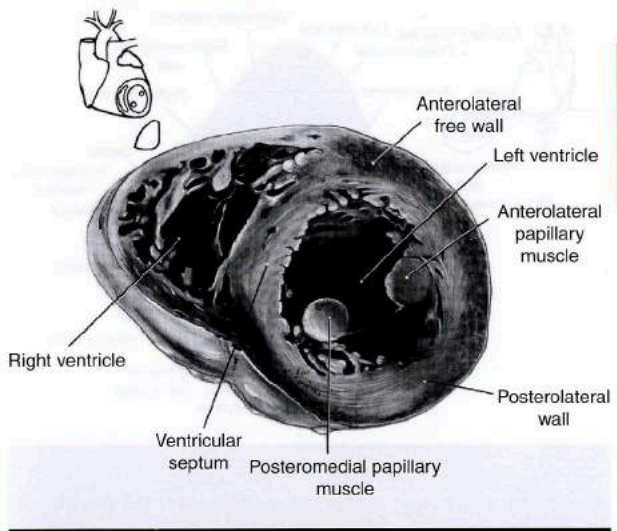


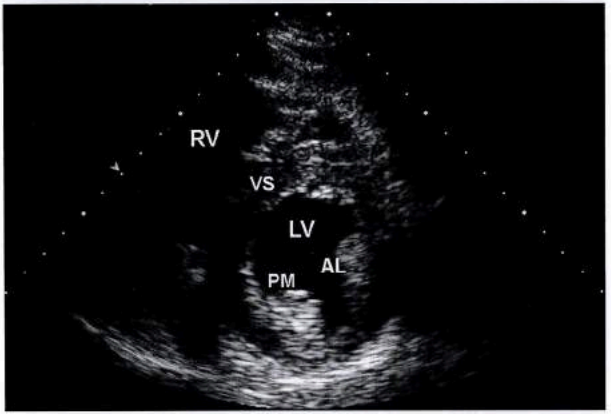
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ventricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)



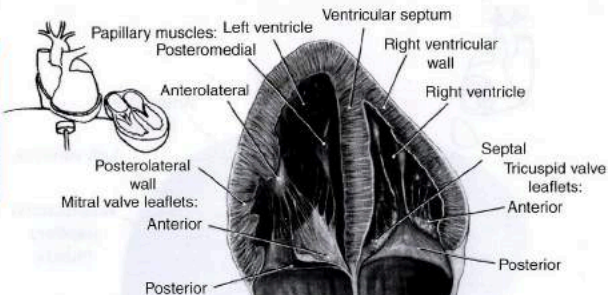


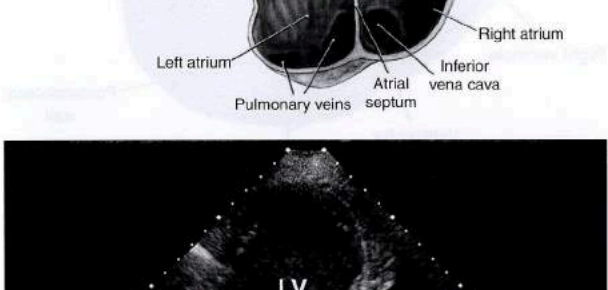
2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: 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.)





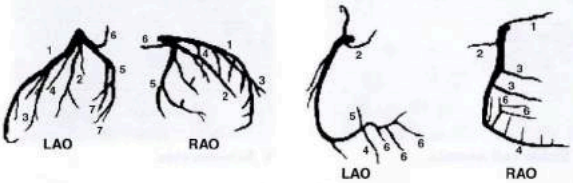
3 Parasternal short-axis view at the level of the papillary muscles: AL, anterolateral papillary muscle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum; LV, left ventricle. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time 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

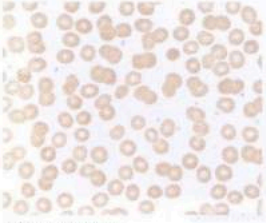


1. **Left anterior descending artery (LAD)**
2. Ramus medianus artery
3. Diagonal branches
4. Septal branches
5. **Left circumflex artery (LCx)**
6. Left atrial circumflex artery
7. Obtuse marginal branches

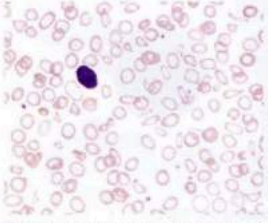
1. Conus artery
2. SA node artery
3. Acute marginal branches
4. Posterior descending artery (PDA)
5. AV node artery
6. Posterior left ventricular artery (PLV)

Coronary arteries. (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

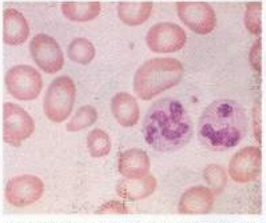
Peripheral Blood Smears



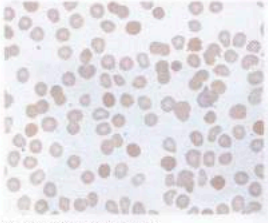
1 Normal smear.



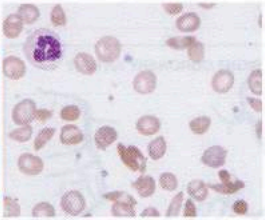
2 Hypochromic, microcytic anemia due to iron-deficiency.



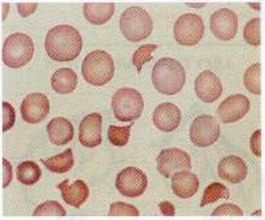
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



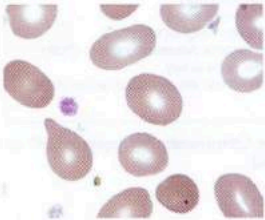
4 Spherocytes due to autoimmune hemolytic anemia.



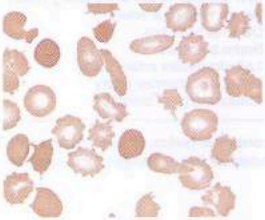
5 Sickle cell anemia.



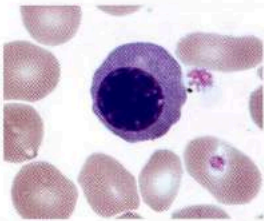
6 Schistocytes.



7 Teardrop shaped RBC (dacrocyte).



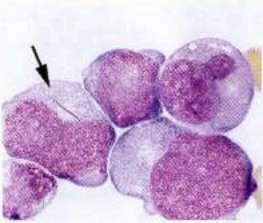
8 Acanthocytes.



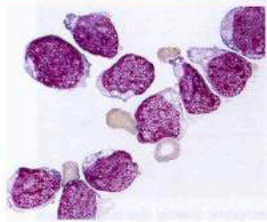
9 Nucleated RBC.

10 Rouleaux.

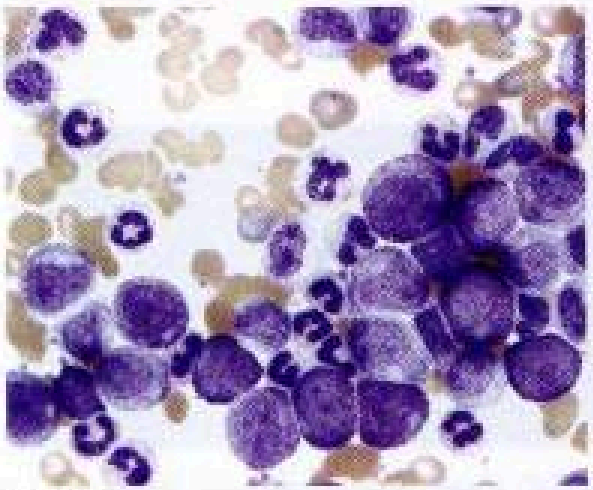
Leukemias



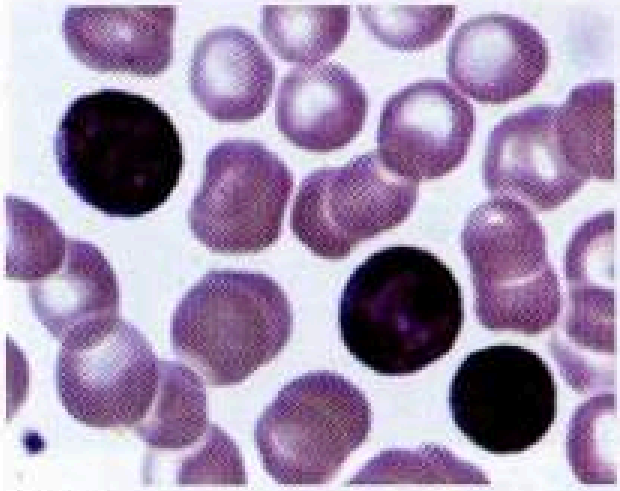
1 AML with Auer rod.



2 ALL.



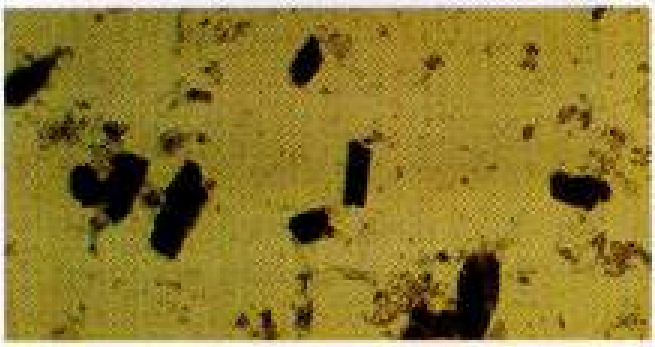
3 CML.



4 CLL.

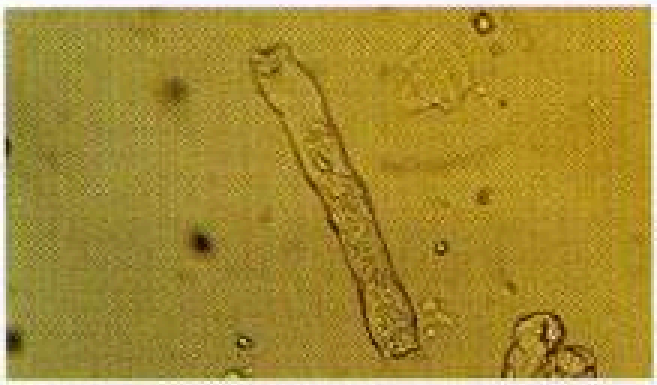
All photos excluding Leukemias Fig. 4: From Wintrobe's *Clin. Hematol.* 12th ed, 2009: Leukemias Fig. 4 From Devita, Hellman, and Rosenberg's *Cancer: Princip. & Prac. of Oncol.* 8th ed, 2008.

Urinalysis



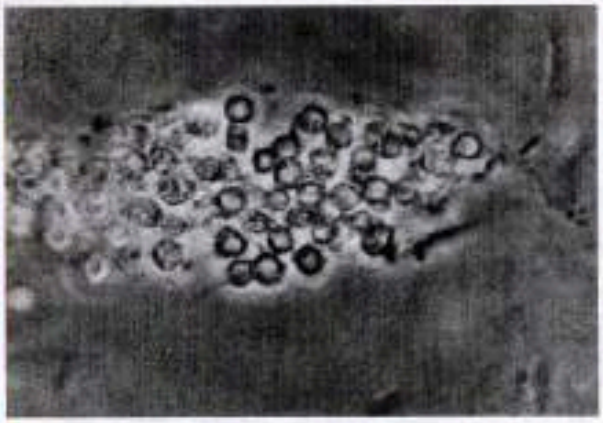
1 "Muddy brown" or granular cast (courtesy Nicholas Zwang, MD)

2 Hyaline cast (courtesy Nicholas Zwang, MD)



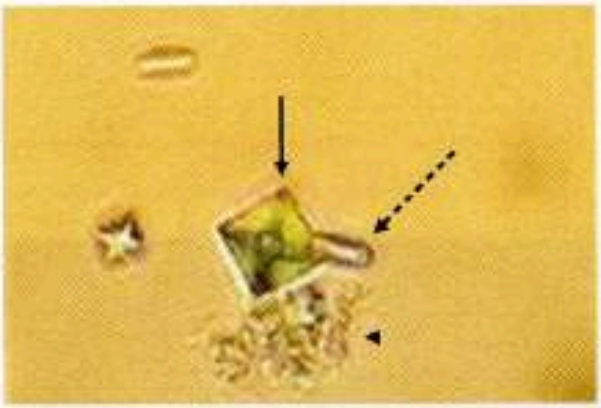
3 "Waxy broad" cast (courtesy Nicholas Zwang, MD)

4 Renal tubular epithelial cell (courtesy Nicholas Zwang, MD)

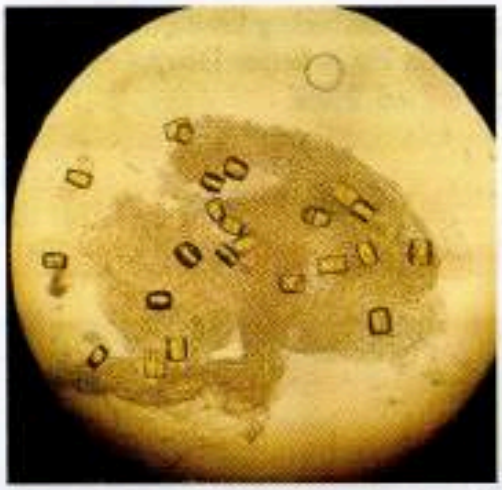


5 RBC cast. (*Dis. of Kidney & Urinary Tract*, 8th ed, 2006.)

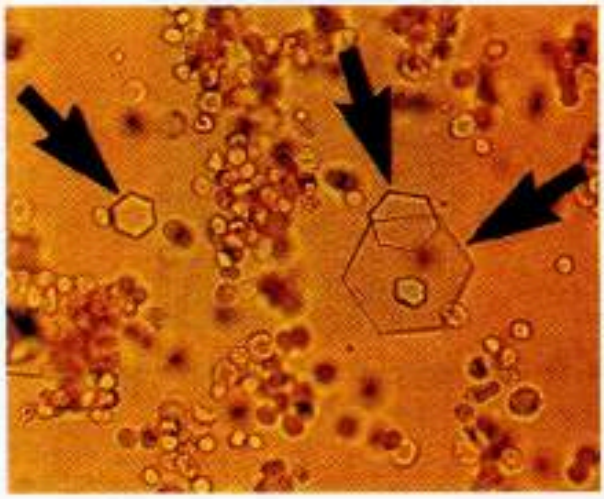
6 WBC cast. (*Clin. Lab. Medicine*, 2nd ed, 2002.)



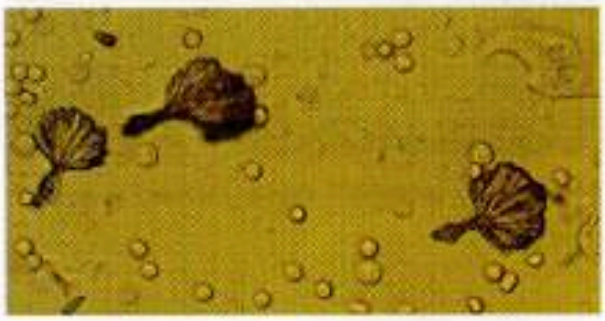
7 Calcium oxalate crystals (courtesy Mallika Mendu, MD). Calcium monohydrate (arrow), calcium dihydrate (dashed arrow), and amorphous calcium crystals (arrowhead)



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)